

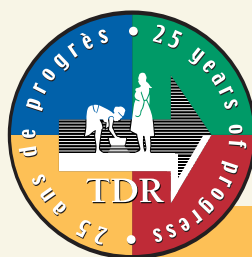
Progress (1999-2000)

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



TDR/GEN/01.5





Progress (1999–2000)

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





© World Health Organization 2001
All rights reserved.

This document is not a formal publication of the World Health Organization (WHO), and all rights are reserved by the Organization. The document may, however, be freely reviewed, abstracted, reproduced and translated, in part or in whole, but not for sale nor for use in conjunction with commercial purposes.

The views expressed in documents by named authors are solely the responsibility of those authors.

The designations employed and the presentation of the material in this publication, including tables and maps, do not imply the expression of any opinion whatsoever on the part of the Secretariat of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

Compilation: Nina Mattock
Design: Marilyn Langfeld
Front cover photograph: WHO/TDR/Martel



Contents

Foreword	v
TDR, a knowledge management and network organization	1
Diseases of the poor: What did TDR do over 12 years? <i>The evolution of TDR. Has TDR been cost-effective?</i>	
Diseases of the poor: What can TDR do in the future? <i>The challenges ahead. The new opportunities. TDR's comparative advantages.</i>	
The 15th Programme Report <i>How it is organized. Why a new reporting format? A bird's eye view of TDR activities in the 1999-2000 biennium.</i>	
References	
New Basic Knowledge	10
New, significant and relevant scientific advances <i>Pathogenesis and applied genomics. Malaria: molecular entomology. Strategic social, economic and behavioural research.</i>	
New and Improved Tools	22
New candidates ready to enter into development <i>Drug discovery research. Vaccine discovery research. Diagnostic discovery research.</i>	
New candidates in development <i>Drug development. Vaccine development. Diagnostics development.</i>	
New and improved tools receiving regulatory approval <i>Malaria drug</i>	
New and improved epidemiological tools <i>Filariasis: Rapid assessment procedures for Loa loa. Filariasis: Rapid mapping methods. Schistosomiasis: Remote sensing and geographical information systems.</i>	
New and Improved Methods	40
Methods for prevention <i>Malaria: prevention of severe anaemia and deaths associated with severe anaemia</i>	
Methods for diagnosis <i>Filariasis: diagnostic tests for disease mapping and monitoring.</i>	
Methods for treatment <i>Malaria: treatment for severe malaria. Malaria: home management. Malaria: drug resistance and policies. African trypanosomiasis: epidemiological impact of treatment. Leprosy: new drug regimens.</i>	



New and improved strategies

50

Improving existing strategies

Malaria: insecticide treated materials. Tuberculosis: fixed dose combinations of four drugs. Onchocerciasis and lymphatic filariasis: community directed treatment. Filariasis: an advocacy campaign. Onchocerciasis: reporting and monitoring of community directed treatment. Filariasis: community based management of lymphoedema. Chagas disease: advancing interruption of transmission. Chagas disease: determining the origin of vectors. Chagas disease: assessing the influence of climate on triatomine populations.

New control policies and strategies

Malaria: defining a strategy for appropriate use of rapid diagnostics. Filariasis: impact of mass treatment on transmission.

Partnerships and capacity building for research and product development

60

Partnerships for new knowledge

The Anopheles gambiae genome network. Parasite genome networks. Immunology.

Partnerships for new and improved tools

Partnerships in malaria. Partnerships in tuberculosis. Technology transfer.

Partnerships for new and improved methods

IFPMA/WHO round table. The MSF/Drugs for neglected diseases working group.

Partnerships for new and improved strategies

Malaria: Roll Back Malaria. Tuberculosis: network of disease endemic country trial sites. Onchocerciasis: the onchocerciasis control programme and the African programme for onchocerciasis control. Chagas disease: multi-governmental initiatives.

Partnerships with a multi-oriented approach

Malaria: MIM/TDR initiative. Health Internetwork. TDR individual/institutional partnerships.

Partnerships for technical information

Global Forum for Health Research.

Technical information

74

R&D initiatives using communications instruments developed by TDR

Use of the website by TDR partners

Contact with R&D partners

Contact with R&D partners: internet connectivity. Contact with R&D partners: research guidelines. Contact with control managers: operations research. Contact with drug and vaccine developers: good practices.

Resources for research

85

Finance and resources

The TDR trust fund mechanism. Source of funds. Current funding situation.

Future funding: reaching new donors

Designated funding: a challenge for management

Use of funds: programme efficiency by control of budget elements

Financial contributions



Foreword

This report describes in detail the main projects and achievements of TDR during the 1999–2000 biennium. Projects described illustrate the diversity of approaches – whether involving the tools of molecular biology or the use of insecticide-treated nets – needed to match the complexity of the difficult diseases that fall within TDR’s mandate. Apart from its value as a record of significant technical work, the report also shows how the Programme, by assessing needs, setting goals, and measuring progress in reaching them, helps stimulate the global scientific community and direct its work towards globally-agreed priorities. These include specific research areas, identified by TDR and its partners, that hold the greatest promise of yielding badly needed practical tools. Equally important is the Programme’s ability to attract the confidence and support of a range of additional partners, including donors.

Despite this support, lack of adequate resources acts as a brake on TDR’s activities, just as the Programme’s target diseases act as a brake on the socioeconomic development of affected populations. In this connection, the March 2001 resource mobilization meeting, hosted in Paris by the World Bank, marked a major event in the Programme’s history. The first of its kind, the meeting provided a unique opportunity to review TDR’s significant past achievements, to consider urgent priorities for current and future work that builds on these achievements, and to address the resource implications.

In a recent Standing Committee meeting, representatives of the co-sponsors of TDR had an opportunity to review an advance copy of this report and to express their views on its contents. In the discussions that followed, my colleagues on the Standing Committee noted their satisfaction with the extent to which TDR has revised its working methods and is developing strategies for sharpening its focus. Especially appreciated was TDR’s responsiveness to the changing practical needs of end-users, including those working in countries at the front-line of prevention and control.

With its committed staff, efficient operating systems, focused agenda, and diversified partnerships and networks, TDR is well-positioned to harness the power of biomedical research in ways that help alleviate the suffering of the many poor and disadvantaged communities where tropical diseases take their greatest toll. In view of mounting evidence of the socioeconomic impact of these diseases, the recent expansion to include implementation research, as documented in this report, is another welcome sign of the Programme’s ability to meet the challenge posed by these diseases on every possible front.





TDR: a Knowledge Management and Network Organization

At the dawn of the 3rd millennium, the world is quite different from 25 years ago, when TDR was created. Scientific and technological advances, as well as economic, political, social, cultural and environmental changes, have dramatically modified the global landscape. We live today in an Internet village, supported by powerful information and communication technologies. Biology has become 'big science', with its own Manhattan project – the sequencing of the human genome. Dolly, the sheep clone, has illustrated the power and challenges of the biotechnological revolution and the implications it will have for the future of humankind. The Berlin wall, symbol of a world split between military superpowers, has given place to a globalized economy.

The 20th century also brought about a global transformation in human health, unmatched in history, with overall improvements in health and human development. But over one billion people entered the 21st century without having benefited from the health and human development revolution, their lives scarred by a ruthless disease categorized under code Z59.5 in WHO's International Classification of Diseases: Extreme Poverty.¹

DISEASES OF THE POOR: WHAT DID TDR DO OVER 25 YEARS?

The evolution of TDR

In May 1974, Resolution WHA27.52 of the World Health Assembly created TDR to address the need for new and improved tools for disease control, and for strengthening the research capability of the disease endemic countries so that they would become active actors in this endeavour.*

Operating in the changing environment of the last 25 years, TDR had to evolve to efficiently fulfil its mandate. In this dynamic process of constant change and adaptation, TDR's top governing body (the Joint Coordinating Board, JCB), top scientific body (the Scientific and Technical Advisory Committee, STAC) and the three *External Reviews* commissioned by the JCB, played a crucial role in the stewardship of the Special Programme. The *External Reviews*, in particular, have been the basis for every major reform of TDR, pushing the Programme into different phases of its own 'life cycle'.

TDR's 1st phase – 'historic/heroic'

The Programme was initially shaped as a funding agency in the area of biomedical research and training, structured on a disease-by-disease basis. The then current idea was that the potential impact of scientific discoveries on disease control would be obvious and therefore would attract the interest of the private sector, which would assure their development into real products. This conception of what we now know to be a very complex development pipeline translated into a simple organizational structure for the Programme: four areas of work, two of them being the major functional areas (Fig 1) with activities organized by disease and operated through steering committees.**

During this 'historic/heroic phase', TDR struggled with the lack of interest in tropical diseases research shown by more advanced laboratories in the North, and with the scarcity of institutions and trained human resources in disease endemic countries. Notwithstanding these immense

* TDR is addressed in the following Resolutions of the World Health Assembly and WHO's Executive Board: WHA27.52, WHA28.51, WHA28.70, WHA28.71, EB57.R20, WHA29.71, EB59.R31, WHA30.42, WHA33(13), EB71.R10, EB77.R4, EB85.R13, WHA43.18.

** The other two areas were related to management: Area I: Technical and Administrative Bodies. Area IV: Programme Management.

Figure 1. The structure of TDR during the 'historic/heroic' phase I





challenges, already during this first phase, important new tools were generated and put into use for disease control (Table I). In spite of its predominantly biomedical orientation, early on in its history, in 1974, TDR established a Social and Economic Research (SER) unit for leading the scientific agenda in social science research related to tropical infectious diseases. SER significantly contributed to a better understanding of how social, cultural and economic factors affect disease control measures and what can be done to overcome them.

Table I –Selected products of TDR and its partners during TDR's three historical phases*

Phase I: Historic/Heroic	Phase II: Growth by Trial and Error	Phase III: Reaching Maturity
1982: Combination drug regimens for pauci- and multi-bacillary leprosy or multidrug therapy (MDT)	1990: Eflornithine for treatment of African trypanosomiasis	1999: Rapid mapping of filariasis
1981-1984: <i>Bacillus thuringiensis</i> for blackfly control	1993: Single-dose diethylcarbamazine (DEC) for treatment of lymphatic filariasis	1999: Albendazole combinations for treatment of lymphatic filariasis
1985: Tse-tse traps for control of epidemics of African trypanosomiasis	1993: Rapid epidemiological mapping of onchocerciasis (REMO)	2000: Artemotil registered for treatment of malaria
1987: Ivermectin for treatment of onchocerciasis	1993: Integrated management of childhood illness	In the pipeline
	1994: Praziquantel combinations for treatment of schistosomiasis	* Miltefosine oral for treatment of visceral leishmaniasis
	1995: Community directed treatment (ComDT) of onchocerciasis and lymphatic filariasis	* Chlorproguanil-dapsone oral for treatment of malaria
	1996: Insecticide treated bednets for prevention of malaria	* Artesunate rectal for treatment of malaria

TDR's 2nd phase –'growth by trial and error'

It soon became clear that the paradigm that had shaped the initial Programme's structure and *modus operandi* – academic research leading to products – was an oversimplification. The *1st External Review*² called attention to the fact that:

- Industry did not show interest in shifting its priorities and activities towards the area of tropical diseases (a phenomenon now well known and denominated 'market failure').
- In most cases the new knowledge generated remained 'on the shelves' – i.e. in scientific and academic publications – and did not have *per se* the power to drive or catalyse the remaining steps of the development pipeline.
- The new products needed to be evaluated in the field in disease endemic countries, and TDR was not giving sufficient priority to field research.

In a first attempt to address these concerns, the steering committees broadened their scope in order to cover all aspects of research within each disease, from basic to operational. However, the *2nd External Review*³ recognized that the needs of product development were still not being met. In 1990, a product development unit was introduced to oversee product development by the steering committees, and to manage a special product development initiative.

It soon became apparent that these incremental changes would not suffice. Steering committees, although a proven mechanism for the peer review of academic research proposals, were not a substitute for the private sector and could not manage the development pipeline alone. The exhaustion of the historic paradigm led TDR into the second phase of its history, which was described as 'growth by trial and error'⁴ In 1994, the Programme had its structure radically changed from a disease basis to a functional area basis. The initial two areas of work gave origin to four areas: Strategic Research (STR), Product Research and Development (PRD), Applied Field Research (AFR) and Research Capability Strengthening (RCS). The relationships among the first three areas were pictured as shown in Fig 2.⁴

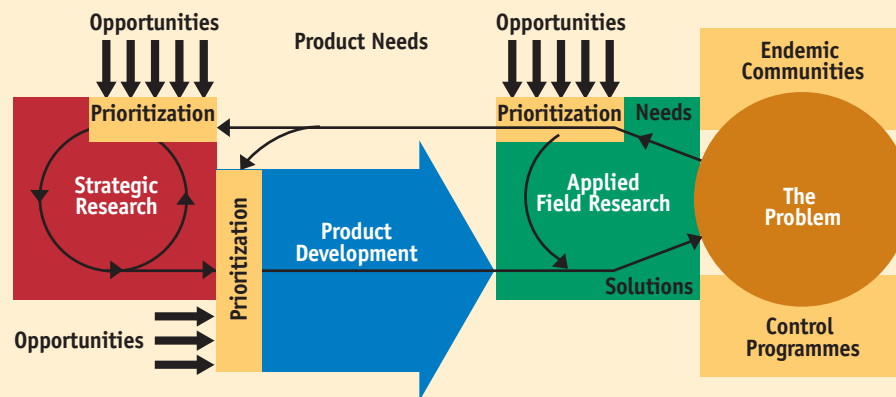
This structure proved to be a real improvement, driving the Programme towards a more active role in product development. During this second phase, TDR delivered new and improved tools

* A comprehensive list of products and corresponding TDR partners in their development has been published (also available at <http://www.who.int/tdr/morel.pdf>).



for disease control (Table I). It is worth noting, however, that RCS does not appear in figure 2 (drawn in 1992) in spite of the fact that TDR's policy on capability strengthening passed through broad phases and major policy changes.⁵

Figure 2. The structure of TDR during Phase II – ‘growth by trial and error’



TDR's 3rd phase –‘reaching maturity’

Although the Special Programme maintained its leadership and productivity, the shift from ‘disease orientation’ towards ‘functional area orientation’ brought unforeseen consequences, identified by the *3rd External Review*.⁵ The following comments and recommendations from this review played a crucial role in shaping TDR's 3rd phase:

- The disease components of the Programme were losing visibility and their role in priority setting was decreasing.
- The interaction between TDR and disease control activities needed fundamental restructuring and strengthening.
- TDR's organizational structure should address both components – diseases and functions. TDR should become a matrix organization.
- TDR should adopt a differentiated approach for capability strengthening, focusing on the least developed countries, particularly those facing a high disease burden.

In the same year that the *3rd External Review* issued its report and recommendations, WHO's new Director-General, Dr Gro Harlem Brundtland, started a reform process that profoundly changed the Organization. Of particular importance to TDR were:

- Adoption by WHO of a new corporate strategy,⁶ which emphasizes the role of knowledge, evidence-base and research in improving health.
- Location of TDR in the cluster of communicable diseases (CDS), facilitating a closer interaction among the Special Programme, the regular departments involved in disease surveillance and control, Roll Back Malaria and Stop TB.

WHO's new corporate strategy and reform process were recognized by TDR as a golden opportunity. To enable the Special Programme to operate in this new environment and efficiently address the health challenges at the start of a new millennium, the issues raised by the *3rd External Review* were used to shape the Strategy 2000-2005,⁷ formally approved by the JCB in June 2000.

The new strategy recognizes TDR as a ‘knowledge management network organization’ in health research and capacity building.* The Programme's major driving force was seen to reside in its operational capability – the ability to bring together a large number of partners and catalyse processes to solve public health problems, and to build research capacity in the disease endemic countries. The new strategy introduced several major changes to the Programme:

- TDR became a real matrix-management organization. In addition to the *team coordinators* of the four functional areas, management also became the responsibility of *disease research coordinators*.
- TDR became more involved in research directly related to disease control. Its mandate was

* For our purposes we define a knowledge management organization as an organization with the infrastructure to serve as both a repository of knowledge and a facilitator for the creation of new knowledge, in forms that are easily usable, customized or suited to varying individual, institutional and national needs, and which allow the distribution of that knowledge to members of the organization and all external audiences, as and when needed and when the recipients are ready to accept, adapt and employ that information to help protect and improve global health.



expanded to go beyond obtaining 'proof of principle' that a new tool works.* Under this new paradigm, TDR will work in a seamless linkage with control programmes and national governments in the area of 'implementation research' – the research needed to answer specific questions arising when an intervention is introduced by health systems.

- Research capability strengthening will invest 60% of its resources on integrated, high-priority R&D projects/programmes ('RCS-plus packages'), shaped, managed and evaluated in close collaboration with the other three TDR functional areas. The remaining 40% of RCS resources

will be used to strategically fund work in the least developed, high burden countries.

- TDR's workplan, budget and management will be implemented adopting an output rather than input approach to planning, centred around 'results/expected products', instead of the current functional area, organigram-based approach.

This new phase of TDR ('reaching maturity' – Fig. 3), although relatively recent, has also seen important developments taking place (Table 1).

Has TDR been cost-effective?

From 1974 to 2000, TDR received US\$600 million (exactly US\$ 607 312 922) from its contributors. A widely quoted 1993 study by the Boston Consulting Group estimated that each new drug that reaches the market needs US\$500 million dollars of investment in R&D, a figure which includes the costs of failures – products that do not make it; others estimate a lower cost, of around US\$300 million.^{8**}

An independent analysis of TDR's action in product development noted that:

"...TDR helped develop 24 tropical disease drug products from 1974 to 1995; 14 were still in trials in 1995, and 10 were in clinical use ... TDR worked with private industry to develop most of these agents..."
[Michael R. Reich⁹]

In order to be able to accomplish these results, TDR established strong collaborations with the private sector,^{10,11} becoming a lead organization in promoting 'PPPs' – public-private partnerships.^{10,12-14 ***}

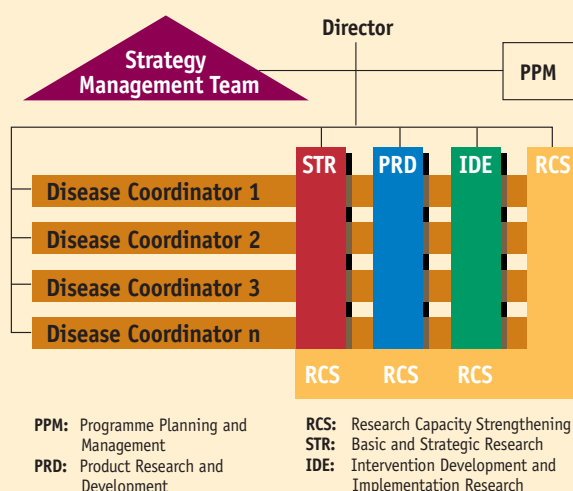
A more careful economic analysis of the cost-effectiveness of TDR will be conducted in the future. However, the above-mentioned evaluation, in just one functional area (product R&D) of TDR activities, indicates that the Special Programme can indeed be regarded as an efficient, cost-effective investment – even had all the funds been used exclusively for product development and not for any other activities (capacity strengthening, strategic R&D, field research).

DISEASES OF THE POOR: WHAT CAN TDR DO IN THE FUTURE?

The challenges ahead

TDR has a formidable challenge ahead. Progress has been considerable in a number of TDR diseases such as leprosy, Chagas disease, onchocerciasis and filariasis,¹⁵ and the overall contribution of TDR has been extensively documented in the *External Reviews* and other publications.^{11,16} The health situation, however, has deteriorated in other areas due to the emergence of new diseases (e.g. HIV/AIDS), spread of drug resistance (e.g. in malaria), socioeconomic deterioration,¹ and resurgence of old scourges such as tuberculosis and dengue, which were added to the TDR disease portfolio in 1999. To keep up with the challenges, the mandate of TDR has evolved from being very simple and focused exclusively on biomedical research, to its present format, which addresses all stages of the development pipeline – strategic research, product development, product registration, 'proof-of-principle' trials, and participation in the implementation of new tools by health systems.

Figure 3. The structure of TDR in Phase III – 'reaching maturity'



* The 2nd External Review recommended "The Programme should participate in and fund field research necessary to demonstrate the utility of new disease control tools in disease endemic countries and to identify the optimal initial approaches for its application.....The responsibility for application of new disease control tools rests with national governments through disease control programmes and primary health care services; WHO technical units should provide assistance to national governments in introducing and applying disease control tools".

** Quoted by B. Agnew.⁸

*** TDR played a key role in the creation, establishment and implementation of the Global Forum for Health Research (GFHR), the Medicines for Malaria Venture (MMV) and the Global Alliance for TB Drug Development (GATB).



The new opportunities

From all viewpoints, there are new opportunities on the horizon underlying the development of new interventions:

- From the 'offer' or 'push' viewpoint, there are new scientific and technological advances resulting from the 'biotechnological revolution' (e.g. genomics, proteomics), and new information and communication technologies.^{17,18}
- From the 'demand' or 'pull' viewpoint, there is a growing consciousness that health is not only a consequence of development and prosperity, but also actually plays a role in the promotion of these issues;¹⁹ and there is growing awareness of the crucial role that social, behavioural, political, economic and health system factors play in the persistence and re-emergence of infectious tropical diseases.

These new opportunities have spearheaded renewed political commitment at the highest level (G8, European Union), while powerful new players in health research have emerged (e.g. the Bill and Melinda Gates Foundation), allowing increased support for an ever-growing number of health initiatives (e.g. International Aids Vaccine Initiative, IAVI; Medicines for Malaria Venture, MMV; Global Alliance for TB Drug Development, GATB; Malaria Vaccine Initiative, MVI; Global Alliance for Vaccines and Immunization, GAVI).

In response to these new opportunities, as well as to WHO's new corporate strategy, TDR re-emphasized its commitment to social science research, including research on the impact of health sector reforms on equity, gender-sensitive interventions, and recently, research on the impact of social and economic inequalities and globalization on the persistence and re-emergence of tropical diseases.

TDR's comparative advantages

As pointed out in the Strategy 2000-2005, the Special Programme is well prepared to seize these new opportunities and remain a key player in coping with the health challenges, particularly those affecting poor and marginalized populations, because:

- TDR has unmatched experience, know-how and operational capability in its area of work as a consequence of constant evolution through 'experimentation and adaptation' during its 25 years of existence.
- As a network organization, TDR can tap into the expertise of a very large number of partners in the North and South, in the public and private sectors – governments, academia, industry, NGOs, communities.
- The Programme's scientific independence, global perspective, quality and leadership in a number of areas play an important role in setting the global health research agenda.
- TDR is considered a trusted broker, able to organize, initiate and monitor large-scale field trials, being at the forefront in training scientists and strengthening institutions in the fields of ethics^{20*} and good laboratory practice.²¹⁻²³
- Addressing all aspects of the development pipeline, the Programme is able to collaborate and partner a range of initiatives in specific, different areas of the R&D process. This allows TDR to play, and be asked to play, the unique role of 'transmission belt' between partners.** TDR's actions span basic research – including in the social, economic and behavioural sciences – product development, field trials, implementation research, and capacity building.

THE 15th PROGRAMME REPORT

How it is organized

This 15th Programme Report addresses the 1999-2000 biennium, which, as described above, was an unusual one. WHO reform, addition of tuberculosis and dengue to the TDR portfolio, adoption of WHO corporate strategy, adoption of the TDR Strategy 2000-2005, proliferation of public-private partnerships – were among the key issues that were addressed in this period.

Far from slowing down TDR's productivity, this new environment became a strong stimulus for change, reform and growth:

- The synergy between the WHO and TDR strategies – both of which underscore the importance of the role of research and knowledge in improving health – created an enabling environment for the Special Programme.

* The 5th Amendment of the Declaration of Helsinki has considerable implications for medical research in developing countries.

** As an example, TDR was requested to play a leading role in establishing the international network to sequence the genome of *Anopheles gambiae*.³³



- The broadening of the TDR disease portfolio to include TB and dengue, and of the TDR research areas to include social, economic and behavioural sciences, on the one hand, and the location of TDR in the Communicable Diseases cluster of WHO, on the other hand, provided the grounds for the ‘fundamental restructuring’ as requested by the *3rd External Review*. The result is a much closer, growing and constructive collaboration between R&D and disease control components.
- TDR was able to keep up the momentum in stimulating PPPs,^{10,12,13,24} as per its historical role, and played a key role in the shaping and implementation of two important new initiatives – MMV and GATB.

As an outcome of the new strategy, this report is structured according to the expected results in the seven areas of work of TDR:

- A. New basic knowledge: New basic knowledge about biomedical, social, economic, health system and behavioural determinants, and other factors of importance for effective prevention and control of infectious diseases, generated and accessible at national and international levels.
- B. New and improved tools: New and improved tools devised for prevention and control of infectious diseases, e.g. drugs, vaccines, diagnostics, epidemiological tools, environmental tools.
- C. New and improved methods: New and improved intervention methods developed and validated for applying existing and new tools at clinical and community levels.
- D. New and improved strategies: New and improved policies for large-scale implementation of existing and new prevention and control strategies framed and validated; guidance for application in national control settings accessible.
- E. Partnerships and capacity building: Partnerships established and adequate support provided for building up capacity for research and product development in disease endemic countries.
- F. Technical information: Adequate technical information, research guidelines and instruments, and advice accessible to partners and users in countries.
- G. Resources for research: Resources for research, product development, and capacity building efficiently mobilized and managed.

Why a new reporting format?

Areas A to D can be seen as steps in the process of product development (the so-called ‘R&D pipeline’), from the early discovery phase to the large-scale implementation of the resulting new interventions by health systems in disease endemic countries.

Areas E and F represent TDR’s knowledge management architecture²⁵ and the needs it will address, such as:

- Building and strengthening the community and network of ‘knowledge workers’.
- Managing knowledge generation, storage and dissemination.
- Conducting analytical work relevant to priority setting.
- Assuring the flow of knowledge.

Area G aims to mobilize and manage adequate resources for both the R&D pipeline and the knowledge management requirements of the Programme.

More than just providing a different reporting format, this new framework is at the heart of TDR’s new strategy:

- Differential investments across the R&D pipeline: Infectious diseases can be considered to be at different stages of their ‘life cycle’. Some are being eliminated or eradicated due to the availability of cost-effective interventions and control strategies; others are re-emerging or continue to impose an unacceptable burden in large areas of the world and require new or better tools. R&D priorities, resources and efforts should therefore reflect: a) the burden of the disease; b) the availability of cost-effective interventions; c) the knowledge base needed for future developments. Diseases undergoing elimination or eradication need more investments in research to improve, refine and better implement control tools and policies (areas C and D), whereas, for other diseases, the acquisition of new knowledge and development of new or better tools (areas A and B) should be priorities.
- Relevance of knowledge management: evidence-based priority setting is becoming more and more important for keeping the Programme’s focus, guiding future investments, and strengthening TDR’s role in the setting of the global R&D agenda in tropical diseases. In addition, investments in TDR’s own operational capability have been defined as critical for successful implementation of the new strategy.

The ‘Expected Results’ framework is therefore a multi-purpose endeavour. On the one hand it fulfils the need to inform and report to our partners – as in the case of this 15th Programme



Report. On the other hand, it represents a major tool for planning, managing, monitoring and evaluating the activities of the Special Programme, now being reshaped as a knowledge management and network organization under the new strategy. TDR's operational capability, defined as its driving force in the new strategy, requires renewed efforts in conducting the analytical work needed to keep the Programme at the forefront of the complex and changing area of health R&D.

A bird's eye view of TDR activities in the 1999-2000 biennium

It is not an easy task to select representative results attained by TDR-funded projects in the last biennium. This section does not aim to be a summary of what was accomplished, nor to list the 'top ten' accomplishments. Its purpose is to illustrate the new results-oriented approach adopted by the new TDR Strategy.

A. New basic knowledge

- The long sought after breakthrough in the area of molecular entomology – stable transformation of *Anopheles* – was obtained by Catteruccia et al²⁶ and represents the first milestone in TDR's 1991 workplan.²⁷ This opens the way to the next goal: obtaining a laboratory strain of *Anopheles gambiae* unable to harbour and transmit *Plasmodium* parasites.
- The identification of the molecular mechanisms by which the leprosy bacillus invades peripheral nerve cells is an example of how new basic knowledge is needed to understand disease pathogenesis. TDR's *Final Report 14* (May 1999) describes the elegant work of Fischetti and collaborators,²⁸ shedding light on the molecular basis of *Mycobacterium leprae* neurotropism.

B. New and improved tools

- The registration of artemotil shows that drug development is a long-term process. TDR started a partnership to develop this drug in 1991 – almost ten years elapsed between the project start-up and formal registration approval by Dutch regulatory authorities.
- In TDR, the term 'tools' does not apply only to physical products such as drugs and vaccines. The second example under this heading is of a quite different nature – it is an epidemiological tool called 'RAGFIL', or Rapid Assessment of the Geographic Distribution of Filariasis.²⁹ The main elements of RAGFIL – the subject of *Final Report 25* – will be used for mapping filariasis in Africa.

C. New and improved methods

- Simple and imaginative interventions can be very effective: iron supplementation and intermittent chemoprophylaxis, administered as components of the EPI vaccination schedule, can effectively prevent severe malaria in young children.^{30,31}
- Reaching the home and the community more effectively with antimalarial treatment can make a difference: more than 50% reduction in progression towards severe disease, and 40% reduction in under-five mortality, are some achievements of improving home management of children with severe malaria (*Final Report 29*).

D. New and improved strategies

- A multicountry study completed during the biennium showed that a combined community/health services system of community directed treatment of lymphatic filariasis in Africa resulted in improved treatment coverage. Community directed treatment (ComDT) was therefore recommended as the drug delivery strategy for lymphatic filariasis elimination in Africa.³⁴
- Molecular biology is being applied in the characterization of wild and domiciliated populations of insect vectors of Chagas disease. From the control programme's perspective, it is necessary to know the origin of the vectors present in rural houses. *Final Report 21* shows how this approach is being used to fine-tune the control strategy under implementation in Andean countries.

E. Partnerships and capacity building

- PPPs to foster new drug development against neglected diseases made the headlines a number of times during the biennium. TDR was a major player in the planning and implementation of MMV and GATB, both now operating as independent, not-for-profit organi-



zations. Another strategy was adopted by TDR to stimulate the participation of major Japanese pharmaceutical companies in the discovery of new drugs: instead of creating a new organization, a partnership was formed among 12 Japanese companies, the Kitasako Institute and the Japanese Ministry of Health and Welfare to screen the companies' chemical libraries for antimalarials.

- The Multilateral Initiative on Malaria in Africa (MIM) is an international partnership to foster scientific research against malaria. Under this initiative, TDR set up the MIM/TDR Research Capacity Strengthening Task Force at the end of 1997. MIM/TDR became a major driving force in malaria research and capacity building in Africa during the biennium.

F. Technical information

- TDR launched its 3rd generation website in 1999, and the results have been most rewarding. In December 2000, the last month of the biennium, the website received approximately 70 000 pageviews – almost twice as many as in 1999. As TDR now positions itself as a knowledge management and network organization, further development of the website into a fully interactive tool is a high priority.
- But information and knowledge do not flow only through cyberspace: 'old style', hard copy paper publications are also absolutely required – and our production in the biennium has been remarkable. Books, meeting and project reports, guidelines, conference proceedings, laboratory and field manuals (including those describing 'good practices' – GLP, GCP – standard operating procedures), as well as formal publications in peer-reviewed journals are, and will continue to be, crucial components of 'knowledge repositories' and knowledge flow.

G. Resources for research

- All this work would not be possible without our core partners, who assure that TDR receives resources compatible with its mandate and responsibilities. As shown in the list of our contributors (pages 88-89), TDR continues to be supported by a broad base of donors – particularly by a faithful core group, who share with us the vision that health research is essential to cope with the burden that neglected diseases impose on poor and marginalized populations.
- The addition of two new diseases to our portfolio in 1999 was a 'high risk' manoeuvre. We knew that finding the corresponding additional resources in the extremely competitive environment of today would be an immense challenge. However, there are both sound evidence and good signs that we are navigating in the right direction. For one thing, new partners have already joined forces with us, supporting our new strategy and mandate; and for another, the growing recognition of the role of health in development brings new hope and sets an optimistic scenario for the future.

I hope you will enjoy reading this report and agree that the 1999-2000 biennium represented a very good 'vintage' for TDR.

Carlos M. Morel – Director, TDR
Geneva, May 2001

References

1. World Health Organization. *Health: A precious asset* (accelerating follow-up to the World Summit for Social Development. Proposals by the World Health Organization). World Health Organization, 2000, WHO/HSD/HID/00.1.
2. Bell DE et al. *Report of the External Review Committee – Special Programme for Research and Training in Tropical Diseases*. TDR, 1982, TDR/JCB(5)/82.6.
3. Otero E et al. *Report of the Second External Review Committee – Special Programme for Research and Training in Tropical Diseases*. TDR, 1988, TDR/JCB(11)/88.6.
4. Godal T. *TDR towards the year 2000: Strategic considerations* (working document for discussion at JCB-16, June 1993). TDR, 1992, TDR/PTR-SCI/92.3 Rev.4.
5. Wigzell H et al. *Third External Review of the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) – Final Report*. TDR, 1998, TDR/JCB(21)98.5, 1-133.
6. Brundtland GH. *A corporate strategy for the WHO Secretariat. Report by the Director-General*. World Health

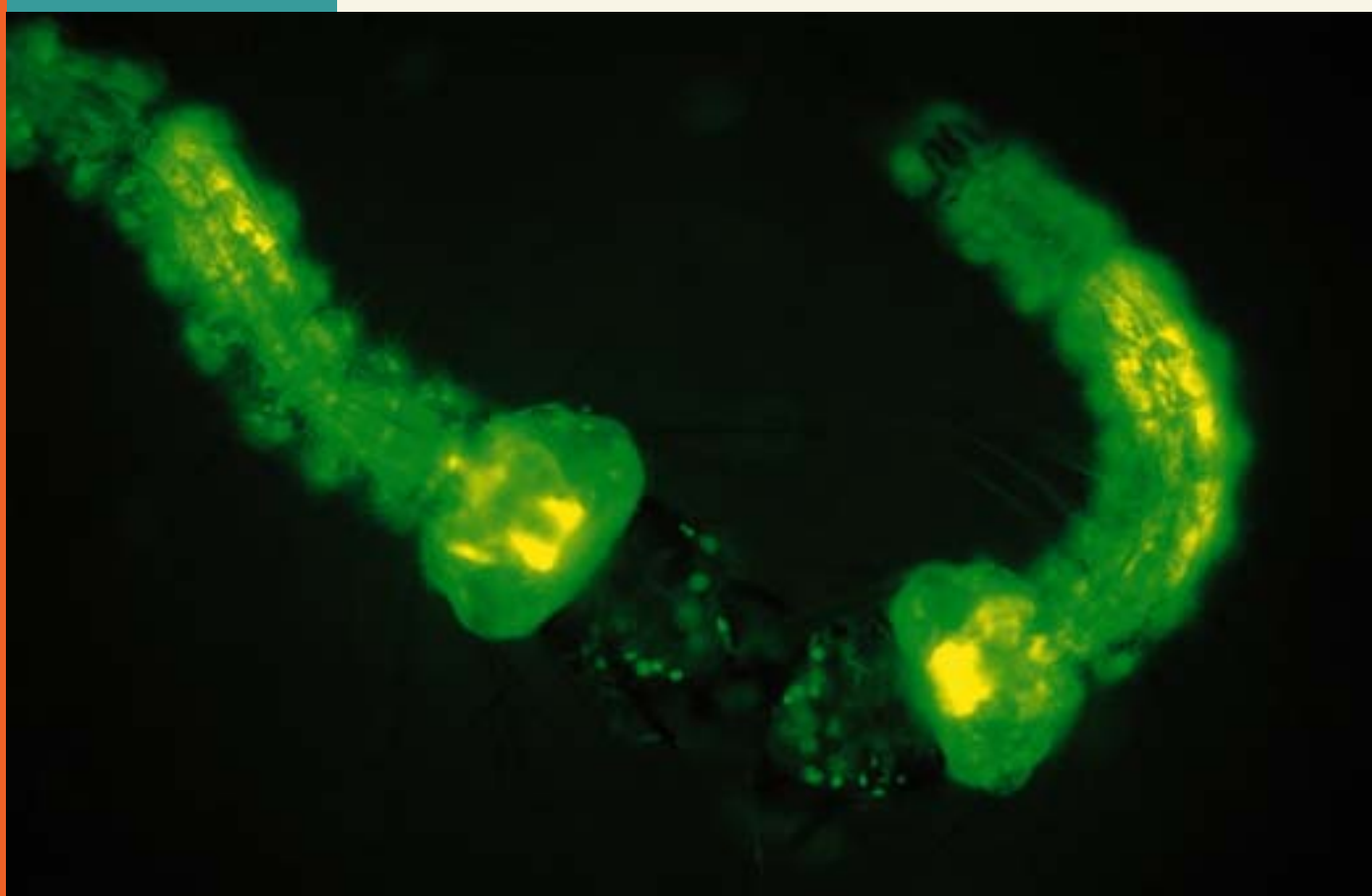


- Organization, Executive Board 105th Session, 1999, EB105/3, 1-5.
7. UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR). *TDR Strategy (2000-2005)*. TDR, 2000, TDR/GEN/SP/00.1/Rev. 1.
8. Agnew B. When Pharma merges, R&D is the dowry. *Science*, 2000, 287:1952-1953.
9. Reich MR. The global drug gap. *Science*, 2000, 287:1979-1981.
10. Lucas A. *Public-private partnerships: Illustrative examples*. Workshop on public-private partnerships in public health, Harvard School of Public Health, April 7-8, 2000. TDR, 2000, TDR/BP/00.1.
11. Morel C.M. Reaching maturity – 25 years of the TDR. *Parasitology today*, 2000, 16:522-528.
12. Buse K, Walt G. Global public-private partnerships: part I – a new development in health? *Bulletin of the World Health Organization*, 2000, 78:549-561.
13. Buse K, Walt G. Global public-private partnerships: part II – what are the health issues for global governance? *Bulletin of the World Health Organization*, 2000, 78:699-709.
14. Reich MR. Public-private partnerships for public health. *Nature medicine*, 2000, 6:617-620.
15. UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR). *Chagas disease, leprosy, lymphatic filariasis, onchocerciasis: Prospects for elimination*. TDR, 1997, TDR/Gen/97.1.
16. UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR). *Snippets of achievement – The past illuminating the future*. TDR, 2001, TDR/GEN/01.1:1.
17. Schoonbaert D. Tropical medicine, the Internet and current trends in biomedical communication. *Annals of tropical medicine and parasitology*, 2000, 94:661-674.
18. Ward JP et al. Communication and information technology in medical education. *Lancet*, 2001, 357:792-796.
19. World Health Organization. *Health – A key to prosperity: success stories in developing countries*. World Health Organization, 2000, WHO/CDS/2000.4.
20. UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR). *Operational guidelines for ethics committees that review biomedical research*. TDR, 2000, TDR/PRD/ETHICS/2000.1.
21. UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR). *Good Laboratory Practice (GLP) Training Manual (trainer)*, TDR, 2001, TDR/PRD/GLP/01.1A.
22. UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR). *Good Laboratory Practice (GLP) Training Manual (trainee)*, TDR, 2001, TDR/PRD/GLP/01.1B.
23. UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR). *Standard operating procedures for clinical investigators*. TDR, 1999, TDR/TDP/SOP/99.1.
24. Godal T. Fighting the parasites of poverty: public research, private industry and tropical diseases. *Science*, 1994, 264:1864-1867.
25. Borghoff UM, Pareschi R. *Information technology for knowledge management*. Springer-Verlag, 1998.
26. Catteruccia F et al. Stable germline transformation of *Anopheles stephensi*, a mosquito vector of human malaria. *Nature*, 2000, 405:959-962.
27. Anon. Report of the meeting *Prospects for malaria control by genetic manipulation of its vectors*. World Health Organization/TDR, 1991, TDR/BCV/MAL-ENT/91.3.
28. Rambukkana A et al. Role of alpha-dystroglycan as a Schwann cell receptor for *Mycobacterium leprae*. *Science*, 1998, 282:2076-2079.
29. Gyapong J, Remme H. The use of grid sampling methodology for rapid assessment of the distribution of Bancroftian filariasis. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 2001 (in press).
30. Menendez C et al. Randomised placebo-controlled trial of iron supplementation and malaria chemoprophylaxis for prevention of severe anaemia and malaria in Tanzanian infants. *Lancet*, 1997, 350: 844-850.
31. Schellenberg D et al. Intermittent treatment for malaria and anaemia control at time of routine vaccinations in Tanzanian infants: a randomised, placebo-controlled trial. *Lancet*, 2001, 357:1471-1477.
32. D'Alessandro U, Boelaert M. The 5th Amendment of the Declaration of Helsinki: implications for medical research in developing countries. *Tropical medicine and international health*, 2001, 6:245-247.
33. Balter M. Gene sequencers target malaria mosquito. *Science*, 1999, 285:508-509.
34. Gyapong M, Gyapong JO, Owusu-Banahene G. Community-directed treatment: the way forward to eliminating lymphatic filariasis as a public health problem in Ghana. *Annals of tropical medicine and parasitology*, 2001, 95(1):77-86.



New Basic Knowledge

New basic knowledge about the biological, social, economic, health systems, and behavioural determinants of ill health is essential for improving and making more effective tools for the control of infectious diseases. In stimulating the generation of, and making accessible, new basic knowledge, TDR works at national and international levels. Success indicators include the number of new, significant and relevant scientific advances that are applied to neglected tropical diseases.



WHO/TDR/STAMMERS

Fluorescing mosquito larvae: genetic manipulation opens up a wide variety of new possibilities for disease control



Innovative research in the biomedical and social sciences, leading to new interventions for tropical diseases, is encouraged through TDR's Basic and Strategic Research (STR) component. The idea that powerful tools will facilitate long-lasting interventions is behind this area of work, in which advances and leads that will move science in new and productive directions are identified. However, the targets and objectives of STR are long-term and the research is often a lengthy process that can take decades rather than years. It includes research on pathologic mechanisms and on social and economic factors of disease, development of research models, and identification of drug, diagnostic and vaccine targets.

Significant changes in TDR's way of working in its STR area were introduced during the biennium. Firstly, the separate steering committees on pathogenesis and genome were combined into one – the Steering Committee on Pathogenesis and Applied Genomics. This is a reflection of the advances in science – great leaps in knowledge in recent years mean that the post-genomics revolution is now well under way. The focus is no longer only on 'sequencing' genomes, i.e. on deciphering the order of bases along the length of deoxyribonucleic acid (DNA), but, based on this information, on identifying and understanding the roles of genes and proteins in each type of organism and on putting this information to use in developing new treatments and other means of disease control (see Box 1 for list of genome websites). For this reason, work on genome and pathogenesis is now seen as a continuum, allowing the exploration of new technologies, e.g. genomics, proteomics, bioinformatics and high-throughput screening, to open new ways for accelerated discovery of new drugs, vaccines and diagnostics.

The second major change introduced in STR during the biennium was to include social, economic and behavioural research, under a new Steering Committee on Strategic Social, Economic and Behavioural Research (SEB). SEB is located in STR to emphasize the importance of the *basic* social sciences for identifying needs and opportunities for improved prevention and control of TDR diseases.

The above steering committees represent two of three major thrusts of TDR/STR. The third area is molecular entomology. Important progress has been made in this area during the biennium.

Research on immunology of leprosy was a separate area managed in collaboration with the World Health Organization's (WHO's) Department of Vaccines and Biologicals through the Immunology of Mycobacteria Steering Committee (IMMYC) since 1994. IMMYC was disbanded in late 2000 in order to promote a broader approach to leprosy research across the spectrum of TDR activities, and all the relevant TDR committees are now open to leprosy research proposals.

NEW, SIGNIFICANT AND RELEVANT SCIENTIFIC ADVANCES

Pathogenesis and applied genomics

When a disease is acute, it is rapidly overcome and very few pathological changes develop in its wake. However, when an infectious disease is chronic, the pathology is much more serious; it arises when the immune system is caught between the need to prevent further invasion by an organism and the need to effect a response to any similar organisms already present in the body. Parasites, in contrast to the great majority of other infectious agents, commonly strike a balance with their hosts and continue to re-infect them. This situation forces the host's immune system to display a bewildering variety of responses in terms of effector cells, antibodies and messenger/signalling molecules. Our understanding of the development of pathology and resistance in most of the parasitic diseases is incomplete, although a consolidated picture of interplay between opposing immunological mechanisms is beginning to emerge.

Box 1. Genomes on the Web

Malaria (*Plasmodium*) Genome Project

<http://www.wehi.edu.au/MalDB-www/who.html>

The WHO/UNDP/World Bank *Schistosoma* Genome Network

http://www.nhm.ac.uk/hosted_sites/schisto/

The Filarial Genome Network

<http://helios.bto.ed.ac.uk/mbx/fgn/filgen.html>

The *Leishmania* Genome Network

<http://www.ebi.ac.uk/parasites/leish.html>

The *Trypanosoma cruzi* Genome Project

<http://www.dbbm.fiocruz.br/genome/tcruzi/tcruzi.html>

The *Trypanosoma brucei* Genome Project

<http://parsun1.path.cam.ac.uk>

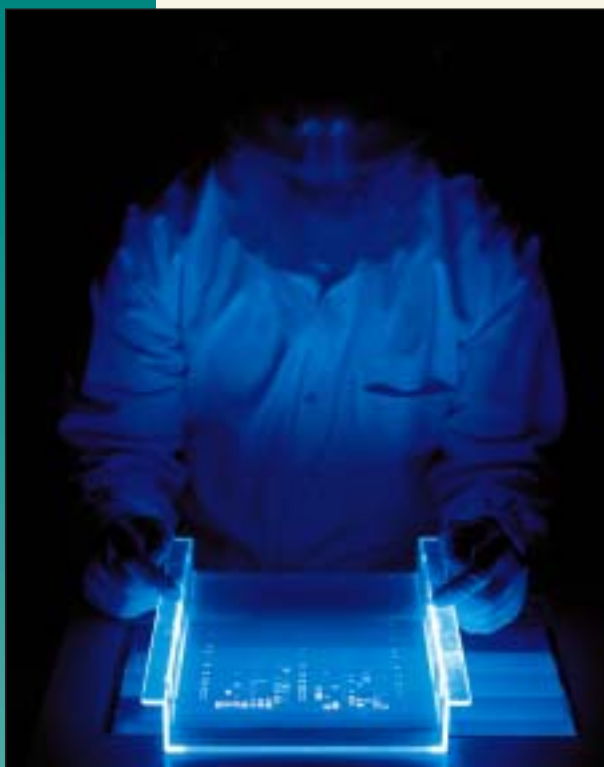
MycDB: *Mycobacterium*

<http://www.biochem.kth.se/MycDB.html>

Database AnnoDB

<http://konops.imbb.forth.gr/AnnoDB/>

TDR research is helping to clarify some of the pathologic mechanisms involved in the etiology and progression of different diseases, including the genetic background, and is contributing to the identification of potential drug and vaccine targets.



DNA gel analysis. Researcher examines an agarose gel containing DNA fragments using ultraviolet light.

SCIENCE PHOTO LIBRARY/FRASER

Each of the TDR target diseases displays its own unique profile of acute and chronic inflammatory responses based on the influence of various effector cells and isotypical antibody stimulated by the invading organism. Typically, malaria is associated with the destruction of red blood cells; lymphatic filariasis with the deformities of elephantiasis; leishmaniasis with an array of different pathologies depending on whether the skin, mucous membranes or internal organs are involved; schistosomiasis with pathology of the liver or urogenital organs; African trypanosomiasis with lesions of the central nervous system; onchocerciasis with blindness and skin lesions; Chagas disease with the heart and/or intestines; and leprosy with lesions of the peripheral nerve trunks, resulting in damage to the skin and distressing deformities. Research is supported with the aim of finding ways and means to modulate these responses in a way that reduces the pathological response without jeopardizing the body's immunological defence system.

MALARIA: The pathology associated with *Plasmodium falciparum* malaria is, in particular, due to adherence of infected red blood cells in the brain, metabolic disturbances, and organ dysfunction.

Research into the mechanism underlying adherence of red blood cells to the lining of the blood vessels (endothelium) in the brain indicates that the parasite

ligand PFEMP1 may be key. The multi-adhesive nature of this molecule enables binding to at least six different receptors in the host. The role of another adhesive molecule, the thrombospondin-related adhesive protein (TRAP), in parasite invasion of epithelial cells of the host's liver (hepatocytes), has been studied in *P. berghei* mutants carrying different variants of the gene encoding TRAP. Production of mutations of the A-domain of TRAP has made it possible to study the mechanism and results indicate that it might be possible to reduce parasite invasion through interfering with the interaction between TRAP and its receptor on the host's hepatocytes.

A different line of research in pathogenesis of cerebral malaria has shown that immunoglobulin E (IgE) levels are elevated in these patients, suggesting that this antibody may be playing a role. This claim is supported by the finding that IgE forms part of immune complexes which induce CD23-mediated production of tumour necrosis factor (TNF), a chemical messenger in the body's immune system (cytokine), in monocytes in vitro.

In the area of drug development, efforts to express and recombine *P. falciparum* dihydrofolate reductase (DHFR) and thymidylate synthase (TS) for rapid drug screening assays have been successful, but stabilization of the bifunctional DHFR-TS is needed to avoid spontaneous aggregation. In addition, a pathway involved in the DNA repair process has been shown to be exclusive for *P. falciparum* and different from in the mammalian host. This is a long-patch base excision pathway involved in repair of apurinic/apyrimidinic sites in DNA.

The role of individual Pxs25 malaria genes in colonization of the *Anopheles* mosquito has been evaluated. These genes have been shown to drastically reduce the capacity of the parasite to complete its life cycle in the mosquito host. However, complete elimination of transmission in this experimental system has not yet been achieved.

In the area of vaccine development, several potent inhibitors of the surface protease responsible for secondary processing of *P. falciparum* merozoite surface protein (MSP-1) have been synthesized. Efforts continue to find *P. falciparum* choline kinase and choline phosphotransferase variants which are sufficiently different from those of human cells to permit exploitation as vaccine targets.

TUBERCULOSIS: Tuberculosis (TB) researchers now have access to the Steering Committee on Pathogenesis and Applied Genomics which meets annually. The first grant in TB was awarded in September 2000 for the identification of genomic sequences potentially useful in the development



of new diagnostic tests. In the future, it is expected that grants will be awarded for use of genomic information to identify and describe targets for the development of new drugs and vaccines.

LYMPHATIC FILARIASIS: In filarial nematodes, a new approach to validating potential drug targets is being developed using the model nematode *Caenorhabditis elegans*. Initially, expression of genes encoding putative drug targets is suppressed using the newly-developed technique of ribonucleic acid interference (RNAi), in which nematodes are exposed to double-stranded RNA encoding a fragment of the gene whose expression is to be silenced. The resulting worms are then examined to determine whether viability, fertility or growth are adversely affected. If they are, and the phenotype is considered suitable, mutants with permanent loss of function are obtained for further analysis and development of drug screens.

The RNAi approach was used to evaluate the suitability of enzymes catalysing the metabolism of the sugar trehalose, which is thought to be important in the formation of the cuticle or outer surface of the worms. So far however, no simple changes in characteristics have been noted for any of the genes silenced individually, i.e. none of the genes has been found to be essential and therefore suitable as a drug target.

Scientists working to unravel the genome of *Brugia malayi* have succeeded in sequencing 2000 new expressed sequence tags (ESTs) from subtracted libraries and the genomic materials have been conserved. In addition, laboratory staff in endemic countries have been trained in bioinformatics.

LEISHMANIASIS: In a move of major importance for our understanding of the biology of cell/parasite interaction in leishmaniasis, investigators were able to block macrophage infection by the *Leishmania* amastigote stage through use of monoclonal antibodies to proteophosphoglycan, a constituent of the parasite's surface. It was further demonstrated that amastigotes can readily infect dendritic cells which are involved in the initiation of immune responses and are known to be crucial to the development of an effective immune response against *Leishmania*.

SCHISTOSOMIASIS: The role of antigen-specific (idiotypic) sites of antibodies in the development and regulation of pathology due to schistosome infection can now be addressed by means of a newly-developed experimental schistosomiasis model. Using this model, it was observed that cross-reactive idiotype present in the sera of experimentally infected mice is of the IgG2a subclass and responsible for the proliferation of CD4 cells (white blood cells bearing the glycoprotein CD4 on their surface). It appears that this antibody subclass in mice is important in inducing Th1 type responses, i.e. cell-mediated immunity, which may be crucial for resistance, at least to certain antigens.

Further studies of the role of the schistosome TNF- α receptor in the reproductive biology of schistosomes indicates that levels of TNF- α in the serum increase in relation to egg production and granuloma formation (growths which form around the eggs as a result of immune reaction). The roles of cytokines in host pathology are being evaluated by studying the responses in 'knock-out' animals, in which the genes for key signalling molecules have been removed. So far these have given some divergent results suggesting that TNF can even be protective against cachexia (general wasting away). Granuloma formation also seems to be influenced by STAT-6 (a signal transducer and activator of transcription), ICAM-1 (an intercellular adhesion molecule) and LFA-1 (a leucocyte functional antigen).

Research on the relation between chemokine receptors and clinical forms of schistosomiasis has shown that distinct cell populations in the blood produce specific cytokines in different clinical situations, e.g. granulocytes produce the Th1 interleukin (IL-) cytokines IL-4 and IL-12, while monocytes are an important source of IL-10 in acute schistosomiasis. Monocytes also produce TNF- α in the chronic form of the disease. CD4+ lymphocytes produce IL-4 and IL-10 while the latter cytokine is also produced by CD8+ lymphocytes in intestinal schistosomiasis.



BCG vaccine electrophoresis under ultraviolet light.

SCIENCE PHOTO LIBRARY/RAGUET/REUTERS



In the area of genome studies, the sequence and gene order of the mitochondrial genomes of all the schistosome species infective for humans have been completed. This information makes it possible to compare gene composition, gene arrangement, codon usage, structure of ribosomal ribonucleic acids (rRNAs) and transfer (t)RNAs, and to provide information on non-coding sequences including intra- and inter-specific variation in schistosomes, opening the way for entirely new research directions. In addition, EST clones from the various stages of *Schistosoma mansoni* and *S. japonicum* have been generated and supplied by the Genome Network laboratories. Although the ultimate goal of generating the whole genome map is still far away, there has been good progress in ongoing work on the production of a low-resolution map for chromosome 3 of *S. mansoni* and the generation of an EST cluster map.

AFRICAN TRYPANOSOMIASIS: An experimental model of African sleeping sickness has been developed using intestinal loops. The infection has been shown to cause marked intestinal damage with increased leakage and elevation of endotoxins closely correlated with nitric oxide and alterations in the levels of the cytokines TNF- α , IL-1b, IL-6, interferon-gamma (INF- γ) in the circulation. Further, the study of metabolic pathways in the parasites has indicated that inorganic polyphosphates play a role in completion of the life cycle and growth of trypanosome populations. For example, there is a build-up of these compounds in the lag phase of *Trypanosoma brucei*. Progress has also been made in proteomic analysis of the proteins involved in the differentiation of *T. brucei* from blood stream procyclic forms.

In the area of genome research, approximately 2000 plasmids with inserts larger than 500 base pairs had been sequenced before the beginning of 2001, and more than half of these were shown to have no homology to ESTs present in public databases (i.e. they show no similarity to genes from other organisms). In addition, great strides have been made towards completing a physical map of the *T. brucei* genome. A physical library is ready, and several high-density filters have been prepared and distributed to the scientific community.

ONCHOCERCIASIS: Recent results indicate that the first step towards the development of blindness is due to certain *Onchocerca volvulus* proteins which are implicated in the growth of new blood vessels in the eye. Identifying these proteins was a breakthrough, but much research remains to be done, e.g. it appears that the proteins are neither immunogens nor mitogens, thus ruling out an immunological explanation. In addition, the role of eosinophil eotaxin (a type of cytokine) in diethylcarbamazine (DEC)-induced skin lesions has been confirmed.

Genetic research on *O. volvulus* has shown there to be intra- and inter-strain variation in polymorphic microsatellite loci between savannah and forest strains of the parasite, suggesting that different genetic constitutions are associated with the different clinical manifestations.

CHAGAS DISEASE: In research on Chagas disease, a common pattern of cardiomyocyte G protein-coupled receptors and *Trypanosoma cruzi* ribosomal P proteins has been found. This antigenic determinant (P proteins), identified and mapped using synthetic peptides, strongly suggests that immunological cross-reaction is the culprit in the commonly seen heart-related pathogenesis in Chagas disease. Further, glycosylphosphatidylinositols (GPIs) that function as anchors for mucins appear to be hundreds of times more active in trypomastigotes (stages in the life cycle that occur in the mammalian host) than GPIs isolated from epimastigotes (forms that occur in the insect host). These anchors appear to stimulate phosphorylation of three distinct mitogen activated protein (MAP)-kinase macrophage cascades, two of which are responsible for TNF- α induction and the third responsible for nitric oxide production. In a different line of research, the 3-dimensional structure of *T. rangeli* sialidase has been obtained and there has been progress on the *T. cruzi* counterpart. Mutagenic studies, based on crystallographic data, have revealed that only very few amino acids confer trans-sialidase activity to a sialidase scaffold. Single or double point mutations in or near the active site were able to abolish or maintain trans-sialidase and simultaneously increase the sialidase effect. As it has been shown that *T. cruzi* trans-sialidase is implicated in the invasion of mammalian cells, elucidating its mechanism of action is relevant for rational drug design against this parasite.

Calreticulin, an important chaperone for glycoprotein folding, has been shown to be important, possibly essential, for *T. cruzi* viability. Research using experimental infection in mice has confirmed that the genetic make-up of the host and the parasite clone used for infection play an important role in tissue tropism (i.e. which tissues the parasites invade).



LEPROSY: A high point of recent leprosy research has been to identify the molecular basis of the *Mycobacterium leprae* attraction to nerve tissue (neurotropism). *M. leprae* needs to invade peripheral nerve cells in order to survive, replicate and establish infection; during this process it causes significant damage to peripheral nerves, leaving patients with disabilities and deformities. Receptors on particular host cells act as initial targets with which the leprosy bacillus interacts. Attachment of the bacillus is either direct, between bacterial 'adhesin' and host cell receptor, or indirect, through absorption onto the bacterial surface of a bridging molecule of host cell origin. The initial and crucial step in the disease process is the attachment of *M. leprae* to the basal lamina that surrounds the Schwann cell-nerve axon unit. A TDR-sponsored study has shown that the G domain of the alpha2 chain of endoneurial laminin (filling material between cells) is crucial to the invasion of peripheral nerves by *M. leprae*. Furthermore, the receptor on the Schwann cell that binds to the laminin alpha2-G receptor has been identified as alpha-dystroglycan, and a candidate protein receptor on the surface of *M. leprae* that binds to this same laminin receptor has also been identified. This work makes a profound contribution to our understanding of the pathogenesis of leprosy and may have important implications for the design of interventions to control leprosy-induced nerve damage.^{1,2}

Sequencing of the genome of *M. leprae* was initiated and catalysed by TDR, even though the majority of funds for the activity came from outside. TDR's initial investment in 1989³ proved a stimulus to in-depth analysis and genome sequencing by an international network of laboratories such that, by the end of 2000, sequencing was completed. The complete sequence, generated from a combination of cosmid and whole-genome shotgun sequencing, is 3 268 203 base-pairs in length. Less than half the genome contains functional genes (1604 protein-coding genes identified), but pseudogenes (with intact counterparts in *M. tuberculosis*) abound. Gene deletion and decay have eliminated many important metabolic activities, and may be the explanation for the extremely slow growth of *M. leprae* and its refractoriness to cultivation in vitro. Both the sequence and annotation have been deposited in the public databases with the accession number AL450380.⁴

Sequence data are being used in TDR-sponsored research to develop a diagnostic skin test capable of determining whether or not an individual has been exposed to *M. leprae*. The test is expected to help in understanding the transmission of leprosy and its epidemiology. *M. leprae*-specific peptides should have unique amino acid sequences, or significant sequence dissimilarity from other mycobacteria. Peptides 15 amino acids in length were synthesized from 33 genes or open reading frames. They were tested against cell preparations from tuberculoid leprosy patients from Brazil, Ethiopia, Pakistan and Nepal, with UK blood donors serving as non-exposed/non-infected controls. Peptides which induced potentially specific responses in leprosy patients but not in UK controls, as well as peptides that were cross-reactive (present both in patients and controls), were identified. A difference of five amino acids from the equivalent *M. tuberculosis* sequence did not, by itself, identify peptides that were *M. leprae* specific, a finding which suggests that many of these peptides may have homologues in environmental mycobacteria. Nevertheless, a number of peptides have been identified that provide greater than 90% specificity and 19-47% sensitivity for diagnosis. These peptides, as well as new candidate peptides identified in the course of the leprosy sequencing project, will undergo further testing. Such peptides would have great potential as T-cell reagents, formulated either as skin test reagents or as antigens for testing in vitro, with which to monitor exposure to *M. leprae* within communities.

MALARIA: Molecular entomology

The vision of the malaria-transmitting mosquito as a harmless insect that doesn't transmit the disease is becoming more tangible year by year. In the last two years, significant progress has been made in this area of TDR's work. The ultimate aim is, through manipulation of mosquito genes, to replace the natural vectors of malaria in the wild with populations of anopheline mosquitos that are unable to support development of malaria parasites. The mosquitos would live in their normal environment but be unable to transmit malaria. This work began in 1991, when 36 specialists were brought together by TDR, the Wellcome Trust and the MacArthur Foundation to discuss the most promising lines of research in this new approach to mosquito control. It was estimated that the task would take 10-15 years to complete. Three main areas of research were recognized.

One area is to identify genes in the mosquito which prevent development of the parasite – even a mosquito that transmits malaria is able to kill off many parasites. The second line of research is to develop methods for inserting genes into the mosquito genome. At first, model genes are

¹ Rambukkana A et al. Role of alpha-dystroglycan as a Schwann cell receptor for *Mycobacterium leprae*. *Science*, 1998, 282:2076-2079.

² Leprosy. *TDR Final Report Series* no. 14, May 1999.

³ to Stewart Cole, Pasteur Institute, Paris.

⁴ Cole ST et al. Massive gene decay in the leprosy bacillus. *Nature*, 2001, 409: 1007-1011.



inserted – such as green fluorescent protein, which makes a transformed mosquito easy to distinguish. But the aim is to insert genes selected from the ongoing projects on gene identification, and this has begun. The third line of research, and potentially the most problematical, not only because of the technology required, but also because of ethical, safety and regulatory issues, is to drive the selected genes into wild mosquito populations. Work in this area covers the genetics and dynamics of malaria-transmitting mosquito populations, and mosquito behaviour. For example, we need to know why a mosquito might prefer to feed on humans rather than animals, what natural chemicals it responds to in its life, and ultimately which genes are involved and might be used to change the mosquito's behaviour by inserting into its genome – changing it into an insect that doesn't like to feed on humans, for example. Developments along these three lines of research in 1999-2000 are outlined below. They mostly concern *Anopheles gambiae*, the main malaria vector in Africa.

Issues of ethics, risk perception, assessment, communication, choice of sites and plans for deploying a genetically engineered mosquito, and the socioeconomic issues associated with such an undertaking, are being addressed through a joint initiative under formulation by the TDR committees of Molecular Entomology, and Social, Economic and Behavioural Research.

Analyzing the mosquito genome and identifying genes

A variety of activities contribute to the analysis of a genome. These include sequencing the mosquito genome and mapping together the fragments of genome information as they arise.

A large number of mosquito genes have already been identified and, in a new international effort, genes of *Anopheles gambiae* are being sequenced directly using the 'shotgun' approach. Two public databases on *Anopheles* species are established.

In 1999-2000, TDR supported a pilot gene discovery project based on EST analysis of high quality complementary DNA (cDNA) libraries from tissues critical to the interaction of the malaria parasite with the mosquito vector. More than 6000 ESTs have been cloned and analysed, leading to the discovery of a large number of genes. Integrated genetic and physical maps compiled through *in situ* hybridization of several hundred bacterial artificial chromosomes (BACs) to polytene chromosomes and a high resolution microsatellite map of *A. gambiae* have been completed. This will permit intensive analysis of regions of the genome associated with malaria related genotypes and coordination of complete genome sequencing efforts.

Building on the above, an international network of partners was formed (see list) and a global effort in sequencing the *A. gambiae* genome matured through the biennium. It was formally launched in March 2001. The project will build on the initial genomics research carried out at some of the participating institutions, and draw on the strengths of the different partners. TDR will play a coordinating role. Research capacity strengthening of malaria endemic country laboratories in contemporary genomics techniques is a priority of the network. It is expected that complete sequencing of a laboratory strain of *A. gambiae* will be available by the end of 2001. The approach being taken is to search for genes directly using the 'shotgun' approach, then to map the physical location of the genes on the chromosomes, from which their DNA sequences can be ascertained.^{5, 6}

Sequencing the *Anopheles gambiae* genome

Current funding partners

- TDR
- National Institutes of Health, USA
- French Government
- Multilateral Initiative on Malaria
- European Commission

Current research partners

- Institut Pasteur (France)
- European Molecular Biology Laboratory (EMBL)
- University of Notre Dame (USA)
- French National Sequencing Centre (Genoscope, France)
- Celera Genomics (USA)
- European Bioinformatics Institute (Ensembl/EBI, UK)
- Institute for Genomic Research (TIGR, USA)
- Institute of Molecular Biology and Biotechnology (IMBB, Greece)
- Organization for Nucleotide Sequencing and Analysis (ONSA network, Sao Paulo, Brazil)
- leading mosquito researchers around the world

⁵ Balter M. Gene sequencers target malaria mosquito. *Science*, 1999, 285:508-509.

⁶ Balter M. Sequencing set for dreaded mosquito. *Science*, 2001, 291:2289-2291.



WHO/TDR/STAMMERS

Anopheles gambiae – a new genomic database established.

To accommodate the data emerging from the network, a new public database devoted to the genome of *A. gambiae* was established – AnoBase. As well as sequence information, this database will include full information about the role and function of genes as it becomes available. Another database, the *Anopheles* database AnoDB (see box 1), was started by TDR in 1996. This database contains data on the biology and genetics of anopheline mosquitos. During 1999-2000, it was enhanced with new software (AceDB) and underwent some restructuring.

Knowledge of the total genomic information of the three organisms that participate in the malaria transmission cycle (the parasite, the human, the mosquito) could open up unprecedented opportunities for understanding and blocking disease transmission, and will lead to the discovery of targets against which new drugs and vaccines can be produced.

Discovering mosquito genes which stop the parasite developing

As a malaria parasite moves through the mosquito, it has to cross several barriers. These include the epithelia of the midgut and the salivary glands, where mosquito defences can stop the parasite's development. Another barrier is provided by the mosquito's immune system. TDR is supporting studies to gain insight into molecules which prevent the parasite from invading the midgut and salivary gland epithelia, and into molecules which allow the parasite to survive these barriers and complete its life cycle.

Activation of parasite gametes begins in the midgut, soon after a mosquito has taken a blood meal from a malaria infected person. More details of gametocyte activation factors have been obtained, and cell surface molecules and their roles in mosquito-parasite interactions have been identified. The localization of peptides that act as signals for the malaria parasite in the midgut is being investigated, and a new high-quality cDNA library has been generated, containing genes expected to be expressed in the adult female midgut. A new cell type – Ross cells – was discovered in the midgut epithelium of mosquitos. These cells are preferentially invaded by the parasite's ookinete stages when they cross the midgut epithelium.^{7,8,9}

Attention is also being paid to the mosquito's immune system. In some strains of mosquito, the immune response is so strong that the malaria parasites are killed, but normally the parasites manage to survive in small numbers. Immune reactions have been demonstrated at the molecular level in the midgut and salivary gland epithelia, in haemocytes, and in the fat body (the insect equivalent of the liver). A pilot study using cultured mosquito immune cells identified 30 putative genes, of which 19 are thought likely to be involved in the mosquito immune system and possibly in blocking development of the malaria parasite. Another study focused on identifying genes which determine the susceptibility of *A. gambiae* to pathogens. Molecular variation in the defensin gene was analysed, defensin being a protein that is active against pathogens. Very high genetic variation was found within a number of mosquito populations – 76 distinct sequences of the defensin gene were found altogether. Extensive analysis is necessary to understand the role and control of this gene.

Knowledge of how the malaria parasite interacts with the various organs and the immune system in the mosquito may lead to development of novel strategies for blocking disease transmission. But because it is difficult to obtain material from mosquitos, TDR supports the development of mosquito cell lines, which are safe to work with and much easier to use than actual mosquitos. Cell lines of mosquito midgut and immune cells have been generated – midguts of early 4th, and perhaps 3rd, larval stages (where most multiplication occurs) were found to be the most successful for this. Cultures of mosquito cells active in immune response have also been developed which,

The focus is on gaining insight into parasite-mosquito interactions at three main barriers in the mosquito – the midgut, the immune system, and the salivary glands. Nineteen immune genes, possibly involved in warding off the malaria parasite, have already been identified. Lines of midgut cells and immune response cells have been generated for further research.

⁷ Malaria. TDR Final Report series, no. 15, October 1999.

⁸ Shahabuddin M, Pimenta PF. *Plasmodium gallinaceum* preferentially invades vesicular ATPase-expressing cells in *Aedes aegypti* midgut. *Proceedings of the National Academy of Sciences, USA*, 1998, 95(7):3385-3389.

⁹ Zeiler H, Nawrocki JP, Shahabuddin M. *Plasmodium gallinaceum* ookinetes adhere specifically to the *Aedes aegypti* midgut epithelium by interaction with a carbohydrate ligand. *Journal of experimental biology*, 1999, 202(pt5):485-495.



when exposed to an infectious agent e.g. a bacterium, respond by switching on specific genes, ultimately resulting in the synthesis of specific proteins to fight the infection. It was from these cells that the 30 putative genes mentioned above were isolated.

Novel immune response genes, and several specific transcriptionally co-regulated gene clusters elucidating new aspects of vector mosquito antimicrobial and antimalarial responses, have been discovered through cDNA microarray analysis. Further definition and dissection of the regulatory pathways and effectors involved in restricting malaria parasite development in the mosquito will be facilitated by global expression profiling of *A. gambiae* immune responses.

The malaria parasite can only be transmitted to a person after it has invaded the mosquito salivary glands. One study supported by TDR is looking at the control of genes in the salivary glands, at identifying sections of DNA which act as control or 'promoter' regions for genes, switching them on and off as directed. The first salivary gland specific gene to be isolated from *A. gambiae* was a putative apyrase gene (apyrase helps prevent coagulation of blood). In another study, a peptide was isolated which strongly inhibits the sporozoite stage of the malaria parasite from entering the salivary glands and midgut. This provides a potential tool – it represents a potential gene that could be inserted into the mosquito genome.

Development of genetic and molecular tools for inserting selected genes into the mosquito genome

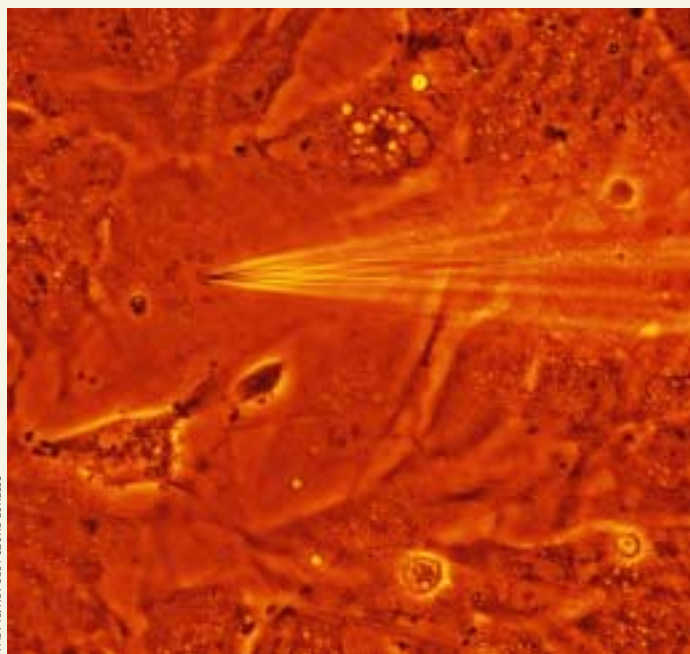
In this area of work, a landmark event announced in June 2000 was the insertion of a gene into *Anopheles stephensi*, a major malaria vector on the Indian subcontinent.¹⁰ This was the first stable germline transformation of an *Anopheles* species. In this instance, the model gene for green fluorescent protein (GFP) was inserted, making the transformed mosquitos glow green when excited by ultraviolet light. At a later stage, the GFP gene might be replaced by genes which inhibit parasite development. Work has already begun on one particular gene family – the *Anopheles* trypsin gene family, which consists of at least seven genes tightly clustered in a single locus. Trypsin is involved in blood feeding, and

Systems have been described for inserting genes into *Anopheles stephensi* and *A. gambiae*.

all the genes are expressed in the gut of female mosquitos (male mosquitos don't feed on blood). Researchers have been able to insert a promoter for the trypsin gene into the germline of *A. stephensi*.

In this work, a transposon – a small mobile piece of DNA which inserts randomly into chromosomes – known as *Minos* was used to help transfer the gene into the *A. stephensi* genome. Preliminary results from work on *A. gambiae* indicate that another transposable element, known as *piggyBac*, can be used to transform this species of *Anopheles*. In the first instance of insertion into the *A. gambiae* genome, the gene for GFP was again used as the model gene.

These studies have now demonstrated the feasibility of transposable element-based systems for transformation of mosquitos. It is likely that more and more laboratories will be able to apply the power of transgenesis in the investigation of the molecular biology of vectors.



Microinjection of a single cell, a technique introducing foreign or increased amounts of DNA into the cell nucleus.

Development of methods to spread selected genes in wild mosquito populations

Steady progress has also been made in this area of work during 1999-2000. In order to develop methods and strategies to spread selected genes through wild mosquito populations, we need to understand how genetic information flows between mosquito populations i.e. how related they are to each other, and what influences mosquito behaviour.

¹⁰ Catterucia F. et al, Stable germline transformation of *Anopheles stephensi*, a mosquito vector of human malaria. *Nature*, 2000, 405:959-962.



An ongoing study is looking at gene propagation between different populations of mosquitos. Results indicate that there is little genetic variation among populations of *A. gambiae* and *A. arabiensis* – in other words, few subpopulations are found across the continent of Africa. However, the Rift Valley of eastern Africa was seen to act as an ecological barrier to gene flow, separating genetically distinct eastern coastal populations of *A. gambiae* from populations west of the Rift Valley which stretch as far as West Africa.

Data collected in another study suggest that this lack of genetic diversity may be accounted for by the amount of gene dissemination among wild mosquito populations. Significant levels of gene flow were found to occur between different molecular forms of *A. gambiae*, as revealed by DNA analysis of sperm from the reproductive systems of female mosquitos. A diagnostic tool, under development to differentiate between chromosomal forms of *A. gambiae* and determine whether there is gene movement between them, showed the amount of genetic diversity to be drastically reduced in laboratory colonies as compared to a field colony. These results were based on microsatellite (highly variable pieces of DNA) polymorphism at nine loci on chromosome 3 in the different colonies of mosquitos.

Populations of mosquitos build up very rapidly after onset of the rainy season – more rapidly than can be explained by the mosquito reproduction rate. Preliminary results in Western Kenya indicated that anopheline eggs are capable of surviving long periods of dry season before hatching into larvae after onset of the rainy season (in contrast to conventional wisdom that anopheline eggs hatch shortly after they are laid). This study on effective population size and gene flow in *A. gambiae* is looking to predict the occurrence and abundance of major malaria mosquitos.

The data produced in all these and similar studies will be useful, in due course, for identifying sites where transformed mosquitos might be released under the TDR molecular entomology programme. But before appropriate strategies to spread new genes among field populations can be designed, baseline information on mosquito behaviour and life history in the field is also needed. Research in this area includes a study of mosquito egg laying behaviour. This work has validated the hypothesis that sites selected by *A. gambiae* for egg laying are associated with certain species of bacteria and with microbial metabolites, which gravid female mosquitos respond to. Another line of ongoing TDR research is to characterize odorant binding proteins (OBPs) involved in mosquito recognition of human odours.

Thus this work helps us to understand gene flow in mosquito populations and to predict how malaria resistance genes will spread. Selected genes will have to be driven into wild populations of mosquitos. Possible driving forces have been described, e.g. transposable elements, which have the ability to spread through natural populations. Another potential gene driving mechanism is the ‘cytoplasmic incompatibility’ induced in mosquitos by infection with the symbiont *Wolbachia*; identification of genes and genome sequencing of two *Wolbachia* strains has begun.

The hypothesis that genetic manipulation of vectorial competence could be used to control the transmission of many vector-borne pathogens has stimulated much research in insect immunity, control of gene expression, transgenic technology, ecology, and prophylaxis of tropical diseases. Gene transfer technology offers a powerful tool to investigate the role of insect molecules involved in parasite-host cell interactions and opens up a wide range of applications with which to explore genomic data for disease control.

Strategic social, economic and behavioural research

The first meeting of the newly established Steering Committee on Strategic Social, Economic and Behavioural (SEB) Research was held in Geneva in September 2000, when a vision was developed for the next five years and a detailed workplan constructed for the coming two years. This committee was created following recommendations from the Joint Coordinating Board (JCB) in June 1999, and was preceded by a Scientific Working Group (SWG) of experts from a range of social, economic and policy sciences who met in Geneva, June 2000, to set the overall direction for SEB.¹¹ The first call for grant applications was issued in October 2000.

Over the next few years, SEB will focus on gaining better understanding of how globalization and changing social, political and civil structures affect people’s access to health care and occurrence of TDR diseases – whether the diseases persist, resurge, or re-emerge. An important aspect of the Committee’s work will be to support capacity building.

Amongst other things, studies have shown *Anopheles gambiae* populations in Africa to be closely related to each other, with little genetic variation across the whole continent.

¹¹ Recommendations of a Scientific Working Group on Strategic Social, Economic and Behavioural Research. Report of a meeting, 31 May-2 June 2000, Switzerland. Document no. TDR/STR/SEB/SWG/00.1 available on request from TDR, and also to download from: www.who.int/tdr/publications/publications/seb.htm

The focus of the new Steering Committee on Strategic Social, Economic and Behavioural Research is on the complex relationship between poverty, inequality, and infectious disease persistence and emergence.



From the beginning, TDR has placed considerable emphasis on the social and economic aspects of tropical infectious diseases and their control. From 1979-1994, social science research was supported through the Steering Committee on Social and Economic Research (SER), and, after 1994, through the Applied Field Research (now Intervention Development and Implementation Research) team. SEB is located within the STR area to reflect a focus on *basic*, rather than *applied*, social, economic and behavioural research issues of trans-disease and global importance.

The focus of SEB reflects the growing interest in the complex relationship between poverty and health. On a worldwide scale, infectious and parasitic diseases disproportionately affect populations living in poverty. Social, political and economic inequalities are central to the persistence and spread of these diseases, and the performance of health systems in protecting vulnerable populations from the impact of these diseases often falls far short of what is needed. Over the next several years, the SEB Steering Committee will examine these issues within the context of globalization, the changing role of the state, and the emerging role of non-state actors (the private sector, non-governmental organizations and civil society).

Gender issues

The Intervention Development and Implementation Research (IDE) Task Force on Gender Sensitive Interventions (GSI) was created in 1998, with the overall aim to develop a conceptual framework and practical guidelines for incorporating gender considerations into tropical disease control programmes and services. To accomplish this, GSI sought to support studies that:

- develop and test methods for identifying potential gender inequities in the way tropical disease control programmes and services are designed, delivered, received and evaluated.
- develop and evaluate interventions that incorporate a gender perspective in tropical disease control.

However, with the creation of the new SEB Steering Committee, it was decided that gender research would benefit from the broader perspective on equity in health care taken by SEB. Therefore, the gender portfolio will be continued under the auspices of SEB, which will seek to develop a more comprehensive research agenda on gender equity in the prevention and control of neglected infectious diseases.

Ongoing work includes a study in Ghana to develop and pilot a district-level participatory planning process to identify and address gender issues in malaria control; a study in Myanmar to develop gender-sensitive approaches to reducing ocular disabilities in leprosy patients; a study in Brazil to identify gender specific barriers to leprosy detection and treatment; a study of the

Research on gender issues is ongoing in a number of the TDR diseases. The aim is to ensure gender equity in the prevention and control of infectious diseases.



Lymphatic filariasis women's support group.

WHO/TDR/CRIMP



feasibility of women's support groups for lymphatic filariasis; two studies on schistosomiasis of the reproductive tract; and a four-country study of gender specific barriers to TB control. This latter work was initiated by the WHO Global Tuberculosis (TB) programme and continues in TDR. It is an investigation into the effects of sex and gender on the performance of TB control services in Malawi, Colombia, Bangladesh, and India. Country level work began following a protocol development workshop in Geneva in December 2000.

Results and experiences from these studies will contribute to the development of general guidelines for identifying and addressing gender specific needs, barriers and opportunities in infectious disease control.

Health sector reform

Following the report of the Ad Hoc Committee on Health Research Relating to Future Intervention Options,¹² TDR managed, outside its normal activities, a research portfolio entitled Comparative Studies on Health Sector Reform. Some of the stakeholders in the then accelerating number of health sector reforms in countries were concerned about the effects of these reforms. With support from the Norwegian Government and in collaboration with the International Clearinghouse for Health System Reform Initiatives (ICHSRI) in Mexico, 54 individual studies were initiated in three rounds (1996, 1997, 1998). On establishment of the Steering Committee on SEB in 2000, finalization of the work was integrated into this committee.

During 1999 and 2000, the studies from the first two rounds were completed and results are being prepared for publication – eight are to be published in an international peer reviewed journal. Most of the 1998 studies, which all address equity, have also been completed. These studies will be supported technically during 2001 and the results made internationally available.

Results from the studies show that health sector reforms do indeed have many unintended and undesirable side-effects, e.g. shifting provider behaviours towards less cost-effective procedures and prescription practices, and increased inequity in access to services. While the intentions of the reforms were good, the problems lay in implementation, lack of monitoring, and lack of timely and adequate corrective measures when things start to go wrong.

The first three rounds of studies did not specifically focus on issues related to tropical diseases, but during 2000, a call for proposals was announced under the heading Health Sector Reform and Tropical Diseases 2000. The overarching aim is to study the opportunities and threats to the control of tropical diseases posed by ongoing health sector reforms. All the TDR diseases disproportionately affect poor and marginalized people, those who are often adversely affected by the approaches to reform as shown in the first rounds of reform studies. Two of the diseases, TB and malaria, are high on the international agenda, while the other eight diseases tend to be more neglected, although four (lymphatic filariasis, onchocerciasis, Chagas disease, leprosy) are targeted for elimination. Sixteen proposals were selected for funding and will be provided with technical support during 2001/2002 to develop appropriate methods and conduct the studies.

Research shows that health sector reforms often have unintended and undesirable effects, e.g. increased inequity in access to services, primarily due to problems in implementation and monitoring.

¹² *Investing in health research and development: report of the Ad Hoc Committee on Health Research Relating to Future Intervention Options*. World Health Organization 1996, document no. TDR/Gen/96.1 (available from TDR on request).



New and Improved Tools

Discovery and development of new drugs, vaccines and diagnostics for the TDR target diseases, under Product Research and Development, is an area that has expanded in recent years. New and improved tools for use in infectious disease prevention and control – drugs, vaccines, diagnostics, epidemiological tools, environmental tools – are being developed. The progress indicators include new candidates (drugs, vaccines, diagnostics)



ready to enter the development pipeline; new candidates in development; new and/or improved tools (drugs, vaccines, diagnostics) resulting in regulatory approval; and new and/or improved epidemiological tools developed for use in control of neglected tropical diseases.



NEW CANDIDATES READY TO ENTER INTO DEVELOPMENT

Drug discovery research

The major changes in Drug Discovery Research in 1999 and 2000 were the updating and restructuring of the screening operations; the progression of candidates for treatment of some target diseases into initial pharmacokinetic studies and, in some cases, further development; an increased emphasis on natural product research; and the preparations to include tuberculosis and possibly dengue in the drug discovery portfolio.

Under the new screening system, compounds submitted for integrated screening are first tested in a single laboratory for activity in vitro against a range of different parasites. If a compound is active, it is sent for more detailed analysis to one or more laboratories that are specialized in individual parasitic diseases. This has resulted in increased throughput and efficiency of the screening operations.

In the natural products area, several projects investigating the activity of purified antimalarial or anti-leishmanial compounds, or semi-synthetic analogues, are being funded (see below). As part of a broader effort to enhance research capability strengthening in disease endemic countries, a meeting on Natural Products for Treatment of Tropical Diseases was organized in August 2000, to address issues of common interest for both traditional and pharmaceutical medicine disciplines and to seek ways in which effective, safe and cheap natural products may be more easily developed.

In malaria drug discovery research, the principal current development candidates are synthetic antimalarial peroxides, several of which have been analysed in detail in pharmacokinetic studies. Further development work on one series of peroxides is now being funded by the Medicines for Malaria Venture (MMV). In the future, it is foreseen that other promising malaria projects which have been nurtured in TDR might also be taken up by MMV. Work on two other peroxide series has produced molecules with improved physical and pharmacokinetic properties, as discussed at a TDR-organized meeting on these candidates in September 2000. Selected molecules from one series are being characterized further. Additional research on identified molecular targets or relevant biochemical pathways (defined kinase families, dihydrofolate reductase, shikimate pathway, choline uptake and metabolism) continues to be supported, and analogues of manzamine and dioncophylline, natural products with interesting antimalarial activity, are being characterized. At the screening level, an important step forward was the successful launch of the JPMW – a partnership between 12 Japanese pharmaceutical companies, the Japanese Ministry of Health and Welfare, and TDR/WHO – in October 1999. Under this agreement, it is planned to screen some 12 000 compounds and natural product extracts for antimalarial activity over a five-year period. Some compounds with good activity in vitro and reasonable activity in animal models have been identified and characterized, and, in most cases, analogues of these compounds are being tested or will soon be available for testing.

For onchocerciasis and lymphatic filariasis, moxidectin was established as the leading candidate for further development. At the discovery level, new approaches to target validation and lead discovery have been introduced. Research using gene knockout and RNA inhibition approaches to target validation is being funded, as are two molecular target screens that were set up following a TDR-organized meeting in 1998 on Molecular Targets for Filariasis. The traditional screening on whole organisms has been reorganized and now incorporates initial in vitro studies on cultured parasites. A meeting on *Wolbachia* bacteria as possible targets for anti-onchocercal drugs¹ (December 1999) led to the testing of a series of antibiotics, some of which show promising anti-onchocercal activity and are being investigated further. Work on possible mechanisms of resistance to ivermectin led to the establishment of a programme to develop diagnostic tools for the detection of drug resistant onchocerciasis.

The standard current treatments for visceral leishmaniasis, and also treatment with miltefosine (an oral treatment under development for visceral leishmaniasis), require multiple administrations of the drug and correspondingly long treatment courses. A natural product with good anti-leishmanial activity after a single injection in animal models, PX 6518, is being progressed through pharmacokinetic and toxicological studies, and would significantly shorten treatment times if successful. Other projects being funded at the basic research level include studies of

Several promising drug candidates have progressed to further development. There is increased emphasis on natural products and increased efficiency of drug screening operations. There are new development candidates for vaccines for malaria, leishmaniasis and schistosomiasis.

¹ Taylor MJ et al. *Wolbachia* bacteria of filarial nematodes: a target for control? *Parasitology today*, 2000, 16:179-180.

² Lazdins J, Kron M. New molecular targets for filariasis drug discovery. *Parasitology today*, 1999, 15:305-306.



WHO/TDR/CRUAP

Harvesting *Maesa balansae*, the source of PX6518, which has good anti-leishmanial activity.

pyrophosphate metabolism as a possible drug target in *Leishmania*, and mechanisms of parasite resistance to arsenical anti-leishmanial drugs.

The search for new molecules with activity against African trypanosomiasis continued. As was discussed at a TDR-funded meeting on 'New drugs for kinetoplastid diseases' (Heidelberg, 1999), there is a lack of validated targets and corresponding leads for developing drugs against the trypanosomiasis and leishmaniasis. It has been especially difficult to identify molecules that combine good activity, lack of toxicity, and ability to cross the blood-brain barrier, all necessary attributes of a drug that is to be effective against sleeping sickness caused by chronic infection with African trypanosomes. Two series of active molecules were investigated in chronic infection models in some detail. A development candidate from the most promising series (amidine derivatives) is now being progressed at the preclinical level with additional financial support from the Gates Foundation. Additional TDR-funded work includes the identification of new leads based on their ability to inhibit trypanothione reductase, one of the few validated trypanosomal target molecules.

New molecules continued to be screened for activity in animal models of Chagas disease, with interest focused on possible treatments for the chronic form of the disease. Some anti-fungal azoles showed good activity in animal models of infection, and one of these, posaconazole (SCH 56592),³ is currently considered an excellent candidate for progression into human clinical trials.

Tuberculosis and dengue were recently introduced into the TDR disease portfolio. The Drug Discovery Research unit is now funding some initial TB screening work, and, in partnership with the Global Alliance for TB Drug Research and Development, has plans

to expand this to the screening of more selected libraries, including natural product-based ones. TDR also commissioned a consultant report to assess if chemotherapy is a viable option for dengue, or whether the initial research should focus more on diagnostics or vaccines (successful treatment for dengue haemorrhagic fever is likely to be very dependent on rapid, accurate diagnosis of the disease).

Vaccine discovery research

Significant progress was made during 1999-2000 in the area of vaccine discovery research, leading to new development candidates for vaccines for malaria, leishmaniasis, and schistosomiasis. Supported were:

- Research projects on pre-erythrocytic and asexual blood stage antigens for *Plasmodium falciparum* and *P. vivax* malaria, based on recombinant proteins, synthetic peptides and deoxyribonucleic acid (DNA) plasmids.
- Long-term research projects on transmission-blocking vaccines, aimed at preventing the successful development of the malaria parasite in its mosquito host. Although the development and eventual deployment of transmission-blocking vaccines is feasible, there is little commercial interest in these vaccines and development is proceeding slowly. The need to develop safe and effective transmission-blocking vaccine candidates to the stage of 'proof of principle' in order to induce industrial commitment to vaccine production was identified as being urgent by an international group of experts at a meeting, sponsored by the World Health Organization (WHO)/TDR, Roll Back Malaria (RBM), the Gates Malaria Vaccine Initiative (MVI), and the US National Institutes of Health (NIAID and Fogarty International Centre), in December 1999.⁴
- Studies aimed at identifying promising second generation recombinant protein antigens as candidates for an effective leishmania vaccine – especially needed for combating visceral leishmaniasis.
- Research and evaluation in large animals (sheep, pigs, cattle, water buffalo) of promising candidate antigens and adjuvants for a vaccine against schistosomiasis japonicum, a disease found in China and the Philippines. If successful at reducing the *S. japonicum* reservoir in veterinary

³ Molina J et al. Activity of the triazole derivative SCH 56592 (posaconazole) against drug-resistant strains of the protozoan parasite *Trypanosoma (Schizotrypanum) cruzi* in immunocompetent and immunosuppressed murine hosts. *Antimicrobial agents and chemotherapy*, 2000, 44:150-155.

⁴ *Malaria transmission blocking vaccines: An ideal public good*. Document no. TDR/RBM/MAL/VAC/2000.1 available from TDR on request, and also to download from: www.who.int/tdr/publications/publications/malaria_tbv.htm



use, the same candidate vaccine antigens would be evaluated for use as a vaccine in humans.

Vaccine research and development for tuberculosis and dengue is currently being addressed by the Health Technology and Pharmaceuticals cluster (Vaccine Development Unit) of WHO. Progress in TDR's contributions to new vaccines for TB and dengue will be carried out under the umbrella of the new Initiative for Vaccine Research (IVR) within WHO. TDR, as part of this IVR initiative, organized the second bi-annual meeting on Novel Adjuvants Currently in Clinical Testing at the Fondation Mérieux, France. This meeting provides an excellent opportunity for research scientists and pharmaceutical companies to exchange information and evaluate progress in this rapidly evolving field.

Diagnostic discovery research

Ivermectin resistance has developed in parasites (worms) of veterinary importance and there is a fear this may happen with *Onchocerca volvulus*. For this reason, TDR has established a product development team to develop a sensitive polymerase chain reaction (PCR)-based assay for detecting ivermectin resistance in *O. volvulus*.

The team is focusing on genetic evaluation of material from adult *O. volvulus* recovered from nodules obtained from naive patients or patients treated with ivermectin at the Onchocerciasis Clinical Research Centre in Hohoe, Ghana. A genomic library of *O. volvulus* has been constructed and restriction fragment length polymorphism (RFLP) analysis performed on seven relevant genes, certain of which appear to be selected. In another approach, based on genetic analysis of candidate ivermectin resistance genes from *Haemonchus contortus*/*H. placei* crosses, several genes have similarly been excluded.

To expand this work, arrangements have been made with the Onchocerciasis Control Programme of West Africa to provide the investigators with *O. volvulus* material from areas with different exposures to ivermectin. A method is being developed for immobilizing DNA on filter paper and subsequently utilizing it for two to three rounds of multiplex PCR from a single *O. volvulus* microfilarial larva (L3 stage) under the conditions of higher humidity likely to be encountered in the field.



SCIENCE PHOTO LIBRARY/STAMERS

Examining DNA sequencing of the nematode worm, *Onchocerca volvulus*.

NEW CANDIDATES IN DEVELOPMENT

Drug development

MALARIA

Rectal artesunate

Survival of a severe malaria patient depends on the speed of obtaining chemotherapy. To survive, such a patient must access a health facility where injectable treatment can be given immediately and safely. If no treatment is given, the disease is fatal. A drug to replace injectable treatment would capture the population at highest risk of death from malaria at a point in the evolution of the disease that provides the greatest potential for reducing the risk of complications and death. There is, at present, no drug that meets these requirements. Such a compound would need to be quickly bioavailable, of high efficacy and safety, and of stable formulation for the tropical areas where malaria is transmitted. Once the patient is able to reach an equipped health facility, a more precise diagnosis can be made and follow-up treatment administered as required.

TDR is completing submission of a regulatory dossier for rectal artesunate to the US Food and Drug Administration, the UK Medicines Control

Partners:

- Scanpharm
- Knoll
- Scherer
- Novartis

Antimalarials under development include one for emergency treatment of acute disease where a patient is unable to access injectable treatment, one for intermittent use during pregnancy, and four for treatment of uncomplicated falciparum malaria.



Agency, and the Swiss Inter Cantonal Office for the Control of Medicines, for registration of the drug under a new indication for malaria: emergency treatment of acute disease where a patient is unable to take drugs by mouth and unable to access injectable treatment. WHO is the applicant for registration and the dossier is currently under review by the three agencies. Stability and bioequivalence data, to be submitted in May 2001, will complete the dossier for registration of the product. Plans for how best to launch the product in malaria endemic countries are being prepared jointly by TDR and Roll Back Malaria.

Partner:

- GlaxoSmithKline

Malarone

Acute malaria in pregnancy is associated with higher than normal mortality and increased risk of spontaneous abortion, especially in non-immune mothers. In semi-immune individuals, it is associated with low birth weight, the most important risk factor for infant mortality. Although women of childbearing age living in endemic areas acquire partial immunity to malaria, which protects them against the acute disease, this protection is lost or lowered during pregnancy due to the immuno-suppression that follows conception. To protect pregnant women against malaria complications, the most effective treatment with the lowest possible risk of clinical failure is recommended.

There are increasing reports of chloroquine (CQ) and sulphadoxine-pyrimethamine (SP) resistant falciparum malaria from most parts of Africa. In south-east Asian countries, particularly Thailand, CQ and SP are now almost ineffective and their use is limited. Thus there is an urgent need to search for alternative drugs that can be used in areas where there is chloroquine resistance and substantial SP resistance, or in situations where SP is contraindicated. It was the increasing resistance to SP, currently promoted for intermittent treatment during pregnancy, that gave rise to the original idea for developing Malarone as a treatment in pregnancy.

Malarone is a fixed-dose combination of 250mg atovaquone and 100mg proguanil hydrochloride per tablet, and is considered a possible alternative to CQ and SP. The drug is now available in more than 30 countries (including the United States, Canada, countries in Europe, Africa, Asia, the Middle East, Latin America) for the treatment of acute, uncomplicated falciparum malaria. Clinical studies have demonstrated excellent safety and tolerance compared to other standard antimalarial regimens such as mefloquine and quinine/tetracycline. While in excess of 200 000 courses of atovaquone/proguanil have been prescribed worldwide, only 122 adverse events have been reported in post-marketing surveillance, suggesting that the drug is well tolerated. However, although Malarone has been shown to be safe in children and adult malaria patients, its safety in pregnancy has not yet been established.

In planning for a Phase IV clinical trial in pregnant women, the toxicological profiles of atovaquone and proguanil, in particular the reproductive toxicology, were reviewed by an independent panel of expert consultants. The panel concluded that the available safety data, which address the two drugs – atovaquone and proguanil – separately, are adequate to support investigations into the potential use of Malarone for the treatment and prevention of malaria in pregnancy.

However, physiological changes during pregnancy such as delayed gastric emptying, decreased motility of the gastrointestinal tract, increased volume of fluid, and increased proteins, may induce significant change in drug pharmacokinetics, particularly as in the case of atovaquone, which has high plasma protein binding capacity (greater than 99%). In addition, drug metabolism can significantly change during pregnancy. With no pharmacokinetic data of atovaquone in pregnant women yet available, conducting a pharmacokinetic study in pregnant patients will provide first-hand information on the pharmacokinetics, efficacy and safety of Malarone prior to the conduct of large-scale trials. However, such a study in this population requires extreme caution.

The primary objective of the study is to investigate the pharmacokinetics of Malarone in pregnancy, allowing for possible racial and geographical variations. The trial is being conducted at two independent sites, one in Zambia (sub-Saharan Africa) and the other in Thailand (south-east Asia), with the purpose of gathering preliminary information for future larger trials of Malarone in acute uncomplicated malaria in pregnant women. The following studies are proposed:

1. Pharmacokinetic study on symptomatic patients (small group)
2. Symptomatic treatment (large group)
3. Intermittent treatment (large group)

The ideal treatment should be very effective, with the lowest possible risk of adverse effects and the highest probability of killing all asexual stages in the blood and placenta.



Pyronaridine/artesunate

An oral fixed ratio combination product containing pyronaridine and artesunate is being developed for the treatment of uncomplicated malaria in Africa and Asia. This combination is seen as a safe, effective, and relatively low-cost replacement for the oral antimalarials commonly used for treatment of uncomplicated malaria, but to which resistance has developed in certain areas. Current data indicate that pyronaridine, when used as a single agent, is effective in cases of chloroquine resistance and is satisfactorily tolerated. But the addition of artesunate to pyronaridine will create an even better treatment for falciparum malaria because it is likely that the artemisinin derivative will: decrease fever and parasite clearance time when compared to the use of pyronaridine as a single agent; prevent the development of resistance; and possibly lower the rate of malaria transmission. There is already good evidence from three small Chinese clinical trials that the addition of an artemisinin derivative to pyronaridine is safe, very effective and well tolerated. Shin Poong Pharmaceutical Co. Ltd. and TDR, via a memorandum of understanding agreement, have already initiated jointly funded preclinical toxicology studies with the two compounds, and plan to study use of the combination in humans beginning in early 2002.

Partner:

- **Shin Poong Pharmaceutical Co. Ltd.**

Chlorproguanil/dapsone

The chlorproguanil/dapsone development project, for the treatment of uncomplicated falciparum malaria in Africa, is nearing completion. Large, blinded, comparative, multicentre Phase III clinical trials, designed to determine the safety and efficacy of a three-day regimen of chlorproguanil/dapsone, were completed in early 2001 and the data are now being analysed. Submission of the regulatory dossier to the UK Medicines Control Agency and African national regulatory agencies will begin in September/October of 2001. Chlorproguanil/dapsone is active against African SP-resistant falciparum strains and has a much shorter plasma half-life than SP, so a low propensity to select resistant parasites. It is seen as an alternative or replacement for SP. Chlorproguanil/dapsone will be made available to the public sector of African countries at a preferential price of <US\$0.50 per adult treatment course. In March 2001, WHO, TDR, Roll Back Malaria, WHO/Essential Drugs and Medicines, the WHO Regional Office for Africa, and the University of Liverpool, inaugurated a Chlorproguanil/dapsone Access Group which will explore mechanisms by which chlorproguanil/dapsone can be equitably accessed by African populations and review evidence gathered to assist national control programmes in making policy decisions concerning their use of chlorproguanil/dapsone.

Partners:

- **UK Department for International Development**
- **GlaxoSmithKline**
- **University of Liverpool**
- **WHO Roll Back Malaria**

Chlorproguanil/dapsone/artesunate

Studies using a fixed ratio combination of chlorproguanil/dapsone with artesunate (under the acronym CDA) for the treatment of uncomplicated falciparum malaria in Africa have recently been initiated. Chlorproguanil/dapsone combination is seen as safe, effective, and low cost (see above), while the potent compound artesunate is a semi-synthetic derivative of artemisinin, derived from a Chinese plant. The advantages of adding an artemisinin derivative to chlorproguanil/dapsone are three fold: faster fever and parasite clearance times; reduced rate of development of resistance; and possibly decreased malaria transmission due to the gametocidal effects of artesunate. Preclinical toxicology citing studies are under way and the team anticipates that CDA will be used in humans in the third quarter of 2001.

Partners:

- **GlaxoSmithKline**
- **UK Department for International Development**
- **University of Liverpool**

Fosmidomycin

As a phosphonic acid derivative, fosmidomycin represents a novel class of antimalarials which work through inhibiting the 1-deoxy-D-xylulose 5-phosphate (DOXP) pathway. Hence, activity against multidrug-resistant strains of *P. falciparum* may be anticipated. Previously investigated as an antibacterial agent in the 1980s, early promise of the drug for treatment of uncomplicated urinary tract infections was countered by the relative lack of activity against recurrent infections. Nevertheless, the drug was well tolerated even at high doses.

More recently, Jomaa et al have identified activity in experimental models of malaria and against the target parasite in vitro.⁵ In collaboration with Jomaa Pharmaka, TDR has contributed to the design of a proof of principle study in which the response to a seven-day therapeutic regi-

Partner:

- **Jomaa Pharmaka**

⁵ Jomaa et al. Inhibitors of the nonmevalonate pathway of isoprenoid biosynthesis as anti-malarial drugs. 1999. *Science* 285:1573-1576.



men will be evaluated in 30 subjects with acute uncomplicated falciparum malaria enrolled at centres in Gabon, Tanzania and Thailand, commencing in January 2001.

It is expected that the results from this study, on which future strategies will be determined, will be available in June 2001.

TUBERCULOSIS

Streamlining the development and registration of new drugs

Throughout 2000, TDR worked with the Rockefeller Foundation and other agencies to establish the Global Alliance for TB Drug Development, launched by the Director-General of WHO in Bangkok, October 2000.⁶ The goal of the Alliance is to bring to registration, by 2010, at least one new agent for tuberculosis (TB) which will make treatment of TB substantially shorter, will be effective against multidrug resistant TB, and/or will be effective in the treatment of latent TB infection.

TDR initiated dialogue with national regulatory agencies (NRAs) in order to standardize guidelines for the registration of new chemical entities effective against TB and of the new four-drug fixed-dose combinations. A meeting of NRAs was convened with industry representatives in September 2000 at which NRA representatives agreed to the proposed guidelines and to lobby for their formal adoption by their respective agencies.

An analysis of the compounds in early development as anti-TB agents within the public domain was carried out by TDR and revised by a meeting of experts in December 2000. The resulting document will provide essential data on the most promising compounds in the discovery, preclinical and clinical phases of development.

Funds have been sought to expand TDR's existing screening activities to include TB. TDR is in discussion with Aventis, the manufacturer of rifapentine, for joint development of rifapentine to the point of determining its proper role in TB control in low income countries. The possibility of partnerships with manufacturers of the most useful looking fluoroquinolones, especially Bayer Ltd for moxifloxacin, will be explored, while dialogue with Chiron on the nitroimidazopyrans will continue.

Activities for streamlining registration of four-drug fixed-dose anti-TB combinations

The development and regulatory approval of new drugs for the treatment of TB is one of the cornerstones of effective TB control and a process of paramount importance to each country for protecting the health of its citizens. But it is a time-consuming process and current regulations are a disincentive to industry. Therefore, TDR and the International Federation of Pharmaceutical Manufacturers Associations (IFPMA) are leading measures to streamline the process of developing and registering new chemical entities and four-drug fixed-ratio combinations – as recommended through the WHO essential drug list – for TB. The development of a standardized regulatory policy framework was discussed at a TDR sponsored meeting in September 2000, to which representatives from developed and developing country national regulatory agencies, other government agencies, the pharmaceutical industry, and academic establishments, were invited.

It is TDR's intention to: (i) develop a single harmonized guideline to guide all actors (industry, international regulators, public health institutions, individual scientists) in the development of new anti-TB agents; (ii) enhance the efficiency and speed of registering new anti-TB agents; (iii) incorporate 'state-of-the-art' science, e.g. surrogate markers, in the clinical development of new TB drugs; and (iv) develop a single international harmonized approach for the registration of fixed-dose combinations of four anti-TB drugs. The national regulatory authorities of 22 high burden TB endemic countries and all members of the International Committee on Harmonisation (ICH) will provide input to proposed guidelines on regulatory harmonization which, it is hoped, will be finalized by the end of 2003.

ONCHOCERCIASIS and LYMPHATIC FILARIASIS

Two types of drug are described for treatment of onchocerciasis and lymphatic filariasis:

- microfilaricides, which kill immature worms.
- macrofilaricides, which kill adult worms.

Existing microfilaricides are effective, but there is no suitable macrofilaricide currently available. Because treatment with microfilaricides must be

Four-drug fixed-dose anti-TB combinations should be the first product to achieve regulatory approval under a standardized regulatory policy framework for new anti-TB agents currently under development.

⁶ Dr Carlos Morel, Director, TDR, was elected Chairman of the Board of the Alliance during 2000, and Dr Win Gutteridge, Coordinator of TDR Product Research and Development, was appointed to the Scientific Advisory Committee.

Studies are ongoing on the use of albendazole in combination with ivermectin, DEC or levamisole for the treatment of onchocerciasis, lymphatic filariasis and geohelminths, while trials in animals have shown moxidectin to be a potential macrofilaricide.



maintained for a number of years, in fact for the length of life of the adult worm in the human host (more than 10 years in the case of onchocerciasis), a suitable, safe and effective macrofilaricide would allow more impact to be made on controlling filarial diseases than is currently possible using microfilaricidal treatment.

Albendazole combinations

TDR, through its network of clinical researchers, is supporting studies to evaluate albendazole in combination with either ivermectin or levamisole as potential macrofilaricidal treatment for *O. volvulus* patients, and albendazole co-administered with either ivermectin or diethylcarbamazine (DEC) for treatment of lymphatic filariasis patients.

The studies in onchocerciasis patients are being conducted at the Onchocerciasis Clinical

Research Center in Hohoe, Ghana. The effects of single-dose co-administration of ivermectin (Mectizan) with albendazole, of albendazole with levamisole, or of ivermectin with levamisole, are being evaluated, the primary end points being safety, pharmacokinetics and effect on microfilaria and macrofilaria. Preliminary results suggest that, although safe, none of the combinations is more effective on adult worms than ivermectin alone. Also, so far, no pharmacokinetic drug interactions have been detected.

The studies in lymphatic filariasis patients are being conducted in light of the WHO/SmithKlineBeecham (now GlaxoSmithKline)/Merck recommendations on use of co-administration of albendazole with ivermectin or DEC for elimination of lymphatic filariasis. Three studies are in progress:

- On the Island of Pemba, Tanzania, a randomized, double blind study in 1000 subjects is under way to compare single-dose ivermectin + albendazole with single-dose ivermectin alone. This study will define: a) unacceptable adverse drug reactions occurring within 7 days of treatment; b) the proportion of microfilaria positive subjects that, one year after treatment, remain microfilaria negative – the primary endpoints being 80% reduction in prevalence for ivermectin alone and 90% reduction in prevalence for albendazole + ivermectin.

As secondary end-points, the study will assess: a) prevalence of microfilaremic subjects 3 and 6 months after

treatment, and reduction in microfilaremia 3 and 6 months after treatment; b) the cure rate (proportion of patients with clearance of eggs from stools) of *Trichuris trichiura* (human whipworm) infections 21 days after treatment, and reduction in the *T. trichiura* egg count 21 days after treatment compared to before treatment; c) cure of other soil transmitted helminths. The results are expected during the 3rd quarter 2002.

- In Alleppey, India, a study in lymphatic filariasis infected vs. uninfected individuals is under way to evaluate the pharmacokinetic profiles of albendazole and DEC when administered as single drugs or when co-administered as in lymphatic filariasis elimination programmes. Besides assessing safety and laboratory parameters, this study will, for the first time, determine if there is any adverse pharmacokinetic drug interaction. Determination of drug plasma levels will be carried out at the University of Iowa, US. Results of the study are expected to be available during the 4th quarter of 2001.

- In Wardha, India, a study in 1347 subjects is ongoing to assess the safety, tolerability, efficacy and population pharmacokinetics of DEC co-administered with albendazole as compared to DEC administered alone. The primary end-points will be information on the number of patients without microfilaraemia at 3, 6 and 12 months after treatment, and on the clinical



Levamisole trial in Ghana

WHO/TDR/GRUP

Partners:

- Onchocerciasis Control Programme
- African Programme for Onchocerciasis Control



signs and symptoms and adverse events in the two arms of the study. The results are expected to be available during the 4th quarter 2002.

LEISHMANIASIS

Partner:

- Zentaris

Miltefosine

Miltefosine, an anticancer drug that TDR and ASTA Medica (now Zentaris) have been developing for visceral leishmaniasis, could be the first oral treatment to become available for this disease (see TDR Programme Report, 1997-1998). During the biennium, Phase II (dose-finding) and Phase III (efficacy confirmation) trials in adult patients were successfully completed. In mid-2001, the drug will be submitted for registration in India and Germany for use in patients aged over 12 years. As well, a Phase II trial in children was completed, and a Phase III trial in children has begun (expected to finish end of October 2001), an indication which could later be added to the criteria for use. A Phase IV (post registration, in a real field situation) trial has been planned for India, Nepal and Bangladesh, which will feed into the control programme. This Phase IV trial will be supported by the WHO Regional Office for South-East Asia and the Government of India.

Miltefosine promises to be the first oral treatment for visceral leishmaniasis. Dose-finding and efficacy confirmation trials have been completed and the drug will shortly be submitted for registration.

Partner:

- IDA

Paromomycin

Further development of this compound is currently on hold due to lack of funding, but it is hoped it can be re-activated during the 2002/3 biennium.

SCHISTOSOMIASIS

Artemether

Chemotherapy using praziquantel has been the cornerstone of schistosomiasis control for more than 20 years. As yet, there is no proof for the emergence of drug resistance, but rapid re-infection is a problem. Artemether, a drug developed for malaria, has been found to interfere with the development of adult schistosome worms after infection, and would conceivably stop morbidity, which is induced by granulomatous effects against eggs not excreted from the host. However, long-term use of artemether would not be financially feasible and it is advised not to use it on a large scale in malarious areas because of the risk of drug resistance. On the other hand, there are large malaria-free areas in China, South America and North Africa where artemether could be useful as an adjunct to elimination of schistosomiasis as a public health problem. TDR is currently involved in field studies to resolve these questions.

The malaria drug artemether promises to be useful as an adjunct to the elimination of schistosomiasis as a public health problem.

AFRICAN TRYPANOSOMIASIS

Each of the drugs currently in use for African trypanosomiasis has its drawbacks. Pentamidine and suramin, used only for early-stage disease, both have adverse side effects. Of the two drugs used for late-stage disease, melarsoprol has serious adverse effects which leads to fatal outcome in 1-5% of patients, while eflornithine, which treats only the gambiense form of the disease, has been out of production. No oral treatment exists.

Companies are donating key drugs for sleeping sickness, funds for drug development, and funds for disease management and control.

A project to discover novel compounds with activity against late-stage disease, using animal models and supported at the Shanghai Institute of Pharmaceutical Industry, has been terminated following the lead compound's (SIPI 1029) failure to cure late-stage infection in the vervet monkey model of African trypanosomiasis at Kenya Trypanosomiasis Research Institute (KETRI), Nairobi. For the same reason, another lead compound – the diamidine CGP 40215 – has been dropped from the development portfolio.



Eflornithine

Eflornithine was discovered in 1980 by Dr Cyrus Bacchi through a TDR-supported study on polyamine metabolism in trypanosomes. Known as the 'resurrection drug' because of its spectacular effect on comatose patients in late-stage gambiense sleeping sickness, eflornithine is well tolerated in patients. However, there are two problems with its availability: first, it has been out of production since 1995, and second, it is expensive.

In 1999, the remaining available stocks of the drug were donated for treatment of sleeping sickness by Hoechst Marion Roussel (now Aventis). These stocks are projected to last until June 2001. Also, in December 1999, this company granted WHO the production rights for eflornithine in order that a third party manufacturer could be found. Some eight pharmaceutical companies were identified by WHO and Médecins sans Frontières (MSF) as potential manufacturers. In November 2000, WHO and MSF approached Bristol-Myers Squibb (BMS), USA (which, with Gillette, has recently introduced Vaniqa™, an eflornithine cream marketed for reducing growth of facial hair in women), for help in finding a source of bulk material that could be formulated into injectable form before the available stocks run out in June 2001. Subsequently, in February 2001, BMS announced that it would donate 60 000 doses of eflornithine annually for three years, starting in June 2001, for use in treatment of sleeping sickness. However, this development was overtaken in May 2001 by an agreement signed between WHO and Aventis, by which Aventis will donate US\$25 million to support WHO's activities in the field of African trypanosomiasis for a five year period. The donation comprises: a donation of three key drugs, pentamidine, melarsoprol and eflornithine, and funds for disease management and control and research. Out of the Aventis annual donation of US\$5 million, US\$750 000 will go to TDR as a designated fund for drug development, focusing on oral eflornithine, development of a new route of synthesis for eflornithine, and development of existing molecules for future treatment. BMS has agreed to fund production of the bulk material for 60 000 doses of eflornithine for the first year and also to provide 140kg of oral eflornithine for Phase III clinical trials.

Several approaches to reducing the cost of eflornithine have been considered by TDR in the past. One approach was to look at synthesizing eflornithine by a new route, but this was put on hold due to lack of funds. It will now be reactivated. Another approach was to compare 14-day treatment with 7-day treatment, as reported in the TDR Programme Report for 1997-1998, which showed the 7-day regimen to be significantly less effective than the 14-day regimen for new cases although, for relapsed patients, the 7-day treatment is as effective as the 14-day treatment and can be recommended.⁷ Another approach being followed is based on use of an oral formulation of the drug, which would not only be much less expensive than the i.v. formulation, but also much easier to administer. Pharmacokinetic studies on oral eflornithine, in which two oral doses are being compared for efficacy and safety, are in progress in Côte d'Ivoire. If the results are satisfactory, Phase III multicentre clinical trials will start in 2002, according to good clinical practice (GCP).

Another approach to improving availability concerns the use of drug combinations. There is experimental evidence for synergism between eflornithine and melarsoprol, and clinical trials involving combinations of these two drugs could be envisaged.

Vaccine development

MALARIA

Significant progress has been made over the last biennium with respect to the development and clinical evaluation of promising candidate vaccines for malaria, and specifically, vaccines for *P. falciparum* malaria, the cause of over one million deaths annually, mainly in children under five in Africa. In general during the biennium, TDR played a catalytic and facilitative role in the various vaccine development programmes described below. The vaccine candidates target different antigens from different stages in the life cycle of the malaria parasite.

Pre-erythrocytic vaccine candidates

These are designed to prevent the parasite's infective sporozoite stage from entering or developing within liver cells of an individual bitten by an infected mosquito.

Partners:

- **Aventis (was Hoechst Marion Roussel)**
- **Médecins sans Frontières**
- **Bristol-Myers Squibb**

⁷ Pepin et al. Short-course eflornithine in Gambian trypanosomiasis: a multicentre randomized controlled trial. *WHO Bulletin*, 2000, 78 (11):1284-1295.

A variety of malaria vaccine candidates are under development; one has reached Phase III efficacy trials.



Partners:

- Institut de Biochimie, U. de Lausanne
- Dictagene, Suisse
- SEDAC, Lille

CS-102 plus Montanide ISA 102

The circumsporozoite protein (CS), comprised of a central repeat region and two flanking domains, has been well characterized in murine malaria models and human malarias. CS-102 is a 102 amino acid synthetic peptide segment of the C-terminal region of the *P. falciparum* CS protein (amino acids 282-383) shown to be highly immunogenic in mice and monkeys. A homologous peptide from *P. berghei* conferred protection against sporozoite challenge in mice, and preclinical studies using sera and lymphocytes from Africans living in malaria endemic areas demonstrated that B, CD4+ and CD8+ epitopes (particular sites on antigens to which particular antibodies bind) are recognized in the 102 amino acid sequence. An initial Phase I trial conducted in Lausanne, Switzerland, has provided promising results for safety and immunogenicity and, when sufficient good manufacturing practice (GMP) grade peptide becomes available, additional Phase I/II trials are planned for Europe prior to evaluating the vaccine candidate in Africa.

Partners:

- GlaxoSmithKline Biologicals
- Walter Reed Army Institute for Research
- Medical Research Council, The Gambia

RTS,S plus SBAS2

RTS,S is a leading vaccine candidate comprised of the *P. falciparum* circumsporozoite coat protein co-expressed with hepatitis B coat protein particles and formulated with a novel adjuvant SBAS2. This promising version of a pre-erythrocytic malaria vaccine has evolved from extensive preclinical and clinical studies over the years, conducted in collaboration with the Walter Reed Army Institute in Washington, DC, and the Armed Forces Research Institute of Medical Sciences (AFRIMS) in Bangkok, Thailand. Initial Phase I/II clinical studies with a mosquito challenge showed over 80% protection; however, the duration of this protection appears to be limited to several months only. Subsequent Phase II field studies conducted in The Gambia have confirmed these findings in semi-immune adult volunteers. TDR's input to date has consisted mainly of provision of independent monitoring and review of the project. Currently plans are under way to conduct de-escalation studies in children in The Gambia, using lyophilized RTS,S antigen mixed with the SBAS2 adjuvant at the time of injection. The Malaria Vaccine Initiative has recently agreed to provide major financial support to GlaxoSmithKline (GSK) Biologicals for taking this project forward.

Asexual blood stage vaccine candidates

Vaccines which target these stages of the malaria parasite prevent it from entering or developing in red blood cells.

Partners:

- The CRC for Vaccine Technology, Walter and Eliza Hall Institute of Medical Research (WEHI)/ Queensland Institute of Medical Research (QIMR)/ LaTrobe University
- IMR-PNG Vaccine Solutions
- Biotech Australia

AMA-1 plus Montanide ISA 720

The merozoite apical membrane antigen (AMA-1) represents a leading asexual blood stage vaccine under development in Australia and Papua New Guinea with TDR support. In extensive preclinical studies, AMA-1 has been shown to provide partial protection in rodent and monkey malaria models and to produce high titres of growth inhibitory antibodies when tested in vitro. The current *P. falciparum* version under development by TDR is a recombinant protein expressed in *E. coli* and formulated with the adjuvant Montanide ISA 720. An initial Phase I study in Brisbane, Australia, demonstrated safety but low immunogenicity, likely due to loss of potency. The current focus is on the reproducible production of adequate amounts of GMP clinical grade material for additional Phase I/II trials in Australia and Papua New Guinea.

Partners:

- The CRC for Vaccine Technology, WEHI/ QIMR/LaTrobe University
- IMR/PNG Vaccine Solutions
- Biotech Australia

Combination B plus Montanide ISA 720

Combination B consists of a mixture of three *P. falciparum* merozoite and ring stage-derived recombinant protein antigens (MSP-1/MSP-2/RESA) formulated with Montanide ISA 720 as adjuvant. Clinical studies successfully completed to date include Phase I and Phase II studies in Brisbane, Australia, and Phase I/II studies in Papua New Guinea in children 5-10 years old. A significant reduction in parasite densities was observed in a recent Papua New Guinea Phase II field study, with a 47% efficacy against the 3D7 allele of MSP-2, suggesting that MSP-2 was an active component of the vaccine. The current focus is on production of sufficient quantities of clinical grade materials to conduct Phase III efficacy studies. TDR's input to date has consisted mainly of provision of independent monitoring and review of the project.



EBA 175 plus adjuvant TBD

Erythrocyte Binding Antigen-175 (EBA-175) is a sialic acid binding protein from *P. falciparum* that serves as a ligand for the parasite to bind to the red blood cell with subsequent junction formation leading to invasion. TDR is supporting the development of Region II, a functional binding domain of EBA-175. Rabbit antibodies raised against the pure, functionally active PfF2 region II antigen have been shown to block the binding of erythrocytes and to inhibit parasite growth in erythrocyte cultures in vitro. The methods used to produce the recombinant protein in *E. coli* are currently being scaled up at the International Centre for Genetic Engineering and Biotechnology (ICGEB), New Delhi, India, for use in the production of clinical grade PfF2 for use in Phase I trials. Monkey studies aimed at the identification of a suitable adjuvant for formulation with EBA-175 are under way in collaboration with the Malaria Vaccine Institute in Cali, Colombia.

Partners:

- International Centre for Genetic Engineering and Biotechnology (ICGEB) New Delhi
- ENTREMED

MSP-1-19 plus alum

The major merozoite surface protein-1 (MSP-1) represents the leading asexual blood stage vaccine candidate to date. The 200 kDa MSP-1 precursor undergoes proteolytic processing to yield a series of peptides including a membrane-bound 42 kDa C-terminal moiety. This MSP-1.42 fragment is further cleaved to yield the MSP-1.19 candidate antigen. Several of these MSP-1 candidate antigens have been shown to provide protection in various murine and monkey malaria model systems, and multiple versions of the MSP-1.19 antigen are under development globally. A homologous version of the *P. cynomolgi* MSP-1.19, together with CFA as adjuvant, provided solid protection in the naturally occurring malaria model in TDR-sponsored Toque monkey studies conducted in Sri Lanka. TDR is currently supporting development by the Institut Pasteur of a MSP-1.19 C-terminal version of the *P. falciparum* antigen expressed in baculovirus and initially formulated with alum as adjuvant.

Partners:

- Institut Pasteur, Paris
- European Union
- Swiss Serum Vaccine Institute

MSP-1.42 plus QS-21

As mentioned above, the merozoite-derived MSP-1 is a leading asexual blood stage candidate antigen and up to 12 different versions of candidate recombinant proteins expressed in *E. coli*, yeast, baculovirus and transgenic mouse milk, as well as synthetic peptides, are under development globally. TDR is currently funding the development of a synthetic gene version of the *P. falciparum* MSP-1.42 molecule using insect cell codon composition and not containing a hexa-his tag. A conventional purification scheme has been worked out for the baculovirus-expressed protein, with a satisfactory recovery of purified protein exhibiting the required folding and functional activity. Two novel adjuvants (QS-21 and Montanide ISA 51) have provided promising protection results when tested in challenge studies in *Aotus* monkey experiments conducted in Hawaii. Current activities are focused on the scale up and production of clinical grade MSP-1.42 to be used in Phase I trials in the USA.

Partners:

- University of Hawaii
- AQUILA/ANTIGENICS
- National Institutes of Health, USA

LEISHMANIASIS

The first trial of a vaccine against visceral leishmaniasis in humans was completed.⁸ The trial was conducted by scientists of the Institute of Endemic Diseases, University of Khartoum, Sudan, supported by TDR and assisted by Médecins sans Frontières-Holland, using a vaccine composed of autoclaved *Leishmania major* promastigotes (Fesharki et al at Razi Vaccine and Serum Institute, Iran) mixed with a low dose of bacillus Calmette-Guérin (BCG) (as adjuvant), which was compared with BCG alone. The presence of extensive cross-reactivity between different species of *Leishmania* was the rationale behind this trial of a vaccine, made from *L. major*, which had proved almost 100% effective in langur monkeys against *L. donovani* infection.⁹

The trial was carried out in the Sudan where visceral leishmaniasis is a major cause of morbidity and mortality (a prevalence of 80-130 per 1000 in the study area). Here, as in many other endemic countries, the development of a safe, effective and cheap vaccine would be a long-term solution for controlling visceral leishmaniasis. Drug treatment does exist, but is prohibitively expensive, not easy to administer, not always available, and resistance to it develops rapidly. Vector control is also a possibility, but requires infrastructure that is not available.

Results of the first trial of a vaccine against visceral leishmaniasis showed it to be associated with a lower incidence of disease.

⁸ Khalil EA et al. Autoclaved *Leishmania major* vaccine for prevention of visceral leishmaniasis: a randomised, double-blind, BCG-controlled trial in Sudan. *Lancet*, 2000, 356(9241): 1565-9.

⁹ Dube et al. *Vaccine*, 2001 (in press).



Sudan: leishmaniasis vaccine trial.

In the double-blind study, no evidence was found that two injections of *Leishmania* + BCG offered significant protective immunity against visceral leishmaniasis compared with BCG alone. However, the *Leishmania* + BCG vaccine did induce significantly higher rates of leishmanin skin test (LST) conversion (30%, vs. 7% by BCG alone) at 42 days, which was associated with a significantly lower incidence of disease – responders had a 43% lower incidence of leishmaniasis as compared to LST non-responders (7.2% vs. 12.7%, $p < .003$). Similar results, i.e. lower incidence of disease in LST converted than non-converted individuals, have been obtained in other studies. As BCG alone might have some protective activity against leishmaniasis, as seen in the therapeutic trials of Convit et al in Venezuela, the real prophylactic effect of the vaccine, compared to no vaccine (and not to BCG as in this trial), might be higher. In this trial, BCG was used for ease of keeping the trial blind.

To improve the immunogenicity of killed *Leishmania* vaccines, different adjuvants used in humans are being sought. Safety and efficacy trials of alum-precipitated *Leishmania* + BCG have begun in the Sudan. Preliminary results showed that a single injection produces a dramatic immune response – a strong LST conversion – in every recipient (better than three injections without alum). Multiple doses of *L. major* + BCG vaccine did not prove to be more effective than a single injection in preventing cutaneous leishmaniasis, so development of this vaccine is not being pursued without the addition of alum. Following a successful comparative safety and immunogenicity trial of different formulations of Mayrink's vaccine (killed *L. amazonensis*, produced by Biobras, Brazil), with or without adjuvant,¹⁰ a trial of three injections without adjuvant has begun in Colombia (Velez ID, Universidad de Antioquia, Medellin).

A dozen or so recombinant antigens were recently evaluated as potential second generation vaccine candidates in independent testing coordinated by TDR and conducted in two laboratories in Brazil and Denmark. Unfortunately the results were inconclusive, as not all the control preparations were active. Several second generation vaccines (synthetic peptides and multi-fusion recombinant proteins) are being developed outside TDR, and efforts are being made to create a collaborative programme for these activities, ideally through a consortium which will coordinate the definition, testing and advanced development of promising candidate antigens.

SCHISTOSOMIASIS

There has been some progress in the field of schistosome vaccine development, both in strategic research on the basic immunological mechanisms and in practical field work. In searching for a vaccine, reduction of reinfection without stimulation of the egg-associated granuloma reaction is sought, rather than complete immunity. In this case, transmission would likely not be fully interrupted and natural infection could be counted on to boost vaccine-induced protection. Since schistosomes do not replicate in the human host, even a partially effective vaccine would have a role in control, while the combination of chemotherapy followed by vaccination promises to be an effective intervention with long-term effect. There is evidence that people living in endemic

¹⁰ Velez ID et al. Safety and immunogenicity of a killed *Leishmania (L.) amazonensis* vaccine against cutaneous leishmaniasis in Colombia: a randomized controlled trial. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 2000, 94: 698-703.

Partners:

- Pharos
- Bachem



areas naturally acquire immunity against schistosomiasis, supporting the notion that it should be possible to protect by vaccination against infection and morbidity.

Currently TDR is monitoring two Phase II human field trials, in Senegal and Niger, on a *S. haematobium* glutathione-S-transferase (GST) vaccine candidate developed in France. Results are expected in 2003.

The Schistosomiasis Vaccine Development Programme (SVDP), based in Egypt and supported by USAID, is planning to scale up GMP production and carry out human field trials with an invertebrate muscular protein paramyosin. Another vaccine candidate, a synthetic peptide construct containing multiple antigen epitopes (MAP) of the schistosome triose phosphatase isomerase (TPI), is also being supported but has not reached the same level of development. Sm14, a fatty acid-binding *S. mansoni* antigen, is a Brazilian vaccine candidate which has also reached the scale-up stage. This is of particular interest since it shares protective epitopes with *Fasciola*, another zoonotic liver fluke which infects humans. All these activities are being followed by TDR.

TDR is also sponsoring developmental vaccine work with regard to *S. japonicum* which, apart from limited foci in Laos and Indonesia, is only found in China and the Philippines. Several antigens are at the stage of clinical testing in cattle, pigs and water buffalo, experimental hosts which might reflect the situation in man. A veterinary product could have a positive transmission-blocking effect for human populations.

Diagnostics development

TUBERCULOSIS

Successful implementation of the WHO strategy for tuberculosis control (DOTS) depends upon the detection and treatment of infectious TB cases. The inability to do this quickly and with certainty is one of the primary impediments to improved disease control. Sputum microscopy, the primary diagnostic tool available in most areas of the world, is cumbersome, insensitive, and gives no information about antimicrobial resistance. The poor performance of TB diagnostic tests leaves large numbers of patients undetected, erodes faith in public health services, impedes the expansion of DOTS, increases morbidity, and allows continued transmission of disease. The pandemic of human immunodeficiency virus (HIV) has made this difficult situation much worse.

Rapid, simple, inexpensive and sensitive TB diagnostic tests are urgently needed for (in

order of priority) case detection, drug susceptibility determination, and identification of latent infection. Recently, impressive technical advances, including simplified immunoassay formats, superior reagent preparations, improved understanding of mycobacterial biology, and availability of the complete *M. tuberculosis* genome sequence, have brightened the prospect for diagnostic product development for TB. Harvesting this technical progress to create new diagnostic tools appropriate for low-income settings is the mandate of the TB Diagnostic Initiative. This TDR Initiative has been working with a network of partners in industry, academic research, non-governmental organizations, and public health to facilitate the development, testing, approval, and use of improved diagnostic tools to assist in TB control efforts.

A range of tests are now under development including:

- Nucleic acid amplification and hybridization.
- Phage replication.
- Antibody detection.
- Novel culture methods.
- Cellular immune response detection.
- Antigen detection.
- Physicochemical detection.

Trials in humans of *S. haematobium* and *S. mansoni* vaccine candidates are ongoing or about to begin, while several candidate antigens for an *S. japonicum* vaccine have reached the stage of clinical testing in animals.

The TB diagnostics initiative was established to stimulate and facilitate industry to develop a rapid and simple serologic test for tuberculosis. A range of tests are currently under development.



The TB sputum test is cumbersome and insensitive.

WHO/TDR/CRUMP



These tools are being developed primarily by large and small biotechnology companies, often with close academic collaboration. The role of TDR has been to facilitate commercial development by removing intellectual, technical and logistic barriers to TB diagnostic R&D.

SCHISTOSOMIASIS

The greatest problem related to schistosomiasis is the development of morbidity, which is a slow process that varies between individual patients. Most people have only minor signs of infection but as many as 20 million are seriously ill. TDR has contributed to the development of a standardized procedure for gauging pathology due to schistosomiasis using ultrasound. This technique can be used for all types of morbidity including female genital schistosomiasis which is an important, yet neglected, feature of the disease. TDR has taken the lead in promoting research on forms of

schistosomiasis after transmission has ceased because, even if the disease is eradicated, morbidity from it will continue. For example, in spite of eradication of the disease in Japan more than 25 years ago, there are still many patients in the country with morbidity due to schistosomiasis.

Ultrasonography has become an invaluable extension of the clinical investigation of patients with schistosomiasis as it provides direct evidence of the pathological changes associated with the infection. The manual published by TDR in 2000¹¹ was developed through various draft stages separated by experience in use of the technique. It is expected that a final meeting will be needed

to finalize work on the manual, which began in Cairo in 1990. This final meeting, tentatively planned for 2002, will focus on schistosomiasis (caused by *S. japonicum*) in the Far East but will allow adjustments to be made with respect to examination of patients with *S. mansoni* and *S. haematobium* infections, if necessary.

Ultrasound provides direct evidence of the pathological changes associated with schistosomiasis. An updated practical guide to use of the technique has been produced.



WHO/TDR/CRUMP

Ultrasound can be a valuable tool in investigations of schistosomiasis patients.

¹¹ *Ultrasound in schistosomiasis: A practical guide to the standardized use of ultrasonography for assessment of schistosomiasis-related morbidity.* Document no. TDR/STR/SCH/00.1 available from TDR on request and to download at: www.who.int/tdr/publications/publications/ultrasound.htm



NEW AND IMPROVED TOOLS RECEIVING REGULATORY APPROVAL

MALARIA: Artemotil treatment

Artemotil has been under development by TDR and partners since 1991. During the biennium, clinical development of the compound was completed and the final parts of the clinical dossier were submitted to the Dutch regulatory authorities. On 22 May 2000, the Dutch registration authorities approved two artemotil products (in sesame oil) for the treatment of severe *P. falciparum* malaria by intramuscular injection.

Artemotil (previously known as β -arteether, see Figure 1) is a semi-synthetic derivative of artemisinin, a compound first isolated by Chinese scientists from the plant *Artemisia annua* in 1972, since when a number of derivatives have been developed and registered and have entered use in a variety of countries. Artemotil is the ethyl ether of dihydroartemisinin and is active against all blood schizont stages of *P. falciparum*, including the very early ring forms. It is the first artemisinin derivative to be registered as a single entity according to European standards, and is indicated for patients with severe malaria. Until now the only possibility for treatment of severe malaria, according to European standards, was through intravenous quinine, which currently remains the drug of choice in most parts of the world, despite its sometimes serious adverse effects.

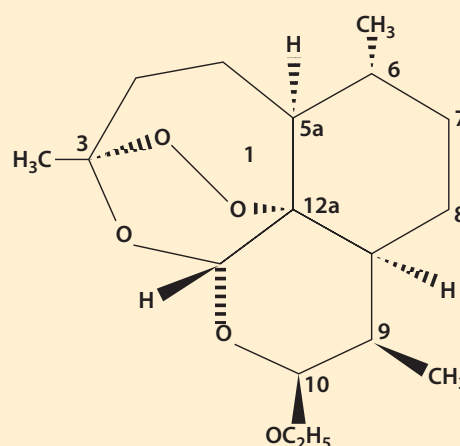
Clinical studies in patients with severe malaria were carried out first in adults, and later in children who could not be treated with oral medication, or who had critical cerebral malaria, in Africa and Thailand. Administration is by intramuscular injection over three days and is restricted to hospitals. No serious or inconvenient side-effects were reported during clinical trials. The drug represents an excellent alternative to quinine, over which it has clear advantages: it causes a swifter decrease in parasite numbers; is simpler to apply; has far fewer undesirable side-effects. Artemotil also has advantages in cases where the patient is not able to retain food (and thus cannot be treated with oral medication).

Now that artemotil is registered in the Netherlands, a programme to extend regulatory approvals to disease endemic countries is to be initiated. If initial experience is good, the drug could be considered for inclusion in WHO's Essential Drugs List, and would then likely be used widely by malaria control programmes.

Partners:

- Netherlands Ministry of Development Cooperation
- Artecef B.V.
- Walter Reed Army Institute of Research

Figure 1. The molecular structure of artemotil



NEW AND IMPROVED EPIDEMIOLOGICAL TOOLS

FILARIASIS: Rapid assessment procedures for *Loa loa*

There is a need to identify areas where people have very high loads of *Loa loa* worms, especially in areas where loiasis co-exists with onchocerciasis, because of the high risk of serious adverse reactions to ivermectin treatment in patients with a high intensity of *L. loa* infection. This information is urgently needed to allow planning for mass treatment campaigns with ivermectin for onchocerciasis in central African countries where *L. loa* may be endemic.

Partly based on earlier work supported by TDR, the threshold for *L. loa* endemicity above which the risk of severe reactions becomes too high for routine treatment with ivermectin has provisionally been set at 20% prevalence of microfilariae (mf), or 5% prevalence of high intensity (more than 8000mf/ml) of *L. loa* infection. A study under way in Cameroon and Nigeria will determine whether a rapid assessment procedure for *L. loa*, based on history of eye worm or Calabar swelling, will effectively identify villages with a prevalence above the stipulated level. The study will also help to better quantify the relationship between prevalence and intensity of *L. loa* infection. History of eye worm (whether worms moving along the white of the lower part of the eye have ever been experienced) or Calabar swell-

A method to help in planning for mass treatment campaigns of onchocerciasis is under development.



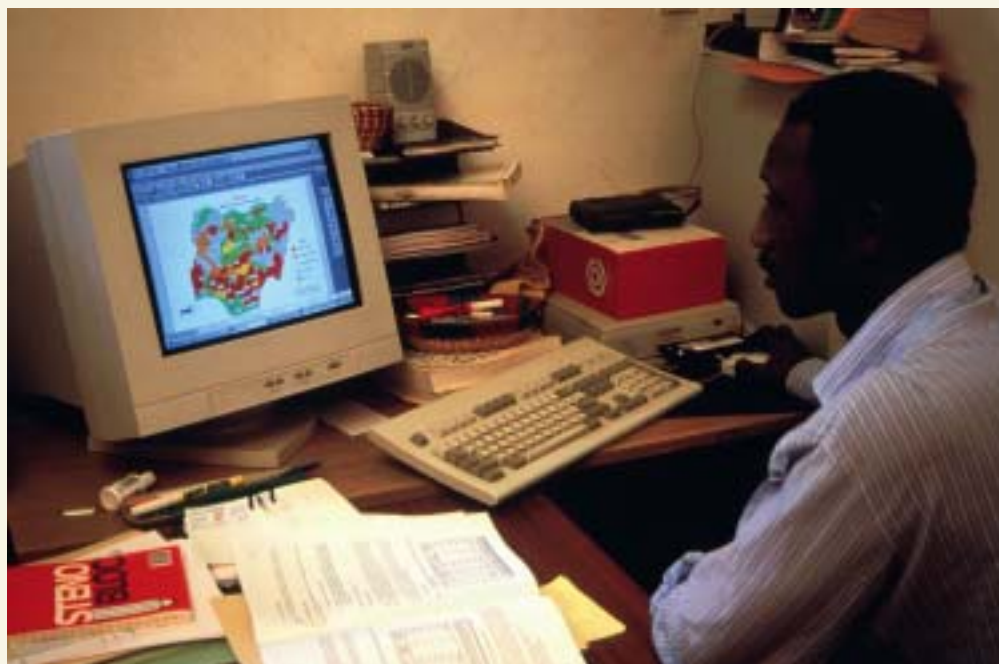
ing (whether swellings under the skin which change position or disappear have ever been experienced) will be gleaned by interviews at both community and individual level.

FILARIASIS: Rapid mapping methods

The method of Rapid Assessment of the Geographical Distribution of Filariasis (RAGFIL) was developed by TDR, as reported in the Fourteenth TDR Programme Report (1997-1998). RAGFIL is based on a 50 km grid sampling technique.¹² In the multicountry study completed in 1999 and carried out in Ghana, India, Myanmar and the United Republic of Tanzania, the prevalence of lymphatic filariasis was estimated by hydrocele examination or antigen testing using the ICT test (an immunochromatographic whole blood card test). The study showed RAGFIL to be effective for clarifying the distribution of Bancroftian filariasis and mapping the approximate contours of levels of endemicity, including areas of very low or no risk. The antigen test (ICT) was found to be a better diagnostic test than clinical examination for hydrocele by health workers. The results from India were less clear than in the other countries. RAGFIL was recommended for use in Africa, with fine-tuning for the first large-scale applications.

In the meantime however, other ideas had emerged about mapping of filariasis, based on use of the implementation unit – the health administrative unit within which residents would receive mass treatment. A standard method for mapping filariasis in Africa has now been agreed upon which combines the strongest elements of the different ideas, including use of the implementation unit and the spatial sampling and

A method for rapidly mapping the distribution of lymphatic filariasis is being implemented on a large scale to help in planning mass drug treatment for elimination purposes.



Rapid mapping of onchocerciasis, developed by TDR, was a forerunner to the rapid mapping of lymphatic filariasis.

¹² Gyapong J, Remme JHF. The use of grid sampling methodology for rapid assessment of the distribution of Bancroftian filariasis. *Transactions of the Royal Society for Tropical Medicine and Hygiene* (in press).

analysis approach of RAGFIL. The mapping of filariasis in Africa will be implemented in phases. The first phase has started in five West African countries and Tanzania. It is coordinated by the programme to eliminate lymphatic filariasis at WHO with technical support from TDR. Four countries have been mapped, showing a huge lymphatic filariasis focus covering North Ghana and Togo and nearly all of Burkina Faso. On the basis of these results, national plans for lymphatic filariasis elimination have now been developed by each of the four countries concerned.



SCHISTOSOMIASIS: Remote sensing and geographical information systems (GIS)

In collaboration with other UN agencies, such as the Food and Agriculture Organization (FAO) and regular budget WHO programmes, TDR promotes research in the field of epidemiology using remote sensing by earth-observing satellites and geographical information systems to produce maps showing the real risk for health. There has been good progress in this area, promising a rapidly improving database of the risk for schistosomiasis in the world. At a team residency in Bellagio, Italy, sponsored by the Rockefeller Foundation in April 2000, an organizational plan was conceived to create a global network of collaborating health workers and earth scientists dedicated to the development of computer-based models that can be used for improved control programmes for schistosomiasis and other snail-borne diseases of medical and veterinary importance. The proceedings are published as a special issue of *Acta tropica*.¹³



GIS mapping in China

WHO/TDR/GRUMP

¹³ A global network on schistosomiasis information systems and control of snail-borne diseases. *Acta tropica*. Eds. Bergquist NR, Malone JB. April 2001, 79 [1]:1-113



New and Improved Methods

Field trials of methods, new drugs and other tools take place under TDR's Intervention Development and Implementation Research (IDE) area. The expected result featuring in this chapter is new and improved intervention methods for using existing and new tools in the clinic and the community. The output and performance indicators include the number of new and improved methods that become valid for prevention,



diagnosis and treatment of neglected tropical diseases, and for rehabilitation of populations exposed to these diseases. This chapter outlines those intervention methods that were validated, or were under validation, during 1999-2000.



METHODS FOR PREVENTION

MALARIA: Prevention of severe anaemia and deaths associated with severe anaemia

In areas of intense malaria transmission, a leading cause of severe disease and death in young children is severe iron deficiency anaemia. *Plasmodium falciparum* malaria contributes significantly to the etiology and severity of anaemia – this role is supported by evidence that, in areas of endemic malaria, the incidence and age pattern of severe anaemia are strongly dependent on the intensity of malaria transmission. The more intense the transmission, the younger the child at risk and the higher the risk of death from severe anaemia, malaria or the two conditions together.

A study funded by TDR and others confirmed the role of malaria, in areas of intense transmission, as the largest contributor to the etiology of severe anaemia in infants, and has also shown that iron supplementation is safe and effective when given orally and daily during the infant's first year of life.¹ In these areas of intense transmission, iron supplementation replenishes the body's iron stores and does not increase susceptibility to malaria. Chemoprophylaxis against malaria, on the other hand, protects against reduction of the body's iron stores and lowers the rate of severe anaemia episodes. The policy question which has followed from these results is whether the World Health Organization (WHO) should recommend iron supplementation or intermittent chemoprophylaxis on a large scale as the most cost effective strategy for preventing severe anaemia in high transmission areas.

To answer this question, three trials have been funded (in Ghana, Kenya and Tanzania) to compare the protective efficacy provided by daily iron supplementation for infants between 2 and 6 months of age through MCH (Mother and Child Health) or EPI (Expanded Programme on Immunization) services, with the protective efficacy afforded by intermittent treatment with sulphadoxine-pyrimethamine (SP) for infants of 2, 3 and 9 months of age through the same delivery mechanism.

The trial in Tanzania has been completed.² The study showed that treatment of infants in a malaria endemic region with a single dose of SP, as a component of the EPI vaccination schedule, led to reduction by half of the incidence of severe anaemia in infancy. These findings open up possibilities for an important new strategy to reduce childhood deaths in malaria endemic regions of the world. The WHO, United Nations Children's Fund (UNICEF) and Global Alliance for Vaccines and Immunization (GAVI) are working in collaboration to prepare for introducing this treatment into practice in selected African countries. The implementation studies will assess how generalizable the findings are in practice in areas of different transmission intensity, and will further investigate the safety (of the drug itself and the effects on EPI antigens) and benefits (avoidance of severe anaemia and mortality) that would accrue through large-scale implementation. Prior to large-scale assessment, a number of issues will need to be clarified, such as the development of an infant dosage form, guaranteed supply of SP, effect of the drug alone in wide EPI implementation on drug resistance to antifolates (if any), and the risk-benefit of other drugs (mefloquine, artecom, pyronaridine) compared to SP for this purpose.

Trials are under way to determine whether iron supplementation or intermittent chemoprophylaxis should be recommended for prevention of severe anaemia in areas of high malaria transmission.

METHODS FOR DIAGNOSIS

LYMPHATIC FILARIASIS: Diagnostic tests for disease mapping and monitoring

A replacement diagnostic test for lymphatic filariasis is being sought because the traditional test is inconvenient and has to be undertaken at night time. For Brugian filariasis, two new diagnostic tests – deoxyribonucleic acid (DNA) diagnostics using a polymerase chain reaction (PCR) enzyme-linked immunosorbent assay (ELISA) or DNA detection strips, and an antibody test – are being evaluated under field conditions. Validation will continue until the end of 2001.

Two diagnostic tests are under evaluation for Brugian filariasis.

¹ Menendez C et al. Randomised placebo-controlled trial of iron supplementation and malaria chemoprophylaxis for prevention of severe anaemia and malaria in Tanzanian infants. *Lancet*, 1997, 350: 844-850

² Schellenberg D et al. Intermittent treatment for malaria and anaemia control at time of routine vaccinations in Tanzanian infants: a placebo-controlled trial. *Lancet*, 2001, 357 (9267): 1471-1477



For Bancroftian filariasis, the immunochromatographic whole blood card test (ICT) has proved to be a rapid, highly sensitive and specific diagnostic test. Following results from a large-scale multicountry trial (see TDR Programme Report 1997-1998), where the test proved excellent in seven countries (Fiji, Ghana, Haiti, Kenya, Myanmar, Papua New Guinea, Tanzania) but not in India (where one-third of the global infected population lives), the test is undergoing re-assessment in India.

METHODS FOR TREATMENT

MALARIA: Treatment for severe malaria

Rectal artesunate has been submitted for registration; discussions are under way as to how best to take the drug into use.

As indicated in the New Tools section of this report, in 2000, TDR submitted a regulatory dossier for rectal artesunate to the regulatory authorities in the USA, UK and Switzerland. It is expected that rectal artesunate will be registered for a new indication for malaria: emergency treatment of acute disease where a patient is unable to take drugs by mouth and unable to access injectable treatment. WHO has submitted an application for accelerated registration of the formulation. Under the US Food and Drug Administration (FDA) regulations (Federal Register Vol 57, No 239), accelerated approval for a drug in a life-threatening disease will, on the basis of the drug's effect on an endpoint that suggests clinical benefit, be given pending completion of studies to establish and define the degree of clinical benefit to the patient.

Trials to verify and describe the clinical benefit of rectal artesunate are currently under way in Tanzania, Bangladesh, Ghana, and will soon begin in Nigeria. These trials will also resolve any remaining uncertainty as to the relation of the surrogate endpoint upon which approval is to be based to the claimed survival benefit.

The purpose of developing rectal artesunate is to reduce the mortality from severe malaria and one of its syndromes, cerebral malaria. It is hoped that the current high mortality levels of 5-35% can be reduced to much lower levels of 0.1-1% through providing early therapy to halt progression of the disease and buy time for the patient to reach definitive therapy.

In the expectation that rectal artesunate will be registered for use in the near future, TDR, Roll Back Malaria and malaria endemic countries are discussing how best to take the drug into use in demonstration projects to resolve anticipated issues such as: the recommended follow-up treatment to rectal artesunate, co-packaging of follow-up treatment with rectal artesunate, making the drug available in countries where the United Nations Children's Fund (UNICEF) has a good presence and where it does not, and health education/information programmes to accompany the drug's launch in a country. It is expected that large demonstration programmes will be funded in three or four malaria endemic countries in the near future to help resolve these issues and demonstrate the potential of the treatment to reduce mortality.



Artesunate suppositories offer hope for reducing mortality.

MALARIA: Home management

Recognition, and early appropriate treatment, of febrile illness in children is the basis of malaria control in endemic countries. In Africa, the majority of children with fever are treated at home, so reaching the home and community more effectively with antimalarial treatment is likely to have an impact on malaria control. Increasing the availability, and improving the use, of effective antimalarials for the treatment of suspected malaria at home has the potential to reduce



the time between onset of symptoms and delivery of treatment, and could result in a reduction in malaria morbidity and mortality.

Research in this area is under the purview of the TDR Task Force on Malaria Home Management. Studies are also funded through the Multilateral Initiative on Malaria in Africa (MIM) and TDR Research Capacity Strengthening (RCS). The focus in 1999-2000 has been in Africa, on the following areas:

- Approaches to providing effective treatment for sick children nearer to the home than in peripheral health units.
- Ways to increase compliance with recommended regimens.
- Mechanisms for appropriate referral for severely ill children.
- Obtaining evidence of the effectiveness and impact of home treatment on the malaria burden.

Within these broad areas, multidisciplinary research has concentrated on the following:

- Investigating appropriate formulations for home treatment (Ghana).
- Exploring the role of unit dose blister packaging and appropriate labeling of antimalarials in improving provider and patient compliance (Ghana, Nigeria, Uganda, Burkina Faso).
- Studying the best ways of delivering blister packs to ensure availability as near to the home as possible (Ghana, Nigeria, Uganda, Burkina Faso).
- Developing and testing methods for providing appropriate information to communities, distributors of blister packs, home care providers and mothers (Ghana, Nigeria, Uganda, Burkina Faso).
- Investigating ways of organizationally sustaining appropriate home treatment (Ghana).
- Identifying and understanding key players in appropriate referral strategies, including investigating the social networks and patterns of referral for children with severe illness, mapping the location of traditional healers and their catchment areas, and exploring ways to involve traditional healers in interventions to promote early referral for appropriate treatment of severe illness in young children (Tanzania).
- Assessing the impact, on under-five mortality, of teaching mothers how to give under five-year-old children early and appropriate treatment with chloroquine (Ethiopia).
- Measuring the impact of home treatment with pre-packaged antimalarials on severe disease (Burkina Faso).

Highlights of achievements during the biennium include the following (see Box 1 for further details):

- Researchers in Ghana found that adherence to treatment with chloroquine syrup was very poor – only 42.4% of clients complied, as compared to 91% of clients who received pre-packaged tablets. About 62% of mothers preferred pre-packaged tablets to syrup.
- Researchers in Ghana, Nigeria and Uganda introduced, for the first time ever, blister packages of antimalarials into community-based treatment outlets.
- There was confirmation that fever and convulsions in children (symptoms of severe malaria) are commonly treated by traditional healers, highlighting the potential role that traditional healers can play in the referral of severely ill children and the need to enlist their support in efforts to improve treatment for severe malaria.
- Researchers in Burkina Faso demonstrated the impact of malaria home treatment on severe disease. The overall reduction of progression towards severe disease among users of pre-packaged treatment was 53.6%.
- A study in Ethiopia showed that a major reduction in under-five mortality can be achieved in holoendemic (where prevalence is fairly uniform) malaria areas through teaching mothers how to promptly provide under-5-year-old children with antimalarial drugs – reducing mortality in this age group by 40%.

More than 50% reduction in progression towards severe disease and 40% reduction in under-five mortality are some achievements of the different practices under trial to improve home management of children with severe malaria.



Prepackaged antimalarials are now being produced in Africa for home use.

WHO/TDR/CRUMP



Box 1. MALARIA: case studies in home management

(1) Researchers in Ghana completed a study to describe and compare the ease of administration of, and costs and adherence to treatment with, chloroquine syrup and pre-packaged tablets in children under five years. The researchers described the problem of adherence to treatment with chloroquine syrup in terms of the kind of measure used, and the frequency and number of days of medication; determined mothers' acceptability of pre-packaged tablets for their children; and compared the costs to the mother of pre-packaged chloroquine tablets and syrup.

The results showed that adherence to treatment with chloroquine syrup was very poor. Only 42.4% of 144 clients who received syrup could do as they were told by the prescriber, compared to 91% of 155 clients who received pre-packaged tablets. A variety of measures with different volumes were used to represent a 5ml teaspoon, ranging in capacity from 1ml to 9ml. Of the clients who received syrup, only 19.4% used an accurate 5ml measure (in the form of a cup or spoon). Others used measures which were either more or less than 5ml. Some clients used two different measures with different volumes to administer the syrup. Adherence to treatment with pre-packaged chloroquine tablets was about twice that with the syrup in all cases. A majority of mothers found the pre-packaged tablets acceptable, convenient and easy to administer – about 61.9% preferred pre-packaged tablets to syrup. The cost of treatment with pre-packaged chloroquine tablets was about one-fourth that of syrup.

(2) Researchers in Ghana, Nigeria and Uganda introduced, for the first time ever, blister packages of antimalarials into community-based treatment outlets. For children aged less than one year, the full-course pack consists of three tablets each of 75mg chloroquine base, to be used at one tablet per day; for children of up to 5-6 years, each tablet consists of 150mg chloroquine base. Results of the impact on early access to high-quality antimalarials and on compliance with the recommended course of treatment will be available in 2001.

(3) Earlier studies in Tanzania based on verbal autopsies for cases of childhood mortality in Bagamoyo District had demonstrated that degedege, a locally defined illness of children characterized by fever and convulsions, was frequently treated by traditional healers. To investigate this further, an ethnographic study was carried out in one village that included in-depth interviews with 14 traditional healers and 3 focus groups with parents. Parents and traditional healers were unani-

mous in their conviction that degedege requires traditional treatments, at least initially, and that these treatments are effective. While traditional healers did refer cases that were not improving to the district hospital, this frequently didn't occur until late in the course of illness, after one or more stages of traditional treatments. Thus the prognosis is poor for children who are suffering from severe malaria.

These results indicated the need to enlist the support of traditional healers in efforts to improve treatment for severe malaria. A larger study was then funded in Kongwe District, Tanzania, to examine the characteristics of social networks and patterns of referral for children with febrile illness between traditional healers, traditional midwives, village health workers and shop owners who sell drugs. It confirmed the potential role that traditional healers can play in the referral of severely ill children. While all the practitioners studied commonly treated or sold medications for mild malaria, severe malaria was most commonly treated by herbalists and specialists in spiritual possession.

(4) Researchers in Burkina Faso demonstrated the impact of malaria home treatment on severe disease. The strategy for prompt and adequate home treatment in Burkina Faso included: re-training of health staff of the local health unit; information and sensitization meetings and training sessions for members of study villages; and availability of pre-packaged antimalarial drugs containing a full course of treatment to homes through trained village volunteers. The drugs were provided in four different colour coded packages for different age groups following the Burkina Faso treatment guidelines (0-6 months, 7-11 months, 12-35 months, 36-69 months), each containing a full course of treatment and labelled with pictorial instructions on how to administer the drugs. The village volunteer sold the drugs at a price previously agreed with the local health management team, which had been calculated to allow for full recovery of the drug's purchase costs and for a 10% incentive margin for the volunteer.

The researchers aimed to increase access to treatment, improve compliance with recommended dosages, and reduce progression of uncomplicated malaria to complicated forms of the disease, thus reducing the incidence of severe malaria. The impact of the approach was assessed through purposely designed, case-controlled epidemiological methods.

At least one volunteer was trained in each of the 375 villages participating in the study. Of the



children that were treated by village volunteers, 56% complied with the treatment over the correct duration.

The rate of progression towards complicated malaria (*benoyaba*) was lower in children with uncomplicated malaria (*memale*) who were treated with pre-packaged antimalarials (5.1%), compared to those who were not treated with these drugs (11.0%) (OR 0.44, 95% CI 0.33-0.58, $P < 0.001$). The overall reduction of progression towards severe disease among users of pre-packaged treatment was 53.6%. In the four target age groups, the progression rate to severe malaria varied between 3% and 7.1% in children who received pre-packaged drugs, and from 8.1% to 18.2% in the control children. In both groups, the highest progression rate was noted in children aged 7 to 11 months, and the lowest in children aged 4 to 6 years.

(5) Researchers in Ethiopia published results of a two-year study which compared the effect on under-five mortality, of teaching mothers how to promptly provide antimalarials to their sick children at home, with an existing community health worker approach.

From 37 tabias (clusters of villages, of total population 70 506) in two districts with hyperendemic to holoendemic malaria, those reported to have the highest malaria morbidity were selected. A census was carried out which included a maternity

history to determine under-five mortality. Tabias were paired according to under-five mortality rates. One tabia from each pair was allocated by random number to an intervention group and the other was allocated to the control group. In the intervention tabias, mother coordinators were trained to teach other local mothers to recognize the symptoms of malaria in their children and to promptly give chloroquine. In both intervention and control tabias, all births and deaths of under-fives were recorded monthly.

Over a 12-month period, 190 of 6383 (29.8 per 1000) children under five years died in the intervention tabias compared with 366 of 7294 (50.2 per 1000) in the control tabias. Under-five mortality was reduced by 40% in the intervention localities (95% CI from 29.2-50.6; paired t test, $p < 0.003$). For every third child who died, a structured verbal autopsy was undertaken to ascribe cause of mortality as being consistent with malaria or possible malaria, or as not being consistent with malaria. Of the 190 verbal autopsies, 13 (19%) of 70 in the intervention tabias were consistent with possible malaria compared with 68 (57%) of 120 in the control tabias.

This study showed that a major reduction in under-five mortality can be achieved in holoendemic malaria areas through training local mother coordinators to teach mothers how to give antimalarial drugs to children under five.

Three factors have influenced plans for the next steps:

- The launch of the Roll Back Malaria initiative with a need for accelerated development of interventions to meet time-specific targets, especially considering the increasing problem of resistance to easily available and affordable antimalarials.
- The commitment by heads of government in Africa for policy change that will make diagnosis and treatment of malaria available as far peripherally as possible, including home treatment, in an effort to make appropriate treatment available and accessible to the poorest groups in the community (the 'Abuja declaration').
- A meeting in Kilifi, Kenya, to identify research gaps and set priorities in malaria home management. Attending were: representatives from universities, institutions and groups likely to undertake the research; groups actively involved in intervention research; advisors/experts in areas relevant to home management of malaria; global, regional and country policy decision makers (from Roll Back Malaria, the WHO Regional Office for Africa, UNICEF).

The main areas of focus have been identified as follows:

- Continued development and testing of feasible and sustainable strategies to change the behaviour and practices of mothers, households and communities in order to increase the extent of early, appropriate care for childhood uncomplicated fever episodes.
- Taking to 'district level' existing experiences in strategies for improving home management for childhood fevers, and measuring their feasibility, effectiveness, cost and impact on the disease burden.
- Development of ways to improve referral practices for severely ill children based on results of studies showing that children with severe malaria symptoms are invariably taken first to traditional healers.
- Determination of how the introduction of new and alternative types and/or forms of antima-



larial drugs can be adapted for providers and users to ensure improvement in home management practices for malaria in children under the age of five years.

- Description of home management of malaria in urban contexts in order to identify potential intervention points and approaches.
- Identification of areas in the process of illness recognition, treatment seeking, referral practices and treatment of childhood fevers that could serve as the focus for future interventions to promote improved malaria treatment in the community.
- Research on how to develop strong links with, and support from, the formal health care system, as home management for malaria cannot stand alone.

Current research to delay drug resistance in malaria is focused on use of an artemisinin drug in combination with other antimalarials. Results from large-scale efficacy and safety trials of combinations are now under analysis, while preliminary data for 'proof of principle' trials, to test the hypothesis that these combinations may delay drug resistance, are being gathered.

MALARIA: Drug resistance and policies

Antimalarial drug resistance is on the increase, particularly in the potentially lethal malaria parasite *P. falciparum*. In some parts of the world, sulphadoxine-pyramethamine has had a useful lifespan of just 5 years, and, in other areas, notably on the Thai-Myanmar border, *P. falciparum* is already resistant to multiple drugs.³ The characteristics of a drug that make it vulnerable to the development of resistance are: a long terminal elimination half-life, a shallow concentration-effect relationship, and mutations that confer marked reduction in susceptibility.⁴ There is now circumstantial evidence from Thailand that the development of resistance can be delayed by combining a well-matched drug pair, i.e. combining one drug that rapidly reduces parasite biomass with a partner drug that can remove any residual parasites.⁵

The total effect of artemisinin combinations (which can be simultaneous or sequential) is to reduce the chance of parasite recrudescence, reduce the within-patient selection pressure, and prevent transmission.

During 2000, TDR tackled drug resistance via two approaches: (i) development of drugs which have different or novel modes of action; (ii) examination of combinations of currently available drugs that have independent modes of action, in particular artemisinin-based combinations. Compliance and cost are important issues in achieving maximum coverage, itself an essential element in achieving the mass effect required to achieve a reduction in resistance and transmission.

The development of new drugs which have different or novel modes of action is covered in the section of this report on New and Improved Tools. The principal drug in new antimalarial combinations (pyronaridine/artesunate and chlorproguanil/dapsone/artesunate) is artesunate. This drug causes a rapid and substantial reduction in the parasite biomass, irrespective of resistance to other antimalarials.^{6,7} Any remaining parasites are then killed off by high concentrations of the companion drugs(s).

In testing the validity of this strategy in the field, three approaches have been used:

- i) Assessment of the efficacy and safety profiles of artesunate (AS) combinations.
- ii) Demonstration of the validity of combination therapy in reducing drug resistance and potentially reducing transmission.
- iii) Assessment of the problems that occur in practice with the introduction of a well matched fixed combination drug such as that based on artemether-benflumetol, recently introduced by Novartis, so that any problems can be avoided when new fixed or sequential dose combination therapies are introduced.

Assessment of efficacy and safety of artesunate combinations has been through randomized, double-blind, placebo-controlled trials in comparison with monotherapy – either sulphadoxine/pyrimethamine (SP), amodiaquine (AQ), chloroquine, or mefloquine. These studies are intended to provide data to policy makers on the appropriateness of different treatment options.

All trials have used a common protocol and analytical plan, amenable to individual patient data meta-analysis, and prepared through an iterative process involving experts and investigators. The studies are conducted according to good clinical practice and are monitored by WHO. Collectively, they represent the largest series of antimalarial drug trials ever conducted, with patients numbering over 4600 enrolled at 11 sites in Africa. Additional studies are being conducted in Latin America. The centres have been selected based on patterns of resistance and

³ Looareesuwan S, Harinasuta T, Chongsuphajaisiddhi T. Drug resistant malaria, with special reference to Thailand. *Southeast Asian journal of tropical medicine and public health*, 1992, 23: 621-34.

⁴ White NJ. Preventing antimalarial drug resistance through combinations. *Drug resistance updates*, 1998, 1: 3-9.

⁵ Nosten F et al. Effects of artesunate-mefloquine combination on incidence of *Plasmodium falciparum* malaria and mefloquine resistance in western Thailand: a prospective study. *Lancet*, 2000, 356: 297-302.

⁶ White NJ, Olliaro PL. Strategies for the prevention of antimalarial drug resistance: rationale for combination chemotherapy for malaria. *Parasitology today* 1996, 12: 399-401.

⁷ White NJ. Assessment of the pharmacodynamic properties of antimalarial drugs in vivo. *Antimicrobial agents chemotherapy*, 1997, 41: 1413-22.



transmission. Capacity building is a specific component of both study conduct and analysis. The primary efficacy end points are parasitological cure at day 14 and day 28. Secondary efficacy parameters are parasite and fever clearance, and gametocyte carriage rates. Studies include molecular genotyping to distinguish between recrudescence infections and reinfections, molecular characterization of mutations conferring drug resistance, and population pharmacokinetic assessments. One study, comparing SP alone with SP combined with either one day or three days of AS, has been published.⁸ The results of the other trials are currently being analysed. Provisional results indicate that AQ is effective in West and Central Africa, but efficacy is declining in East Africa; the addition of AS results in increased efficacy. AQ+AS is therefore an option for use in Africa. SP efficacy is high in West Africa but considerably lower in East Africa; and while the addition of AS results in significantly higher efficacy rates, it is questionable whether AS+SP should be deployed in parts of East Africa because of the increasingly high failure rates seen there. In all cases, the addition of AS to either SP or AQ produces a significantly faster decline in parasite numbers and gametocyte rates.

Preliminary results of the randomized, placebo-controlled studies of artesunate combinations vs. single-agent therapy – three studies with sulphadoxine/pyrimethamine, three with amodiaquine – are shown below:

Outcome	Comparison	Summary no. of events	Summary OR (95%CI)
Radical cure on day 14	AS+SP vs SP	445/485 vs. 404/519	3.05 (2.13, 4.37)
(intent-to-treat analysis)	AS+AQ vs AQ	397/428 vs. 356/422	2.37 (1.54, 3.68)
Gametocyte carriage rate on day 7	AS+SP vs SP	75/485 vs. 307/511	0.13 (0.10, 0.18)
(intent-to-treat analysis)	AS+AQ vs AQ	29/416 vs. 48/419	0.58 (0.36, 0.93)

AS = artesunate combinations

SP = sulphadoxine/pyrimethamine

AQ = amodiaquine

Testing the hypothesis that use of artemisinin combination therapy may delay resistance to antimalarial drugs and, in some epidemiological settings, have an important role in inhibiting the transmission of malaria, is now in its initiation stages. The large-scale trials planned are intended to demonstrate whether the hypothesis is valid through two endpoints: the rate of resistance and the rate of transmission over time.

The main issues to be addressed in the implementation phases are:

- Feasibility and sustainability of implementation of artemisinin combination therapy.
- Elements of successful implementation.
- Factors related to the development and supply of quality, affordable drugs for combination therapy (blisters, fixed-dose co-formulation).
- Mechanisms to delay/prevent resistance.
- Mechanisms to reduce transmission.
- Improvements to individual and/or social welfare through combination therapy: policy instruments and financial factors required.

Two implementation studies have started. Concurrently, potential sites have been funded for the 'pilot' phase, collecting baseline data on drug use, treatment-seeking behaviour and drug expenditure patterns specifically for malaria. Two or more of these sites are likely to be scaled up to the 'demonstration' or 'proof of principle' stage. Concomitantly, mathematical models are being tested for the development and evolution of resistance, and the economic components (cost, cost-effectiveness, cost-benefit) are being studied.

Assessment of problems that occur in practice is a joint effort of TDR and Roll Back Malaria. The main issues being addressed are:

- Choice of appropriate combination treatment, based on the results of the clinical trials mentioned above; the efficacy and safety of other possible options as well as the current first-line treatments; and other factors e.g. predicted longevity, cost, likely adherence to, acceptability of, and development issues concerning the option.
- Elements involved in policy change, including the evidence needed, and better understanding, of the processes involved at national and regional levels.
- Feasibility and sustainability of large-scale implementation of antimalarial combinations through the formal and informal health sectors.

⁸ von Seidlein L et al. Efficacy of artesunate plus pyrimethamine-sulphadoxine for uncomplicated malaria in Gambian children: a double-blind, randomised, controlled trial. *Lancet*, 2000, 355(9201): 352-7.



These and other issues are being dealt with primarily by Roll Back Malaria through consultation with internal and external experts.

AFRICAN TRYPANOSOMIASIS: Epidemiological impact of treatment

The significance of not finding parasites in people who are serologically positive for sleeping sickness has been in question for many years. Of the two cohort studies planned to assess the epidemiological impact of treatment with pentamidine on serologically positive but parasite negative individuals, the study in Uganda commenced during the biennium. The study in the Democratic Republic of the Congo has not yet begun due to political unrest.

LEPROSY: New drug regimens

Since late 1980, three additional antileprosy drugs have been available, namely ofloxacin (a fluoroquinolone), clarithromycin (a macrolide), and minocycline (a tetracycline), each of which acts by a different mechanism. Large-scale field trials of these drugs are ongoing. The drugs have the potential to increase the effectiveness, and shorten the duration, of leprosy chemotherapy. In addition, the use of new drug regimens will help avoid the emergence of drug resistance, and may prove useful for patients who cannot, for one reason or another (e.g. contraindication), take one or more of the drugs that constitute the standard multidrug therapy (MDT). Important ongoing trials are described below.

Ongoing trials of new drug regimens for leprosy should help shorten the duration of treatment and make needed alternative therapy available.

Ofloxacin multicentre trial

With support from TDR, a large-scale multicentre field trial was launched by WHO in 1991-1992, to evaluate the efficacy, safety, acceptability and feasibility of ofloxacin-containing combined regimens in a multicentric, randomized, double-blind, controlled clinical trial in both multibacillary (MB) and paucibacillary (PB) leprosy patients. One of the test regimens was a combination of rifampicin and ofloxacin given daily for four weeks for both MB and PB leprosy. The other two test regimens were for MB leprosy only. One was the WHO recommended multidrug therapy (MDT) for one year, with or without daily supplementation with ofloxacin for the first four weeks, and the control regimen was the standard WHO recommended MDT regimen for 24 months.

Fifteen centres from eight endemic countries are participating in this trial. The intake of nearly 4000 newly diagnosed leprosy patients was completed in June 1994 and the treatment phase was completed in December 1996. Patients will be followed up for a period of 5-7 years after completion of treatment to detect relapses, if any. Final results will be available by mid-2004.

Single-dose ROM trial for paucibacillary leprosy

This trial, in India, is managed by the leprosy programme of WHO through TDR and the leprosy unit's joint Therapy of Mycobacterial Diseases Steering Committee. The objective is to evaluate the therapeutic efficacy of rifampicin, ofloxacin and minocycline (ROM) administered as a single dose for the treatment of

all skin smear negative PB cases. The study is designed as a double-blind, randomized, controlled trial, with two arms. One group of patients is administered ROM as a single dose, with appropriate placebo preparations (PB MDT placebo) for the remaining six months. The other group of patients is administered the standard PB MDT for six months, with appropriate placebo for day one (ROM placebo). Efficacy will be measured in terms of clinical response and relapses. Total duration of the study will be 54 months (12 months of intake phase,



ROM packs, introduced in 1997, are being tested in a single-dose treatment for paucibacillary leprosy.



6 months of treatment and 36 months of post-treatment follow-up). Final results are likely to be available by the end of 2003.

Monthly administration of ROM for multibacillary and paucibacillary leprosy

The main objective of this trial is to study the efficacy of once-a-month doses of the ROM regimen in both PB and MB leprosy patients (3 or 6 doses for PB patients, 12 or 24 doses for MB patients) and in both regular and irregular patients in terms of treatment failure and/or relapse, to assess the strength of the study regimens. The trial is taking place in Myanmar, Guinea and Senegal, and is supported by the WHO leprosy programme. Final results will be available by mid-2007.

Experimental chemotherapy

Recently in the mouse footpad model, three drugs – rifapentine (a rifamycin derivative), moxifloxacin (a quinolone derivative), HMR 3647 (a macrolide derivative) – have shown impressive bactericidal activity. A single dose of a combination of rifapentine, moxifloxacin and minocycline was more bactericidal than rifampicin alone or ROM combination. This work is under support from TDR.



New and Improved Strategies

Research on the implementation of new and improved tools is an area where TDR now places great emphasis. Implementation research is conducted in close collaboration with control programmes. It goes beyond the traditional researchers' terrain, beyond demonstrating that a tool is effective in an experimental field situation, into demonstrating that it is effective in an actual field setting. Implementation research is about putting



research into policy and practice. It produces data needed by control programmes but which they themselves do not have the resources to produce. The expected result is new and improved policies for implementation of control strategies. The progress indicators include improvements in strategies already in use, new control policies and strategies, and new or improved tools brought into routine disease control use.



IMPROVING EXISTING STRATEGIES

MALARIA: Insecticide treated materials

The Task Force on Insecticide Impregnated Bednets held its winding up meeting in April 1999. Although the progress of all uncompleted projects continues to be monitored by TDR, no new projects were initiated during the reporting period.

Ongoing projects are focused on providing staff involved in malaria control at global, regional and national levels with information about the efficacy of treated nets in reducing childhood mortality in Africa, and about how to enhance the effectiveness and sustainability of insecticide treated materials (ITNs, e.g. bednets and curtains) under field conditions.

Completed studies have shown that insecticide treated materials are generally accepted even where they are not commonly used, and are able to repel mosquitos even in areas where there is insecticide resistance. They are more cost-effective than indoor spraying, and can be successfully integrated in most other health and development intervention programmes and community development activities. However, cost and re-treatment practices are always problematical, although the latter issue may be resolved by greater use of the newly-available permanently treated net. Insecticide resistance must continue to be monitored. Community participation in ITN activities is necessary to increase access to these materials, and social marketing techniques have shown promise in this respect. Clear national policies on ITN implementation and promotion are necessary. Continuous interpersonal communication and the use of radio broadcasts are possibly the best channels to use for promotion.

Net Gain 2000, the expanded and revised version of the earlier, very popular International Development Research Centre (IDRC)/WHO/TDR co-publication *Net Gain*, is expected to be completed in 2001. It will be made widely available for use in efforts to improve control strategies in the field.

After the closure of the TDR Task Force on Insecticide-Impregnated Bednets in 1999, reorganization of the communicable diseases cluster of WHO resulted in phasing out of the operational research unit, leaving certain unanswered questions about implementation of ITNs, as posed by the World Health Organization's (WHO's) Roll Back Malaria programme. TDR, through its new emphasis on implementation research, which involves the end-user to ensure that a product can be used effectively and put into practice by control programmes, will be helping to fill these gaps, which include:

- Optimizing the use of ITNs. Currently less than 10% of the target groups in West and East Africa have access to ITNs. To increase access, research will focus on e.g. the effect of community perception of malaria risk on the uptake of ITNs; the trickle down effect on uptake of ITNs of institutional use of ITNs (e.g. in hospitals, boarding schools, hotels) and of implementing ITNs sequentially from urban to rural areas; and perhaps further development and assessment of ITN materials (e.g. hammocks, blankets) for specific population groups including agricultural and forest workers, travellers, refugees.
- Establishing public-private alliances to support ITN implementation. There is evidence that such alliances will be essential to the sustainability and reach of this intervention. Research will help determine e.g. how the two sectors can work together to ensure quality assurance and consumer protection; what is a feasible and effective distribution system for reaching the periphery; what is the role of local production in acceptability, availability, and affordability; what are the optimal regulatory structures for ITNs (taxation, pesticide regulations, etc.).
- Increasing the access to ITNs among the poorest. Unless targeted strategies are developed, there is a risk that the initial costs of ITNs to the buyer will prevent their purchase and lead

TDR studies are helping to improve the use, increase the accessibility, and evaluate the impact of insecticide treated materials.



Kits have been developed to allow people to treat their nets at home.

WHO/TDR/CRUMP



¹ Diallo DA et al. *Child mortality in a West African population protected with insecticide treated curtains for a period of 5 years.* (In preparation.) For further information, please contact: Diallo, DA, Centre National de Lutte Contre le Paludisme, 01 B.P. 2208, Ouagadougou, Burkina Faso.

to low coverage among young children and pregnant women. Research can help resolve what subsidy, financing, and credit options will increase coverage amongst the poorest, and what the relation is between coverage and price of netting and insecticide.

- Increasing the rate of re-treatment of ITNs or the uptake of permanently treated materials. Net re-treatment rates rarely exceed 20-30%. New single-dose, home treatment formulations and alternative technical innovations not requiring re-treatment (e.g. shorter-life low-cost nets, permanent impregnation, wash resistance additives) must be evaluated in terms of compliance and utilization.
- Monitoring of insecticide resistance. Insecticide resistance is a potential threat to the ITN intervention. To develop strategies to monitor and mitigate this issue, we need to know more about: how to identify and manage insecticide resistance; what the epidemiological impacts of insecticide resistance are; how the nuisance induced by non-malaria vectors affects ITN purchase and utilization; and what the effect of choice and dose of insecticide has on properties such as repellence, irritancy, and lethality.
- Evaluating the operational impact of ITNs. Large-scale ITN initiatives are now beginning, so there is a need to develop appropriate monitoring and evaluation tools and strategies. For example, we need to know: what health, social and economic indicators best reflect the impact of ITN use; how we can best document and sustain progress in ITN use in different epidemiological situations; what is the local effect of use of untreated or inadequately treated nets on people who don't have nets (whom the mosquitos are diverted to feed on). More research is needed on the long-term mortality impact of ITNs (although some data are now available from the long-term follow-up in Burkina Faso¹), and on the operational and health impacts of integrating ITNs with other health and nutrition interventions (e.g. integrated management of childhood illness, safe motherhood, vitamin A supplementation).

TUBERCULOSIS: Fixed dose combinations of four drugs

In its current activities, TDR is focusing on assessing the utility of fixed dose combinations of four drugs (isoniazid, rifampicin, ethambutol, pyrazinamide) in TB control in low-income countries. The first priority is operational research to build the evidence base to support the use of four-drug fixed-dose combinations (4FDCs) in developing countries – ease of procurement, ordering, distribution, storage, prescription, and consumption; and the prevention of emergence of resistance. This work will be linked to research capacity strengthening efforts. The second priority is to conduct clinical trials for safety and efficacy of the new 4FDCs.

To properly manage this work, a task manager will be recruited by TDR during 2001. In addition, owing to the shift of epicentre of the global tuberculosis epidemic from Asia to Africa, the need becomes paramount to develop new strategies to combat TB in high HIV prevalence settings. In collaboration with STOP TB and its partners, TDR is developing a workplan for 2002-2003.

ONCHOCERCIASIS and LYMPHATIC FILARIASIS: Community directed treatment

TDR has been developing the method of community directed treatment (ComDT) for onchocerciasis and lymphatic filariasis for a number of years. Because the treatment for these two diseases is safe and simple – single-dose tablets taken just once a year – involving the community in its own treatment is entirely feasible.

For onchocerciasis, community directed treatment (ComDT) with ivermectin has been adopted by all endemic countries in Africa as the principal strategy for drug delivery. It has proved extremely effective in achieving the treatment coverage required to eliminate onchocerciasis as a public health problem – during the year 2000, some 20 million people received ivermectin treatment through ComDT. A recent external evaluation of APOC, which covers 16 endemic countries in Africa, concluded that 'ComDT has been a timely and innovative strategy ... and communities have been deeply involved in their own health care on a massive scale. ...ComDT is a strategy which could be used as a model in developing other community based programmes'.

The objective of the African Programme on Onchocerciasis Control

TDR is focusing on assessing the utility of fixed dose combinations of four drugs.

In onchocerciasis, the emphasis now is on making community directed treatment sustainable when support from the African Programme for Onchocerciasis Control and the Onchocerciasis Control Programme comes to an end. In lymphatic filariasis, a combined community/health services system of community directed treatment in Africa resulted in treatment coverage thought sufficient for filariasis elimination.



Ivermectin is such a safe drug that it can be distributed easily by trained villagers.

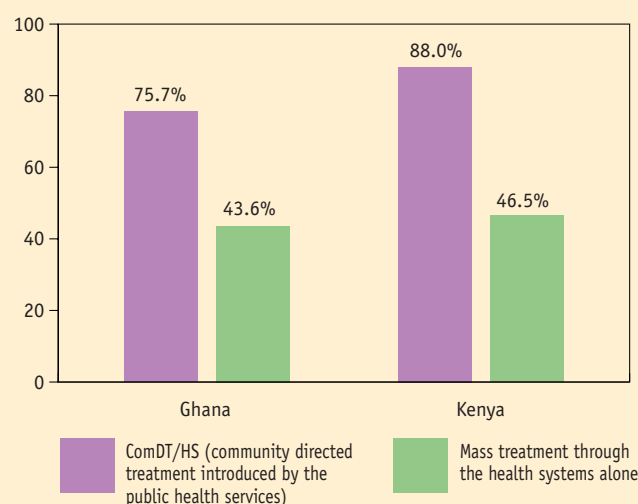
(APOC) is to 'establish effective and self-sustainable community-directed ivermectin treatment throughout the remaining endemic areas in Africa'. APOC will provide support for the introduction and establishment of ComDT for a maximum period of five years, hence the emphasis now is on making ComDT sustainable for onchocerciasis control after this time. A multicountry study recently indicated that interaction between the community and health staff is poor, and that involving health workers and village representatives in local stakeholder's meetings can help reinforce the ComDT process. Stakeholder's meetings bring together community representatives, health workers and members of community based organizations to plan ComDT. Before the introduction of ComDT, health workers had a negative attitude to community involvement in health care activities. However, their attitude became much more positive after they had had experience with ComDT. Measured on a special attitude scale, there was a statistically significant improvement in health workers' attitudes to ComDT, both for regular ComDT and for ComDT with stakeholder's meetings, but more so with the latter approach. The stakeholder's meetings were felt to offer a valuable forum for planning and solving problems, and ministries of health in several APOC countries are now exploring the use of such meetings in their national control programmes.²

For lymphatic filariasis, a multicountry study completed during the biennium compared mass treatment of communities through the public health system alone, with mass treatment delivered through a community directed system but with significant public health services involvement. In the latter system, the community's role is to decide how to implement the treatment, and to select its own drug distributors, who will distribute the drugs at the convenience of the community, while the health service's role is to introduce the concept to the community, train the distributors, and help with monitoring and supervision. The study produced different results in Africa and India.

In Africa, the combined community directed/health services system resulted in significantly greater treatment coverage than achieved by the health services alone, and this coverage was thought to be sufficient for filariasis elimination (Fig. 1). Community directed treatment was particularly

² Implementation and sustainability of community directed treatment of onchocerciasis with ivermectin: report of a multicountry study. Document No. TDR/IDE/RP/CDTI/00.1, available from TDR on request and for download from: www.who.int/tdr/publications/publications/cdti.htm

Figure 1. Filariasis treatment coverage by distribution method





important when a community was situated more than 5km from the nearest health services facility. ComDT was thus recommended as the drug delivery strategy for lymphatic filariasis elimination in Africa.

In India, drug delivery by the combined health services/community approach achieved less coverage than delivery by the health services alone, but even in the latter case, coverage was generally not thought sufficient to achieve elimination. The study showed that good coverage was associated with strong political and administrative commitment, with motivation and training of health workers, with more effective communication between the health worker and community, and with greater involvement of the community. The most effective strategy was drug delivery through the regular health system but with active community involvement.

An important problem was compliance with treatment: 10-15% of the population did not swallow the drug even though they had received it. Reasons included fear of side effects and lack of perceived benefits of taking the drugs. A significant proportion of refusals was due to the number of tablets (up to six DEC tablets for an adult), and the study recommended changing the current formulation of diethylcarbamazine (DEC) tablets. The immediate benefits perceived by the community are very minimal, and the current advocacy materials and strategies were considered inadequate. It was recommended that more effective advocacy approaches be developed for filariasis elimination in India.

LYMPHATIC FILARIASIS: An advocacy campaign

Lymphatic filariasis has been targeted for elimination by 2020. The key elimination strategy is mass treatment with a single dose of two-drug treatment. For the elimination programme to be successful, over 75-80% of individuals within a community must take the two-drug treatment. As mentioned above, research shows that in India it was difficult to achieve sufficiently high rates of coverage in a routine campaign of mass treatment. In an attempt to increase coverage, the TDR Task Force on Filariasis Intervention Research commissioned a multicentric study on advocacy for lymphatic filariasis in India. The research protocol was developed at a workshop in which researchers, control programme managers, and communications experts from a variety of sectors (private and public) took part. Targeting the individual (as opposed to the community) with the advocacy package was felt to be important because people have to see a benefit themselves from the treatment in order to actually take it. The core messages developed for the advocacy campaign were:

- Lymphatic filariasis can affect YOU !
- Get rid of lymphatic filariasis
- Take a single dose of DEC every year

At the time of writing, the draft framework for advocacy and the advocacy package are being tested in several districts in India. The study will indicate if a professional advocacy package can boost treatment coverage to the levels required and, if so, what the cost would be.

ONCHOCERCIASIS: Reporting and monitoring of community directed treatment

As mentioned in the TDR Programme Report (1995-1996), one aspect of community directed treatment that needed improvement was that of reporting. Reporting of treatment coverage was found to be not at all reliable.

A pictorial reporting form was first developed in 1994, then tested by research teams in several countries, and subsequently used in actual studies of community directed treatment with ivermectin. However, the operational use of the form has been limited, as most communities tend to select literate drug

distributors who can use the regular forms.

Recently the Onchocerciasis Control Programme (OCP) has shown renewed interest in the pictorial form for use in some areas with very low literacy rates, and is organizing a final validation before operational application. A concept paper demonstrating the development and testing of the pictorial form was published in 2000.³

TDR enlisted the help of scientists and communications experts to help devise an advocacy campaign.

A reporting form for use in illiterate populations is being validated for operational use by the Onchocerciasis Control Programme in West Africa.

³ Haaland A et al. *Community directed implementation of health projects. Reporting with pictures, a concept paper for researchers and health policy decision-makers*, 2000. Document No. TDR/IDE/RP/00.1 available from TDR on request and for download from: www.who.int/tdr/publications/publications/pictures.htm



LYMPHATIC FILARIASIS: Community based management of lymphoedema

There are two basic components of a lymphatic filariasis elimination programme: the control of transmission through mass treatment, and the control of manifestations of the disease through management of the signs and symptoms. Simple hygiene practices can help alleviate the manifestations of lymphatic filariasis, such as filarial fever and the huge swellings of elephantiasis, and it has been shown that lymphatic filariasis patients can be managed at district health

facilities using basic skin care procedures. A multicountry study using such practices is being undertaken in Africa (where approximately one-third of global cases occur). The aim of the study is to develop a sustainable strategy for management of the manifestations of lymphatic filariasis in Africa.

TDR is undertaking a multicountry study to determine how best to introduce simple hygiene practices to help alleviate the symptoms of lymphatic filariasis (e.g. elephantiasis) into routine use in Africa.



Simple hygiene practices can help alleviate the manifestations of lymphatic filariasis.

CHAGAS DISEASE: Advancing interruption of transmission

The incidence of Chagas disease in Latin America continues its downward trend due to interruption of transmission by vector triatomine ('cone-nosed' or 'kissing') bugs and blood transfusion. TDR sponsored the analysis of epidemiological data on seroprevalence in the early 1980s that were used for comparison with the current figures.⁴

During the biennium under review, ten of twelve endemic states in Brazil were confirmed free of vectorial transmission of Chagas disease, based on epidemiological and entomological data presented by the Brazilian Ministry of Health at the Ninth Meeting of the Intergovernmental Commission of the Southern Cone Initiative in Rio de Janeiro, March 2000.

In 1999, the prevalence of human *Trypanosoma cruzi* infection in the 0–7 year age group for the whole country was 0.28% as compared with 5.0% in 1980, representing a 95% reduction of incidence since 1980 (Fig 2). The prevalence rate of infected blood in blood banks in the country has also decreased by 90% (from 7.0% in 1980 to 0.73% in 1998). Household insecticide spraying activities are now concentrated in the states of Bahia and Tocantins, the two states that are still positive for the vector *Triatoma infestans*.

Ten out of twelve states in Brazil endemic for Chagas disease have been confirmed free of vectorial transmission.

⁴ Camargo M et al. Inquerito sorológico da prevalência de infecção Chagásica no Brasil 1975/1980. [Serological survey on prevalence of Chagasic infection in Brazil 1975/1980.] 1984, *Revista do Instituto de Medicina Tropical de São Paulo*, 26(4):192-204.

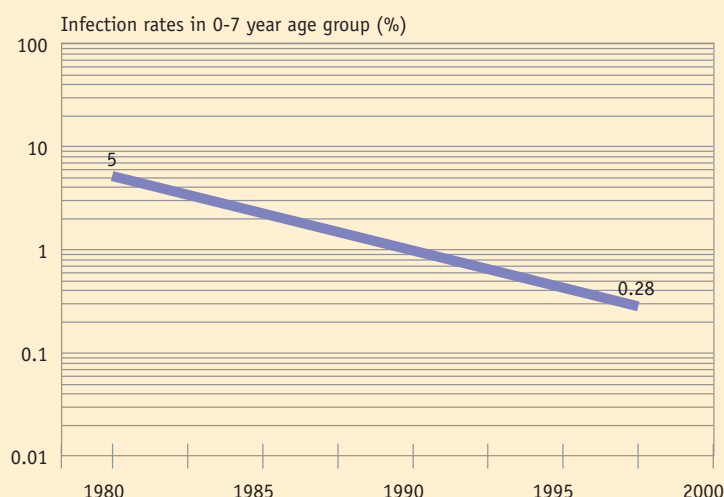
⁵ see: Jaramillo C (principal investigator). Chagas disease. TDR Final Report Series No. 21 December 2000.

CHAGAS DISEASE: Determining the origin of vectors

From the control programme's perspective, it is necessary to know the origin of the Chagas disease vectors present inside rural houses, i.e. whether they originate from domiciliated or wild populations of *Rhodnius prolixus*, the insect which transmits Chagas disease in Colombia. This vector is not strictly domestic as it is found also in the sylvatic and peridomestic environments, from where it can invade human dwellings in rural areas.⁵

Use of the randomly amplified polymorphic DNA

Figure 2. Interruption of transmission: Brazil 1980–2000



Source: Ministry of Health, Brasília, Report to the IX Intergovernmental Commission, Rio de Janeiro, March 2000



Application of the randomly amplified polymorphic DNA technique indicates that domestic populations of *Rhodnius prolixus* are genetically distinct from wild populations.

(RAPD) technique has now shown that each of the two vector populations – the domestic and the sylvatic – has a distinct genetic identity. In the study, the domiciliated population was composed of insects captured inside houses, where different stages in the life cycle, eggs and faeces, provided evidence of the permanence of infestation. The sylvatic population came from palm trees situated within a radius of 3-100 metres of the dwellings.

On application of the RAPD technique to insects captured in houses that had previously been sprayed with insecticide, it emerged that all the insects belonged to the domestic population. There were visible and consistent differences in electrophoretic RAPD patterns between the two insect populations, which might provide evidence of reproductive isolation and discontinuity between the populations.

Genetic distances were calculated, and phenograms with different numbers of markers were constructed, using pair group analysis. The analysis showed clearly that the two populations had distinct origins. The rate of migration of 0.6 insects per generation is not enough to maintain genetic homogeneity between the populations and confirms that there is very low, if any, genetic flow between them. Moreover, the sylvatic population showed higher intrapopulation variability and the domestic population reduced genetic variability, which implies that selection for new attributes – e.g. development of resistance to insecticides – will be less likely.

CHAGAS DISEASE: Assessing the influence of climate on triatomine populations

Changes in climate, whether due to modifications at the regional or global levels, are likely to affect the distribution or population dynamics of triatomine bugs only to the extent that they affect the insect's microenvironments e.g. relative humidity, temperature, illumination. Studies of the impact of microclimate variables on the insects have continued during the biennium.⁶ For several species of triatomine, field measurements have been consistent with laboratory results, underscoring the relevance of conducting both kinds of study simultaneously. *Triatoma brasiliensis*, in Ceará, Brazil, prefers a dry microclimate, although egg hatching and ecdysis in this species are successful in a wide range of relative humidities which characterize the natural refuges of this species. In contrast, both laboratory and field studies indicated that *T. infestans* in Argentina is a species that is more dependent on low relative humidity.



Rhodnius prolixus : domestic and sylvatic populations can be identified.

WHO/TDR/STAMENIS

The effects of climate need to be monitored to evaluate the impact of control programmes and the efficacy of insecticides.

NEW CONTROL POLICIES AND STRATEGIES

MALARIA: Defining a strategy for appropriate use of rapid diagnostics

The recent evolution of diagnostic technologies has added a new dimension to malaria control efforts. The most widely used diagnostic approach for malaria – clinical diagnosis – is unreliable (because the symptoms of malaria are non-specific and overlap with other febrile diseases), while technical and logistic requirements make microscopic confirmation difficult at the peripheral level. Thus the introduction of rapid diagnostic tests for malaria is of considerable interest.

Rapid immunochromatographic dipstick tests have been developed that detect parasite antigens from a fingerprick blood sample. These tests are simple to use, require minimal training, and show reasonable sensitivity and specificity. There has been no consensus, however, on their appropriate use. To address this issue, TDR joined with Roll Back Malaria and the US Agency for International Development (USAID) to sponsor an international consultation, in October 1999, on malaria diagnostics, focusing on the role of rapid diagnostic tests. The meeting brought together experts

⁶ Lorenzo MG et al. Aspectos microclimáticos del hábitat de *Triatoma brasiliensis* [microclimatic properties of the *Triatoma brasiliensis* habitat]. *Cadernos de Saúde Pública*, Rio de Janeiro, 2000, 16(Sup.2):69-74.



from the field, leading test developers and manufacturers, potential users and other interested partners.

A consensus emerged that rapid diagnostic tests would be most useful in areas where there is low or moderate transmission of malaria, especially in remote regions where microscopy is not available and where multidrug resistance requiring the use of expensive drugs is common. Other suitable settings for use include suspected malaria epidemics, complex health emergencies, care of non-immune persons such as travellers or military personnel, and confirmation of severe malaria. In contrast, dipstick diagnostics are unlikely to be of any value in regions where prevalence is fairly uniform and where asymptomatic parasitaemia is common. An important product of the meeting was a list of laboratory and field research studies that must be performed before the use of rapid diagnostic tests can be optimized. A full meeting report is available in hard copy and on the TDR website.⁷

LYMPHATIC FILARIASIS: Impact of mass treatment on transmission

TDR is involved in the development of a computer simulation model – LYMFASIM – which will be used to predict the impact of mass treatment campaigns on the transmission of lymphatic filariasis. The model is still under development at the University of Rotterdam. A beta version is ready, and the final computer programme is likely to be available before the end of 2001, along with a manual. The model will be used to predict the effect of treatment coverage, treatment duration, and drug regimen on elimination of transmission.

A number of critical issues are being addressed before the model becomes fully operational for disease control. One issue is meta analysis of published data on the age-specific patterns of prevalence and intensity of *Wuchereria bancrofti* infection. Age-specific patterns of infection are indicative of the effect of immune factors and hence are a key factor for modelling the transmission dynamics and predicted impact of mass treatment. Currently the model is fitted to an infection pattern for an urban area in India, and it was important to determine how representative this pattern is for all endemic areas. Preliminary results indicate that there exists one general age-specific pattern for India and another slightly different pattern for Africa, but both showing a plateau in infection levels after the age of 30 years. The analysis was done by an epidemiologist from a research team in India who,

Rapid diagnostic tests for malaria might be most useful in areas where there is low or moderate transmission of malaria, specifically in suspected epidemics, confirmation of severe malaria, and care of non-immune persons.

TDR is helping to develop guidelines for lymphatic filariasis elimination strategies. A computer simulation model is being developed to predict the impact of mass treatment, and large trials are under way to determine the effect of mass treatment on transmission of the disease.

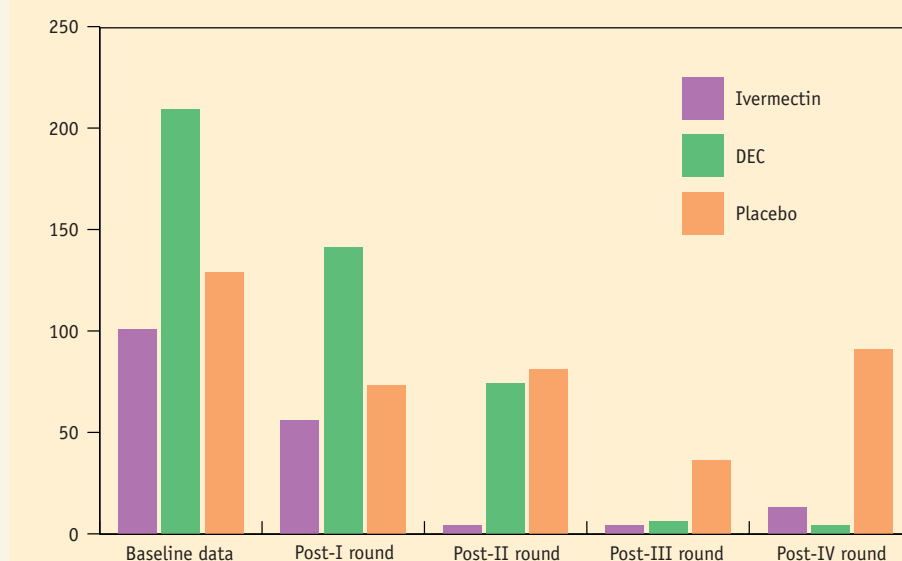


LYMFASIM computer simulation model of the transmission of lymphatic filariasis.

⁷ Malaria diagnosis: new perspectives. World Health Organization, 2000. Document no. WHO/CDS/RBM/2000.14; WHO/MAL/2000.1091 available on request from TDR and for download from: http://www.who.int/tdr/publications/publications/malaria_diagnosis.htm



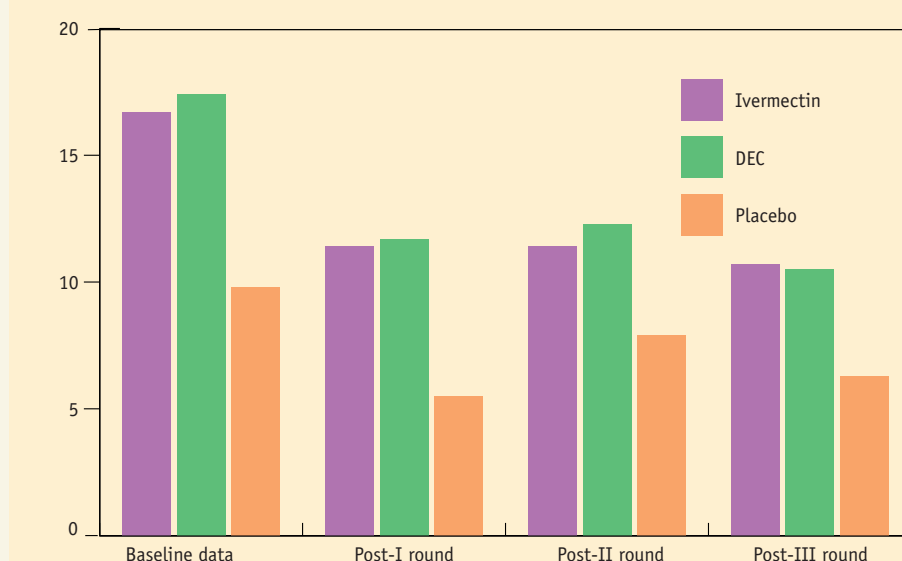
Figure 3: Impact of four rounds of treatment on mean monthly transmission potential



with TDR/Research Capability Strengthening support, also received training in meta analysis of epidemiological data.

The model is part of a package to develop guidelines for lymphatic filariasis elimination strategies based on current drug combinations. Other parts of the package include transmission trials and related field experiments. For example, a large transmission trial is under way in rural areas of Tamil Nadu, South India, to determine the effect of six years of treatment on transmission of lymphatic filariasis. Results after four rounds of single-dose treatment, with either ivermectin or DEC, are now available (Fig 3). After four cycles of treatment, the prevalence and intensity of *W. bancrofti* microfilaraemia in the human population was significantly reduced, and, more importantly, so was the infectivity of the culicine mosquito vectors and, therefore, transmission. Although transmission continued to occur, mosquito infection and infectivity rates declined

Figure 4: Impact of three rounds of treatment on monthly incidence of acute adenolymphangitis episodes in treated communities





steadily throughout the time period. The primary effect in humans seems to be on infection rather than morbidity however, and no effect was apparent on the incidence of the acute form of the disease – adenolymphangitis (ADL) or filarial fever – which contributes to the burden of disability (Fig 4). This apparent lack of effect on acute filariasis after the first rounds of mass treatment may discourage compliance with treatment and contributes to the low perceived benefit of treatment as shown in other studies.



Partnerships and Capacity Building for Research and Product Development

From early on, TDR realized that the key to progress was to establish networks of organizations, forming partnerships across the world, across countries, across scientific disciplines and across political boundaries. Today, TDR is at the hub of the largest and most successful partnership network of its kind – thousands of researchers and research institutions are involved in the creation of new knowledge and in research



WHO/TDR/GRUMP

and development (R&D) for new and improved approaches to control of tropical diseases. Since 1975, TDR has worked to strengthen the capacity of disease endemic countries (DECs) in research skills, in conducting the necessary research to develop and use new disease control technologies, and in better identifying needs. Now that considerable research expertise is available in DECs, TDR is promoting use of this capacity, the individuals and the institutions, in TDR R&D and research training activities. Thus, the emphasis is on setting up partnerships and providing specific capacity building support to enable countries to carry out needed R&D.

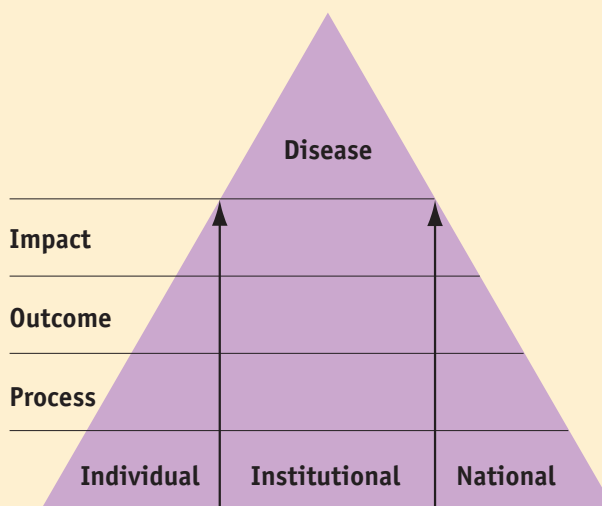


The output indicators used to evaluate this area of work are those recommended by the 1999 Prospective Thematic Review of TDR Research Capacity Strengthening,¹ which fall into three categories (process, outcome, impact) and are applied at three levels of action (individual, institutional, national), as represented in Fig 1.

In accord with the World Health Organization (WHO), TDR is reaching out, initiating and promoting partnerships which work towards common specified goals. From their unique global standpoint, WHO and TDR are able to reach out to all corners of the globe, forming relationships with a diversity of partners in health. In her speech to the Fifty-first World Health Assembly in 1998, Dr Brundtland, Director-General of WHO, said that reaching out to others was a basic need for making a difference in world health. She invited those who had real contributions to make, to join with WHO, and called on the international community (“they carry a major responsibility”), the nongovernmental organization (NGO) community (“Where would the battle against leprosy, TB or blindness have been without the NGOs?”), the private sector (which “has an important role to play both in technology development and the provision of services”), and the public sector (“Countries need a well performing public sector”), to take up the challenge. “We must help the health systems to cope. We must help make the scientific advances available also to the developing world.” This is not to forget also the academic sector, so essential for making those scientific advances through research and training – the specialties of TDR.

Since that time, the number of partnerships has been increasing exponentially. Below are described a selection of the partnerships within which TDR is currently interacting, grouped according to where the action is focused.

Figure 1. Schematic presentation of the levels of evaluation and impact of investments in research capacity on disease prevention and control



PARTNERSHIPS FOR NEW KNOWLEDGE

The *Anopheles gambiae* genome network

TDR now coordinates an international network of partners in efforts to decipher the genome of *Anopheles gambiae*, a mosquito which transmits malaria in Africa. This network grew out of the initial studies supported by TDR before and during 1999-2000. See pages 16-17 for further details of this partnership.

Parasite genome networks

The parasite genome networks stimulated by TDR² continued during 1999-2000. Sequencing activities are still ongoing, but in some of the networks, efforts are now concentrated on identifying genes and targets for drugs and vaccines. Activities and progress of TDR supported studies in conjunction with these partnerships are described on pages 11-15.

Immunology

Targeted training in the area of immunology of infectious diseases has been implemented by the WHO Immunology Research and Training Centre in Lausanne, Switzerland, for some years. The major aim of these training activities is to reinforce, in DECIs, the human and technical resources for applying immunological and biotechnological means to fight infectious diseases. Since the end of 1998, the activity has been fully integrated in TDR. Two external reviews in the last eight years have recognized the value and importance of the training. Its impact in DECIs is

In the generation of new knowledge, the international partnerships in genome are good examples. In the dissemination of knowledge, the partnership with the Immunology Research and Training Centre in Switzerland is cited.

¹ Prospective Thematic Review of TDR Research Capacity Strengthening, 15-17 November 1999. Geneva, TDR, document number: TDR/RCS/PTR/00.1, available on request from TDR and for download at www.who.int/tdr/publications/publications/rsc.htm

² Johnston DA et al. Genomics and the biology of parasites. *Bioessays*, 1999, 21:1331-147.



becoming clearly visible – an observation also reflected by the results of a thorough retrospective evaluation among participants (more than 800 to date) and the increasing number of applications (now >200/year). In order to optimize the impact, the training courses are constantly evaluated by the participants, the facilitators and the organizers, and periodically by external reviewers.

Basic ‘core’ courses are held in Switzerland. These are complemented by regional courses, co-organized by former participants to a core course. The courses comprise specific teaching modules which cover, comprehensively, selected topics and include practical sessions. For further details, see Box 1.

Box 1. Immunology training courses

Two advanced courses of eight weeks each, on *The applications of immunology, biotechnology and vaccinology to the control of infectious diseases*, were organized at the WHO Centre in Lausanne in 1999. Thirteen professionals participated in a course given in French (May-June) and 20 professionals participated in a course given in English (September-October). The participants came from: Bolivia, Burundi, Cuba, Guinea, Laos, Mali, Mauritania, Morocco, Niger, Senegal, Togo, Viet Nam, Brazil, Egypt, Ethiopia, Guatemala, India, Kenya, Myanmar, Nigeria, Sri Lanka, Sudan, Thailand and Uganda. An advanced refresher course on *Immunology, biotechnology and vaccinology applied to infectious diseases*, of three weeks duration, was also organized in 1999 at the National Institute of Virology in Pune, India (December 1999). Such continuing education courses are mainly addressed to professionals from a given area who have previously attended a core course in Switzerland. This particular course was attended by 21 professionals from: India, Iran, Mongolia, Myanmar, Sri Lanka, Thailand and Viet Nam.

In 2000, an advanced training course on *The applications of immunology, vaccinology and biotechnology to the control of infectious diseases*, of 8 weeks duration, was again organized at the WHO centre in Lausanne. This course was attended by 18 professionals from: Bangladesh, Bhutan, Brazil, China, Colombia, Cuba, Egypt, Ethiopia, Ghana, Kenya, Myanmar, Nepal, Nigeria, Sri Lanka, Sudan, Thailand, Uganda and Viet Nam. An advanced refresher course (three weeks) on *Immunology, vaccinology and biotechnology applied to infectious diseases* was again organized, in December 2000, this time at the National Institute of Health, Maputo, Mozambique. The 23 participants (of whom 20 had previously attended a core course in Switzerland) were from: Cameroon, Ethiopia, Ghana, Kenya, Mozambique, Nigeria, Sudan, Tanzania, Zambia, and Zimbabwe.

A total of 58 facilitators, each an expert in his/her respective field, participated in the teaching during these courses. The facilitators came from: Italy, Switzerland, France, Korea, the Netherlands, United Kingdom, Canada, South Africa, Nigeria, India, Zimbabwe and Mozambique.

Funding partners

- **Swiss Agency for Development and Cooperation (SDC)**
- **WHO/TDR**
- **WHO Regional Office for South-East Asia (SEARO)**
- **International Union of Immunological Societies (IUIS)**

PARTNERSHIPS FOR NEW AND IMPROVED TOOLS

Partnerships cited in the area of new tools include several multi-institutional partnerships in malaria and TB drugs and diagnostics, and technology transfer partnerships.

Partnerships in **MALARIA**

MMV – The Medicines for Malaria Venture³

During 1999-2000, TDR was instrumental in helping to conceptualize, incubate and establish the Medicines for Malaria Venture (MMV), a novel public/private partnership for the discovery and development of antimalarial drugs. MMV was launched as an independent not-for-profit Swiss Foundation in November 1999 with the assistance of its founding co-sponsors (see list).

MMV co-sponsors

Founding co-sponsors:

- **World Health Organization (WHO)**
- **International Federation of Pharmaceutical Manufacturers Associations (IFPMA)**
- **World Bank**
- **UK Department for International Development (DFID)**
- **Swiss Agency for Development and Cooperation**
- **Global Forum for Health Research**
- **Rockefeller Foundation**
- **Roll Back Malaria Partnership**
- **Minister of Development Cooperation of The Netherlands**
- **TDR**

During the past year, the

- **Bill and Melinda Gates Foundation**
- has also become a major funding partner.*

³ www.mmv.org



MMV is a response of the private and public sectors to the growing crisis of malaria. MMV aims to fund and manage the discovery and development of new medicines for the treatment of malaria in DECs – see Box 2 for projects currently being funded. MMV's vision is a world in which the impact of malaria is significantly reduced by available, affordable and effective new medicines.

Box 2. MMV: Current projects

Project funding was initiated in 2000 with the selection of three highly rated major 'discovery' projects (see below). It is anticipated that MMV will take on drug development projects in 2001. Much effort was put into securing appropriate agreements that enabled this funding to take place in a manner consistent with MMV's mission, namely that MMV will have the rights to antimalarial development candidates arising from this research and the ability to take them forward into development. These rights will enable MMV to secure a price that is appropriate for the final products resulting from this research.

Project 1: Inhibitors of lactate dehydrogenase

MMV funding earmarked for this project is around US\$1 million per year. Its real value however, is substantially higher because of the 'in kind' contributions of GlaxoSmithKline (GSK), particularly related to high throughput screening of its compound libraries. The project is based around a key enzyme involved in malaria metabolism, lactate dehydrogenase, that has not previously featured as a drug target, but which is essential for parasite growth.

Partners:

- University of Bristol
- London School of Hygiene and Tropical Medicine
- GlaxoSmithKline

Project 2: Synthetic peroxide antimalarials

This project will cost MMV around US\$1 million per year. Its real value, however, is again substantially higher because of Roche's 'in kind' contributions of equipment and preclinical development support. The project is based around a class of low-cost synthetic peroxide antimalarials that address the deficiencies of the current artemisinin derivative drugs.

Partners:

- University of Nebraska
- Swiss Tropical Institute
- Monash University
- F. Hoffmann-La Roche

Project 3: Inhibitors of cysteine proteinases

MMV is providing support to this project of around US\$2 million per year and, again, 'in kind' contributions from GSK increase its true value. The project is based around a cysteine proteinase involved in malaria haemoglobin degradation, falcipain 2, that has not previously featured as a drug target, but which is essential for parasite growth.

Partners:

- University of California San Francisco
- GlaxoSmithKline

Seedcorn projects

MMV is supporting three smaller projects on:

- inhibitors of dihydrofolate reductase (US\$50 000) – at Mahidol University, Thailand.
- inhibitors of dihydroorotate dehydrogenase (US\$100 000) – at Leeds University, UK.
- inhibitors of haem polymerization (US\$100 000) – at University of California Berkeley, USA.

A second call for proposals

Due to enhanced funding, notably from the Gates Foundation, MMV has been in the position to advertise for a second round of project proposals. Over 85 applications were received in late 2000, with over 15 of these falling into the category of drug development. A preliminary short-listing of 12 projects (six discovery projects and six development projects, many involving industrial partnerships) was made in November 2000 for a final selection in March 2001. The goal was to select at least three more projects to enter MMV's portfolio in 2001, with at least one of these to be a development stage project.

MMV operated throughout 1999 and much of 2000 from temporary premises in TDR. After the appointment of a chief executive officer in 2000, MMV moved to its own premises in Geneva, Switzerland. However, TDR remains in close operational partnership with MMV through the coordinator of TDR's Product Research and Development unit, who sits on the Board for MMV.

It is envisaged that MMV and TDR will continue to collaborate and interact closely in the area of malaria drug R&D and on broader issues relating to malaria chemotherapy.

**JPMW partners:**

- Chugai
- Daiichi
- Dainippon
- Eisai
- Fujisawa
- Sankyo
- Shionogi
- Sumitomo
- Suntory
- Takeda
- Yamanouchi
- Yoshitomi
- Japanese Ministry of Health and Welfare

The JPMW

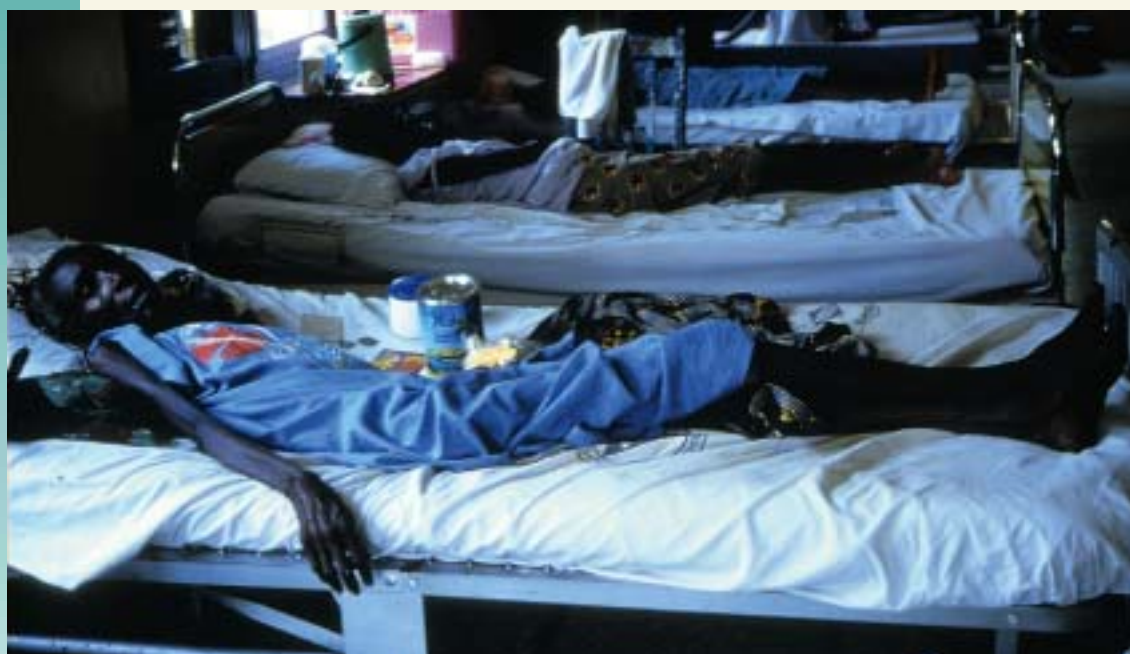
A partnership between 12 Japanese pharmaceutical companies, the Japanese Ministry of Health and Welfare, and TDR, under the acronym JPMW, was formally launched in Japan in October 1999, when plans were laid to screen different chemical entities from the chemical libraries of the involved pharmaceutical companies and Kitasako Institute. TDR was involved with the JPMW from the beginning, since initial discussions in Japan in 1995.

Some of the chemicals in the libraries to be screened have already given rise to successful medicines, but have never been examined for antimalarial activity. First the compounds will be screened in vitro against the intra-erythrocytic stages of chloroquine-resistant *Plasmodium falciparum* at Kitasako Institute in Tokyo. Any compounds that show activity will be examined in further detail in vitro, including testing of structurally related compounds. Any compound that still looks promising will then enter TDR's drug development pipeline. The different partners in the initiative contribute from their pool of human and financial resources, from their confidential chemical libraries, and from their store of knowledge and experience of antimalarial R&D; while they will accrue benefits from intellectual property rights and public relations, and from the prophylactic antimalarial market in developed countries.

On average, 10 000 different molecules are screened for every new product that emerges from the pharmaceutical industry. So, in screening some 2000 compounds a year, the expectation is that a new class of antimalarial drug will emerge within 5-10 years.

Partnerships in tuberculosis**The Global Alliance for TB Drug Development⁴**

Like MMV, the Global Alliance for TB Drug Development (GATB) is a not-for-profit venture that aims to accelerate the discovery and development of new drugs, in this case, for tuberculosis (TB). GATB is committed to developing drugs that are accessible and affordable by those countries worst affected by the disease – drugs that will shorten and simplify treatment, and be effective against multidrug resistant TB. Provision of leadership, raising funds, advocacy, and coordination of efforts in developing new treatments are among the functions of GATB, which



Treatment of TB is vital in people co-infected with HIV.

estimates a 60% chance of first registering a drug by 2010. Capabilities in endemic countries will be employed whenever appropriate.

TDR played a key role in shaping the GATB. Representatives from academia, industry, major development agencies, non-governmental organizations, and donors from around the world met in early 2000 to discuss obstacles and opportunities for the development of new drugs for tuberculo-

⁴ www.tballiance.org



sis, and the GATB was formally inaugurated later in the year. TDR Director Dr Carlos Morel was elected Chairman of the Board.

One third of the global population is currently infected with TB and nearly 6000 die from the disease each day. Although the present multidrug schedule of treatment (an integral part of the WHO's DOTS strategy for TB control) cures some 82% of those receiving treatment under DOTS programmes, only some 25% of all TB patients are gaining access to such programmes. One of the major reasons for the low penetration of the DOTS strategy is thought to be the long duration of treatment and its complexity. The same applies to the reasons for the 6-7% of patients who default. A shorter, simpler treatment is therefore urgently needed, with a total duration of not more than 2-3 months. Similarly, new drugs are also needed to combat the rise of multi-drug resistant disease. Prevention of TB in those latently infected is vital especially in people co-infected with human immunodeficiency virus (HIV). No new anti-TB drug has been introduced into routine practice in the last 30 years.

Diagnostics initiative⁵

The Tuberculosis Diagnostics Initiative (TBDI) was established in 1997 to facilitate the development and evaluation of new tools, appropriate for low-income settings, for the diagnosis of tuberculosis. The Initiative functions as a partnership involving disease control officials, public health experts, academic researchers, regulatory agencies and representatives of the diagnostics industry. The TBDI strategy relies on the fruitful collaboration of these partners and the expertise of the diagnostics industry. With a small initial budget, TBDI worked to facilitate the sharing of resources and to stimulate commercial investment in the development of TB tests for use in DEC. The biotechnology industry responded quickly, recognizing the urgency of the problem and the huge size of the diagnostic market for TB. The number of commercial and academic/industry collaborative groups has increased markedly in the past three years, with over 50 such groups now identified in an ongoing survey of commercial activity in TB diagnostic development.

The most pressing obstacle to industry progress in new diagnostics identified by TBDI partners in the past was the availability of reference clinical materials. This led to the development of the TB Specimen Bank, now holding over 10 000 aliquots of material from six different collaborating clinical sites. Recent funding from the Bill and Melinda Gates Foundation will allow TDR to markedly augment the scale of its TB diagnostic activities in 2001. In addition to an expanded TB specimen bank, TBDI will be able to provide guidelines for trials, revised goals for technical performance, suggestions for trial design, specimen and isolate banks, and good clinical practice capable trial sites. In addition, TBDI will initiate direct funding of trials to evaluate test performance and the impact of implementation.



The TB specimen bank in Boston was developed to fulfil the need for clinical reference materials.

WHO/TDR/CNMP

Technology transfer

TDR's technology transfer initiatives aim to help advanced developing countries improve their own research and development (R&D) capacities.

⁵ www.who.int/tdr/diseases/tb/tbdi.htm

Thailand Tropical Disease Research Programme

An excellent example of such an initiative is the Thailand Tropical Disease Research Programme (T-2). This programme, established in 1997, focuses on the discovery and development of new products such as drugs, diagnostic kits and vaccines for tropical diseases. It promotes the transfer of technology and know-how to Thailand as well as strengthening of collaboration between Thai and foreign scientists in the field of tropical diseases.

During the first 3 years (1998–2000), key activities have included:

- Exchange of Thai and foreign investigators and training of investigators in specialized fields (e.g. medicinal chemistry, screening of biological activity) in Thailand and abroad.

Partners:

- Thailand Research Fund
- National Science and Technology Development Agency/
National Center for Genetic Engineering and Biotechnology of Thailand (NSTDA/BIOTEC)
- TDR



- Workshops on good laboratory practice (GLP) and preparation for the development of good clinical practice (GCP) in the clinical development programme. The implementation of these principles will ensure that the data produced from drug and vaccine development studies are reliable, of high quality and acceptable to regulatory authorities internationally.
- Initiation of development of an artemisinin derivative for use by the Thai malaria control programme. This will be the first drug developed and registered by Thai scientists, in Thailand, to international quality standards.
- Use of a high throughput screening system – a newly-developed and simplified method – to screen some 6500 samples of Thai natural products and synthetic compounds, of which almost 1000 returned positive antimalarial indicators. Some of these are being further evaluated.
- Development of a polymerase chain reaction (PCR) method to detect *Wuchereria bancrofti* in mosquitos. This could be used as a tool to monitor and evaluate the filariasis control programme in Thailand.
- Establishment of two special tuberculosis laboratories. In one, more than 2200 samples of pure compounds and natural products have been screened for anti-TB activity. In the other, research is ongoing on characterization of strains of *Mycobacterium tuberculosis* in Thailand (over 1500 strains collected in the first two years).

PARTNERSHIPS FOR NEW AND IMPROVED METHODS

IFPMA/WHO round table

The International Federation of Pharmaceutical Manufacturers Associations (IFPMA) is a non-profit, non-governmental organization having consultative status with many international organizations including the WHO. Members of the IFPMA include regional and national associations

representing research-based pharmaceutical companies and manufacturers of prescription medicines, but not individual pharmaceutical companies as such. Objectives of the IFPMA are to advance the health and welfare of the peoples of the world through dealing with questions such as health legislation, science, research, and promotion of ethical principles and practices.

TDR works with the IFPMA through the IFPMA/WHO Working Group on R&D for drugs for neglected infectious diseases. This working group set out, during the biennium, to identify barriers that prevent industry from re-engaging in this area, and to prioritize the needs in neglected infectious diseases and the best incentives to ensure that industry becomes re-engaged.

Considering the two main priority diseases of malaria and tuberculosis, in 1999, the Working Group supported the development of MMV and the GATB and developed product profiles for new antimalarial drugs, which were passed to MMV, and profiles for anti-TB drugs, which were passed to GATB. The Working Group continues to monitor the activities of MMV and the GATB. A second tier of priorities for drug development, based on disease burden and future trends, existing interventions, drug R&D needs and priorities, has now been identified and includes: African trypanosomiasis, Chagas disease, filarial infections, gastro-intestinal roundworm infestations, leishmaniasis, non-specific diarrhoeas, schistosomiasis. Mechanisms for drug R&D for these diseases are now under discussion, and proposals are expected by November 2001.

As to incentives for re-engaging industry, it is agreed these would include mechanisms to improve the financial returns on R&D investment, e.g. introducing mechanisms for lowering R&D costs such as tax credits, and models such as MMV, where costs are paid by a third party ('push' mechanisms). Additionally, new means by which R&D costs can be recouped in the market place would be needed, e.g. extending patent rights or periods of market exclusivity, or establishing a drug purchase fund ('pull' mechanisms). Instituting such incentives would involve not only the commitment of WHO and industry but also the commitment of all governments of developed and developing countries and NGOs.

The MSF/drugs for neglected diseases working group

TDR and Médecins sans Frontières (MSF) have established a close collaboration for accelerated development of, and improved access to, drugs for the treatment of neglected diseases, in particular for drug combinations for malaria.

Cited here are multi-institutional partnerships with non-profit/non-governmental status and a focus on neglected infectious diseases.



TDR contributes to the Drugs for Neglected Diseases (DND) Working Group, a multidisciplinary and independent working group, initiated under MSF's international Campaign for Improved Access to Essential Medicines. The DND was created to elaborate new and creative strategies, involving both the public and the private sectors, to ensure that new and affordable medicines are developed for the treatment of life-threatening and debilitating diseases that predominantly affect impoverished populations. Cognisant that such endeavour requires a significant re-orientation of drug development and access, the DND approach emphasizes the greater role that DEC's need to play in the development of such drugs, through capacity building and technology transfer, in order to produce sustainable solutions to the problem. Specific areas of activity are: the R&D agenda and advocacy; capacity building and technology transfer; the legal and regulatory framework; finance and market access. The DND is currently generating comprehensive background papers and in-depth analyses of the different aspects of the neglected disease problem, and is producing an inventory of partnership matches to develop, primarily in DEC's, specific drug treatments for African trypanosomiasis, leishmaniasis and malaria.

TDR and MSF are also jointly funding clinical trials to assess the efficacy and tolerability, as well as the pharmaceutical development, of blister packs and fixed-dose co-formulations of antimalarial drug combinations including artesunate.

PARTNERSHIPS FOR NEW AND IMPROVED STRATEGIES

In these partnerships, mostly of governmental/inter-governmental nature, action is focused on methods for control and on the best ways to introduce these methods into use.

MALARIA: Roll Back Malaria⁶

Launched in October 1998, the Roll Back Malaria (RBM) partnership is committed to halving the global malaria burden by 2010. RBM places much emphasis on research and development (R&D) and supports TDR's technical leadership role in this area. A collaboration between TDR and RBM aims to review progress, identify gaps and define priorities in intervention research, product development and capacity strengthening in

R&D for malaria; to work with the global scientific community through a range of partnerships and initiatives to effectively pursue identified research priorities; and to quickly transfer the products of research and development into policy and practice.

TDR and RBM plan to achieve this goal through composite workplans, joint organization and funding of technical expert meetings, and direct funding of priority research areas.

Priority research areas in 1999-2000 included trials of antimalarial drug combinations to reduce drug resistance, development of rectal artesunate for use at community level, strategies to improve home management of uncomplicated malaria, and research capacity strengthening. RBM also provides financial support for various other TDR activities such as monitoring of disease burden through TDR/Multilateral Initiative for Malaria in Africa (MIM); development of new drugs (e.g. LAPDAP-artesunate triple combination), vaccines (blood-stage and transmission-blocking vaccines), diagnostics (rapid diagnostic tests), and intermittent treatment in pregnancy. Many of these activities can be read about in the pages of this report. With the RBM emphasis on getting research findings into policy and practice, there is particularly close interaction in the area of implementation research. R&D meetings that were co-funded during 1999-2000 included those on home management, in Nairobi, Kenya, and on malaria diagnostics. In addition, an RBM Fellow works with TDR in the area of drug resistance. There has also been a series of joint seminars.

TUBERCULOSIS: Network of disease endemic country trial sites

As soon as TB was incorporated into the TDR disease portfolio in 1999, TDR began to develop a network of TB researchers and trial sites for new methods and strategies through support to research capacity strengthening activities. A variety of training grants are available to individuals and institutions, for training support and research projects which support 'on-the-job' training. A first call for applications for TB-related work was made in late 1999, from which two projects were supported in Mongolia. A more focused call for applications, for institutional capacity strengthening and individual training, was made in September 2000. This call was addressed to least devel-

RBM: Founding partners

- World Bank
- United Nations Children's Fund (UNICEF)
- World Health Organization (WHO)
- United Nations Development Programme (UNDP)

⁶ www.rbm.who.int



oped countries only. From some 40 projects received, about 30 were reviewed by the Research Strengthening Group (RSG) in mid February 2001.

ONCHOCERCIASIS: the Onchocerciasis Control Programme and the African Programme for Onchocerciasis Control

TDR works closely with two partnerships in river blindness – the Onchocerciasis Control Programme (OCP) and the African Programme for Onchocerciasis Control (APOC). These two control programmes aim to eliminate onchocerciasis from Africa. OCP operations are based on insecticide spraying, whereas APOC operations are based on treatment with ivermectin as vector control is not cost-effective in APOC countries. Current work in conjunction with these two international control partnerships can be found in the section of this report on New Strategies.

Chagas disease: Multi-governmental initiatives

In 1999-2000, the three separate multi-governmental initiatives formed in the past two decades for elimination of Chagas disease have continued to make their impact felt. TDR's role in these initiatives is, along with regional organizations and bilateral agencies, to help mobilize resources at the global level to finance research on Chagas disease (on new drugs, elimination of the parasite from blood banks, diagnostics, vector control methods), and to help in international coordination and linking of researchers. A network of national institutions, working in collaboration with government control programmes, has been established as a result.

The first initiative was that of the six countries in the Southern Cone region. In this region, house infestation with triatomine vectors fell by up to 90% between 1982 and 2000. Disease transmission by vectors and blood transfusion has now been halted in Uruguay, Chile and Brazil, while interruption of transmission in Argentina, Bolivia and Paraguay is expected by 2003. In 1998, the World Health Assembly approved a resolution (WHA51.14) acknowledging the advances in interruption of transmission in the Southern Cone countries and indicating the entomological and epidemiological research needed to carry out and evaluate the other two initiatives – of the Andean and Central American countries. TDR is now helping with some of this research.

In the Southern Cone, specific legislation requiring serological screening of donors was introduced in all the countries to prevent transmission of *Trypanosoma cruzi* through blood transfusion. Since 1995, 325 000 new cases annually of infection by *T. cruzi* have been prevented and 127 000 cases of cardiomyopathy and sudden death have been prevented. Economically speaking, the countries have saved more than US\$1140 million in health care expenditure and social security costs.

Table 1. Changes in epidemiological parameters due to interruption of transmission and decrease in incidence of Chagas disease, 1990-2000

Epidemiological parameters	1990	2000
Annual deaths	>45 000	21 000
Cases of human infection	16-18 million	18 million
Annual new cases	700 000	200 000
Population at risk	100 million	40 million
Distribution	18 countries	15 countries

The average reduction of incidence in the Southern Cone is 94%, which translates to a reduction of 65% in the whole of Latin America. From an estimated 700 000 new cases per year in 1983, there were less than 200 000 cases per year in 2000, as shown in Table 1. The major challenge in the Southern Cone countries now is to ensure sustainability in a situation of very low *T. cruzi* where decentralization of operations in ongoing health sector reforms could mean that priorities change. The model implemented in the Southern Cone has been adapted in the other two initiatives, of the Andean and Central American countries, where the vectors are different and control is based on insecticide spraying as well and blood screening. TDR has sponsored entomological and epidemiological studies to help the control programmes of these countries define vector distribution and mobility in endemic areas, and prevalence of infection among young age groups as a baseline for measuring the impact of vector control activities.



The target date for interruption of transmission in the Andean countries is 2010. Some countries of this initiative have identified areas of transmission, completed the early exploratory phases for their control programmes and introduced blood screening. Other countries (e.g. Venezuela) have been running control programmes based on insecticide spraying and improved rural housing since the 1960s, and here the incidence of infection is already substantially reduced.

The Central American Initiative was launched in 1997. The objectives of this initiative are to eliminate the vector *Rhodnius prolixus* from El Salvador, Guatemala, Honduras and Nicaragua (feasible by 2005 in the latter three countries); reduce infestation with the vector *Triatoma dimidiata*, a sylvatic vector that also lives in houses, throughout Central America; and screen 100% of blood donors for the presence of the *T. cruzi* parasite.

PARTNERSHIPS WITH A MULTI-ORIENTED APPROACH

MALARIA: MIM/TDR Initiative⁷

The Multilateral Initiative on Malaria in Africa (MIM)⁸ is an international partnership in scientific research against malaria. Under this initiative, TDR set up the MIM/TDR Research Capacity Strengthening Task Force in 1997. This task force promotes capacity strengthening in Africa through R&D of new tools for malaria control, and through promoting partnerships and collaborations, and technology transfer and training opportunities.

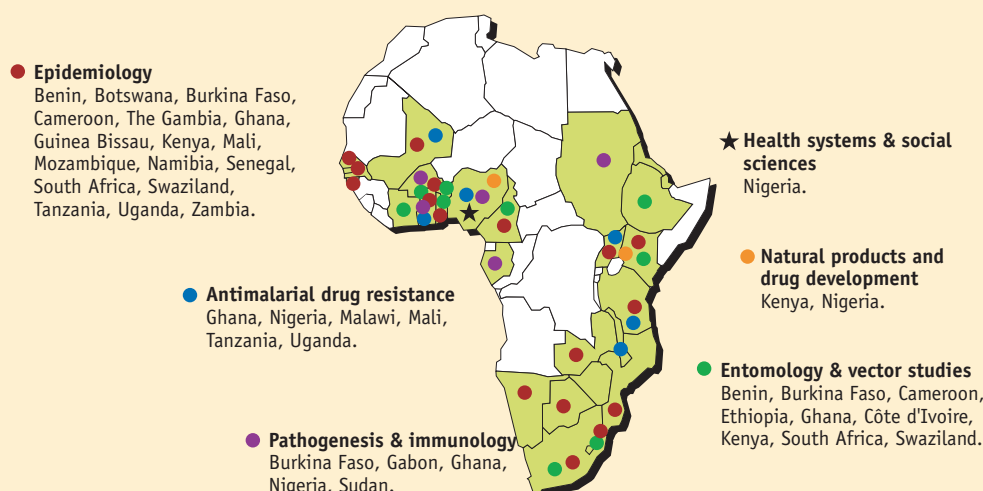
During the biennium, the second (1999) and third (2000) rounds of grant proposal reviews were completed. Of the 112 proposals reviewed since 1998, 23 are being supported, in the following areas:

Epidemiology. Analysis of the severity, risk and impact of malaria at regional and national levels, and monitoring and evaluation of malaria control activities, are contributing to various ongoing international networks devoted to these issues (the Mapping Malaria Risk in Africa project; International Network of Field Sites for Continuous Demographic and Health Evaluation; WHO's Roll Back Malaria partnership).

Immunology and pathogenesis of malaria. Five projects are being supported under a network for malaria immunology and pathogenesis. The projects focus on: the relationship between transmission intensity and clinical malaria and immunopathology; risk factors and the immunopathology of severe anaemia in falciparum malaria in children; antibodies that (indirectly) prevent malaria parasites from infecting red blood cells.

Many of these partnerships are concerned with training capacity for research in DEC's. Some of the partnerships are multi-institutional; TDR also forms partnerships with individual researchers and individual institutions through a variety of research and training grants.

MIM/TDR projects and networks in Africa



⁷ www.who.int/tdr/diseases/malaria/mim.htm

⁸ <http://mim.nih.gov/>



Chemotherapy. Eight projects in the area of antimalarial drug policy and chemotherapy, coordinated through a network, provide information on the pharmacokinetics of drugs used in management of malaria, employ common protocols to evaluate the different elements which contribute to antimalarial drug resistance, and provide data to inform antimalarial drug use and policy.

Natural products. Identification of antimalarial and insect repellent components in plants used by indigenous populations for (respectively) treatment of fevers and as insecticides are the focus of three projects. The TDR/MIM scientists interact with indigenous communities and traditional health practitioners to obtain information, select and identify lead plants.

Entomology. Three multicountry research projects in entomology and insecticide resistance are being supported. Techniques used to detect resistance and identify species have been integrated into African laboratories, and a regional insecticide resistance monitoring network and research programme is being instituted in collaboration with the WHO Regional Office for Africa.

Health systems research. In this area, a project to improve home management of malaria through better community knowledge of the disease, improved practices, development of new products and improved collaboration between public and private health care providers, is being supported.

The TDR/MIM task force also coordinates group learning activities, to enhance collaboration among African investigators and promote interaction with investigators from more advanced laboratories in Europe and North America. During 1999-2000, these activities were focused on: safe handling and management of biological materials; access to new malaria research opportunities e.g. the Malaria Research and Reference Reagent Resource Center (MR4); markers of antimalarial drug resistance (practical, clinical and epidemiological applications); molecular markers of antimalarial drug resistance; immunology and pathogenesis of malaria.

These activities of the MIM/TDR task force are now yielding tangible results with the emergence of a new corps of young African scientific leaders who conduct research in their home countries in collaboration with African, European and North American institutions.

Health Internetwork

In 2000, four TDR research partners in Africa were awarded, along with other centres in Asia and Eastern Europe, a 'package' by a team of public and private partners including the World Health Organization (WHO). These awards are part of a wider United Nations programme called Health Internetwork, which aims to improve global public health by facilitating the flow of health information worldwide using Internet technologies. The package consists of hardware, wide band connectivity, and full access to several databases and more than 100 medical journals. In the pilot phase, the selected centres will help work out how to introduce locally-produced information to the Internet, stressing priority public health programmes and local translation and adaptation as necessary. They will also work out how to expand the project to the rest of their country and region, and how to evaluate its impact. The four TDR partners selected for the awards in Africa were:

- Noguchi Memorial Medical Research Institute, Accra, Ghana.
- Malaria Research and Training Centre, University of Mali, Bamako, Mali.
- Makerere University Medical School, Kampala, Uganda.
- National Institute for Medical Research, Dar es Salaam, United Republic of Tanzania.

TDR individual/institutional partnerships

TDR works with a great many individual researchers and research institutions. During 1999-2000, there were 402 renewals of contracts and 763 new contracts for projects. A variety of grants are available for these partners, as described below.

Small grants programmes

Small grants programmes are viewed by TDR as an effective mechanism to support young investigators, particularly graduate students, beginning their research career. The programmes are conducted with the WHO Regional Offices for the Americas (AMRO), the Eastern Mediterranean (EMRO), and Europe (EURO), and are especially important in least developed countries and countries with less developed research capacity. The focus of the scheme is on high burden coun-



tries, with particular attention to postgraduate student theses (AMRO), control-related research (EMRO), and operational research (EURO). In 1999-2000, a programme in Sudan supported the graduate research work of, primarily, Master's students engaged in field research; a programme in Tanzania was aimed at training physicians to encourage them to consider a career in research; and a programme in China supported Master's students in the less developed endemic areas, while a second promoted graduate training in social sciences.

Institutional grants

Along with providing training grants to increase research capacity in DEC's, support is provided to institutions to strengthen centres of excellence and create critical masses able to sustain research. TDR support, among others, has helped establish the Ecole Nationale de Médecine et Pharmacie in Bamako, Mali, as a world class centre for malaria and schistosomiasis research. In Nigeria, TDR institutional support led to the establishment of a pathophysiology laboratory and a malaria research group at the University of Ibadan College of Medicine, which has expertise in monitoring and combating drug resistance in infectious diseases. At the University of Colombo,

Sri Lanka, TDR Research Capability Strengthening (RCS) institutional support to the Malaria Research Unit has strengthened its capacity for immunological studies in malaria such that the centre is producing candidate vaccines and has set up an animal model for evaluation of malaria vaccines.

In the current biennium, support is being provided for epidemiology training at universities in Benin, South Africa and Uganda. Funds have also been allocated to the Tropical Medicine Research Institute, Khartoum, Sudan, to support research by Master's degree level students.

Under the new TDR strategy, a large part of RCS support (60%) will go towards capacity building activities in support of the TDR research and development agenda ('RCS-Plus' – see below). By taking advantage of previous investment in research capacity strengthening, institutions in DEC's will be involved in the creation of new basic knowledge and in development of new and improved tools and new intervention methods to combat tropical diseases. The remaining 40% of funds will be used to strengthen the research capacity of least developed countries and those with low research capacity.

Research training grants

Training of young scientists contributes not only to individual development but also to the development and sustainability of institutions in developing countries. During 1999-2000, 91 new training grants

were awarded, while 16 MSc students, 41 PhD students, and a number of students undertaking short-term specialized attachments, completed their training programmes. As in the past four or five years, PhD training is increasingly being conducted in developing countries or regions. Of particular note is the increasing number of students who take up field-related research with implications for control. Disciplines include geographic information systems and remote sensing, health economics and health services research, clinical pharmacology, epidemiology and biostatistics.

While TDR continues to develop human resources, it also helps to improve developing countries' abilities to train these resources. During the period under review, TDR funded, through a competitive call for applications, the development of three Master's programmes in clinical epidemiology in Africa. These were in collaboration with the National University of Benin, Makerere University (Uganda) and the University of Witwatersrand (South Africa).

Finally, RCS supports specialized fellowships, often in cooperation with external partners as well as with the TDR R&D programmes. In support of developing capacity to conduct GCP clini-



Institutional grant: Master's student in Sudan benefits from an RCS grant

WHO/TDR/GRUMP



cal trials in Africa (see section of this report on Technical Information), TDR is co-funding a fellowship with GlaxoSmithKline in Belgium. The candidates spend a year working with industry experts prior to returning to their home country where they can be a resource for industry, TDR, and others.

RCS-Plus initiatives

In a new approach known as RCS-Plus, RCS activities are being tuned more closely to countries' research capacity and to TDR R&D activities.

Unlike 25 years ago, today, in some part due to TDR investment in human resources and institution development, there is plenty of research capacity in DEC's which can contribute to the global effort for developing tools for disease control. So whenever possible, these resources will be used for R&D priorities. Thus, in RCS-Plus, TDR will develop capacity building based on selected initiatives, and RCS activities will be funded according to R&D priorities.



African trypanosomiasis is a very neglected disease and is the first area of emphasis for RCS-Plus

WHO/TDR/CRUMP

For a start, RCS-Plus has two important emphases. Firstly, on African trypanosomiasis, it being a very neglected disease, and, secondly, on RCS for tuberculosis. It is hoped that RCS-Plus will reinforce the involvement of all TDR R&D areas in research capability strengthening and, as well, increase the participation of DEC's across the whole range of TDR activities.

RCS-Plus: tuberculosis

The RCS-Plus initiative began recently, so there is little to report on for the biennium 1999-2000. However, activities so far include the RCS-Plus initiative in TB, which is designed to strengthen capacity in three or four key institutions within 40 high TB burden countries. The institutions will be supported to establish or strengthen capacity to address selected areas of TDR's TB research strategy, including carrying out clinical trials and setting up mechanisms for in-country health policy, systems and services research.

The first focus for clinical trials will be the new four-drug fixed-dose combinations of isoniazid, rifampicin, ethambutol, and pyrazinamide. These combinations need to be registered urgently – they promise advantages in ordering, transport, storage, prescription and consumption of TB drugs, and in reducing the risk of emergence of resistance. TDR has accepted responsibility for establishing the evidence base for registration of the combinations.

Selected institutions will act as national, and hopefully in the future, regional centres for training and research in the conduct of strategic studies aimed at improving TB control in high burden countries. The awards, of up to US\$80 000 annually, are intended to be pathfinders for the new research-control linkages that are part of the new TDR strategy. Applicants will be judged on the extent to which the national TB control programme is a partner in the proposed studies.

A first call for applications resulted in 78 letters of intent. These are currently being evaluated



by a team of eight external reviewers; 6-10 candidates will be chosen to prepare a full proposal and develop a protocol at a workshop. Implementation of the protocols is expected to begin around September 2001.

PARTNERSHIPS FOR TECHNICAL INFORMATION

Global Forum for Health Research

TDR and the Global Forum for Health Research (GFHR) share the goal of addressing the 10/90 disequilibrium – only 10% of the world's R&D expenditure in health addresses the diseases that cause 90% of the deaths of people in low-income countries. TDR has worked with the GFHR in developing tools for priority-setting in health research, especially in malaria. This work is now being built upon in 2001 as the new TDR strategy is being applied to all ten TDR diseases and new emphases for disease specific research are being developed. Many TDR staff attend the GFHR annual fora where new ideas in health research are presented and debated. Dr Carlos Morel presented TDR's successes over its first 25 years at the IVth Forum in Bangkok in October 2000, where the Global Alliance for Anti-TB Drug Development was also launched. TDR will be working with GFHR on research resource flow estimations over the next biennium.

Cited here is a multilateral partnership in health research.



Technical Information

Provision of new information, its conversion into knowledge, and speedy dissemination of this knowledge to those who need it, is at the heart of the TDR strategy for 2000-2005. TDR is a knowledge management organization, for which making adequate technical information, research guidelines and instruments, and advice available to partners and clients is the expected result. TDR is creating new channels for generating, processing, and disseminating this knowledge, in written and electronic form. There is emphasis on intensive use of new and appropriate technologies.

www.who.int/tdr

TDR Home Page

TDR website
[www.who.int/tdr]

PC & MAC
June 2001

Leishmaniasis | **Onchocerciasis** | **Chagas disease** | **Lymphatic filariasis** | **Malaria** | **Leprosy** | **African trypanosomiasis** | **Tuberculosis**

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



In managing knowledge, in bringing a new technology into use in a community, TDR begins with the intended user of the technology, looking first at the culture and work practices before fathoming the best way of introducing the technology to them. This helps to ensure that the community adopts the new technology. In providing research guidelines and advice, TDR begins with intense discussion, consensus building and priority setting, so that its research and development (R&D) partners receive knowledge as opposed to information. This knowledge enables them to take correct action and, for example, adopt the TDR research agendas and priority lists of tools.

R&D INITIATIVES USING COMMUNICATIONS INSTRUMENTS DEVELOPED BY TDR

A variety of instruments and materials are developed by TDR for use in R&D. Access to, and exchange of, information has increasingly become a determinant for progress in science. At the start of the 1990s, TDR began to investigate ways in which it could improve its position and become a major global source of information and knowledge about its target diseases. Attempts began to explore and exploit the possibilities of electronic publishing for the production and dissemination of materials, to help meet the global need in research and training and, in particular, to satisfy the requirements of TDR's primary target audiences. The focus on electronic publishing has allowed the programme to move toward a better, more cost-effective mechanism of integrating the production and distribution of all its information and communications materials.

At this time, TDR was among the first in the area of health research to exploit the potential of the Internet and World Wide Web and, in 1993, began to use the electronic publishing possibilities offered by the Internet, starting an email listserv, the tdr-scientists list, with 50 subscribers. The number of participants has since grown to over 1500, 35% of whom are scientists in diseases endemic countries (DECs). More and more people post relevant materials on the list, e.g. information about meetings, vacancies, grants, new information sources.

In 1995, TDR published its first web page. Today, with some 1000 pages and 350 links to external websites, the TDR website (www.who.int/tdr) forms the backbone of TDR's electronic communications activities. Continually evolving using the latest and most appropriate technologies, the website represents a major vehicle through which TDR reaches its target audiences throughout the world, and through which researchers can reach each other. During 1999-2000, the website was totally redesigned, allowing global access to some of TDR's databases for the first time, and with much richer content.

As well as electronic publishing, TDR continues to produce and distribute a variety of printed research documents and meeting reports, and a thrice-yearly newsletter, *TDRnews*, which is currently distributed to over 19 000 people. All TDR documents are free of charge and available to download from the TDR website (see Box 1 for list of documents produced during 1999-2000).

In 1991, TDR broadened its ongoing traditional printed publication operations by establishing an image library, which contains still and moving images covering all aspects of its target diseases. The library meets both in-house and external needs and helps fill the gap that exists in the availability of such materials. The TDR catalogue now contains some 12 000 images, fully searchable and available for downloading from the TDR website, or as 35mm slide copies or electronic files on CD. The images may be used freely for non-commercial purposes. Use of the images is more or less entirely for R&D purposes – 90% of requests are for use in scientific and medical journals, from teachers for use in teaching materials, or from students.

In addition to expanding the breadth and depth of its coverage of still images, TDR continues to produce video materials (broadcast-quality original footage and edited videotapes). TDR is now one of the world's primary sources of free images on all aspects of the programme's target diseases. During 1999-2000, video material was recorded in a number of countries (in Africa, Asia, Europe and South America) and videobite tapes on all ten TDR diseases were updated to incorporate new footage. Other specific topics included good clinical practice and good manufacturing practice; miltefosine trials for leishmaniasis; re-launch of albendazole for treatment of lymphatic filariasis; 50th anniversary of the Jiangsu Institute, China. Users included national and global TV stations

TDR provides technical information and responds to information requests through all available channels (electronic, print and multimedia). The primary audience for TDR communications is R&D personnel.



Box 1. Documents produced and distributed during 1999-2000

- TDR – Final Report Series. 1998/99** www.who.int/tdr/publications/publications/finalreport9899.htm
- TDR – Final Report Series. 2000/01** www.who.int/tdr/publications/publications/finalreport0001.htm
- Ultrasound in schistosomiasis: a practical guide to the standardized use of ultrasonography for the assessment of schistosomiasis-related morbidity.** TDR/STR/SCH/00.1 www.who.int/tdr/publications/publications/ultrasound.htm
- Incentives and disincentives for new anti-tuberculosis drug development.** TDR/PRD/TB/00.1 www.who.int/tdr/publications/publications/anti-tuberculosis.htm
- Conference report on the first international meeting of the Research Initiative on Traditional Antimalarial Methods (RITAM).** TDR/PRD/MAL/00.1 www.who.int/tdr/publications/publications/ritam.htm
- Operational guidelines for ethics committees that review biomedical research.** TDR/PRD/ETHICS/2000.1 www.who.int/tdr/publications/publications/ethics.htm
- Implementation and sustainability of community-directed treatment of onchocerciasis with ivermectin: report of a multicountry study.** TDR/IDE/RP/CTD/00.1 www.who.int/tdr/publications/publications/cdti.htm
- Community-directed treatment of lymphatic filariasis in Africa.** TDR/IDE/RO/CTD/00.2 www.who.int/tdr/publications/publications/cdti2.htm
- A focused research agenda to influence policy and practice in home management for malaria. Report of a meeting, 8-11 May 2000, Kilifi, Kenya.** TDR/IDE/MHM/00.1 www.who.int/tdr/publications/publications/home.htm
- Recommendations of a scientific working group on dengue. Report of a meeting, 3-5 April 2000, Geneva, Switzerland.** TDR/DEN/SWG/00 www.who.int/tdr/publications/publications/dengue-swg.htm
- Recommendations of a scientific working group on strategic social, economic and behavioural research. Report of a meeting, 31 May-2 June 2000, Switzerland.** TDR/STR/SEB/SWG/00.1 www.who.int/tdr/publications/publications/seb.htm
- Prospective thematic review of TDR research capacity strengthening, 15-17 November 1999, Geneva, Switzerland.** TDR/RCS/PTR/00 www.who.int/tdr/publications/publications/rcs.htm
- Recommendations of a scientific working group on tuberculosis. Report of a meeting, 9-11 February 2000, Geneva, Switzerland.** TDR/TB/SWG/00 www.who.int/tdr/publications/publications/tb-swg.htm
- TDR strategy (2000-2001).** TDR/GEN/SP/00.1/Rev.1 www.who.int/tdr/publications/publications/strategy.htm
- Haaland A, Akogun OB, Oladepo O, Kale OO. **Community directed implementation of health projects: Reporting with pictures, a concept paper for researchers and health policy decision-makers.** TDR/IDE/RP/00.1 www.who.int/tdr/publications/publications/pictures.htm
- Adetokunbo Lucas. **Public-private partnerships: illustrative examples.** TDR/BP/00.1 www.who.int/tdr/publications/publications/partnerships.htm
- Good laboratory practice training manual.** TDR/PRD/GLP/00.2. Not available on the web at the time of going to press.
- Tropical disease research: progress 1997-1998. Fourteenth TDR programme report.** www.who.int/tdr/publications/publications/PR14.htm
- Report of a meeting: Novel adjuvants currently in clinical testing.** TDR/PRD/99.1 (not available on the web)
- Report of an informal consultation on clinical neurological investigations required for patients treated with artemisinin compounds and derivatives.** TDR/TDF/99.1 www.who.int/tdr/publications/publications/artemisinin.htm
- Standard operating procedures for clinical investigators.** TDR/TDP/SOP/99.1 www.who.int/tdr/publications/publications/sop.htm
- Malaria transmission blocking vaccines: An ideal public good.** TDR/RBM/MAL/VAC/2000.1 www.who.int/tdr/publications/publications/malaria_tbv.htm
- The THELEP controlled clinical trials in lepromatous leprosy.** TDR/IDE/THELEP/99.1 www.who.int/tdr/publications/publications/thelep.htm

(e.g. National Geographic); industrial partners (e.g. Merck & Co. Inc., SmithKline Beecham); institutions and foundations (e.g. United States Centers for Disease Control and Prevention – CDC); partner organizations (e.g. African Programme for Onchocerciasis Control, Onchocerciasis Control Programme); and a variety of WHO departments (e.g. Roll Back Malaria, StopTB, Health Technology and Pharmaceuticals).

Through TDR distribution and information services, some idea can be gained of the use of TDR materials by R&D partners and clients. The majority – some 74% – of all requests for TDR documents come from scientific and technical people, mostly from institutional addresses. This represents use of TDR printed documents by R&D personnel. After technical people, the



WHO/TDR/CRUMP

A TDR mission to Samoa for the first mass drug administration of albendazole formed the backbone of SmithKlineBeecham's media activities.

next highest requesters of printed information (12% of all requests) are from health and governmental institutions.

Each month, TDR Communications responds to several hundred requests for information, which arrive via all available means (mail, telephone, fax, email, website, in person). Of all the requests that TDR responds to, significantly more document requests (70% of the total) are received from DEC, while 81% of the total information requests received via the newsletter email address come from DEC, indicating perhaps that more people in DEC than in industrialized countries use the TDR newsletter as a source of information. Significantly fewer requests for use of images (25% of the total) are received from DEC. Otherwise, requests arrive with about equal frequency from DEC and industrialized countries.

USE OF THE WEBSITE BY TDR PARTNERS

Serving initially as an outlet for providing information on grants, research priorities and deadlines for proposals, the website underwent a major redesign in June 1999 to also include:

- General information on TDR: strategy, organization, governance, resources and outcomes.
- Interactive versions of TDR's Programme Report and research highlights.
- A complete set of TDR's Final Report Series presenting leading examples of TDR-supported projects.
- Multimedia resources, including videos, and searchable access to the TDR image library.
- Online application form.
- A complete listing of TDR publications and reports available to download.
- Latest news from TDR.
- Web-based discussion forums and trainee profiles to facilitate contact and information exchange between researchers (in the pipeline).

New content is posted to the website and the tdr-scientists email listserv on an almost daily basis. Users of the site tend to navigate by disease, and analysis indicates that TDR is a major web-based information provider for some orphan/neglected diseases (e.g. Chagas disease, African trypanosomiasis).

The so-called 'digital divide' still puts researchers from developing countries at a disadvantage as compared to their colleagues from industrialized nations. TDR therefore has adopted a proactive policy that tries to narrow this information gap for DEC scientists, addressing the needs of those with zero, poor or unreliable connectivity through:

- Production of periodic compact disc-read only memory (CD-ROM) versions of the website.
- Support for initiatives to improve Internet connectivity at DEC institutions.
- Posting of key information simultaneously on the website and email listserv.
- Coordination of use of the TDR website with other electronic and traditional publishing methods.

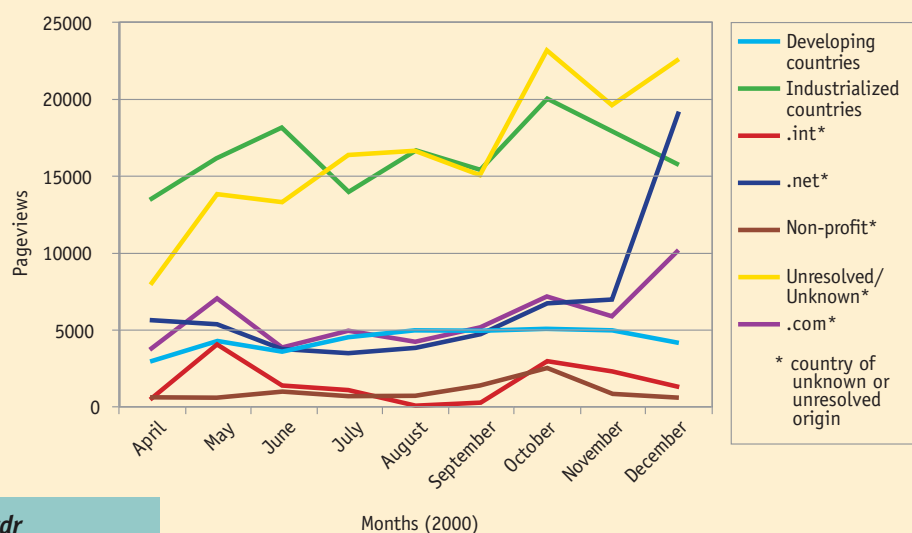
In order to follow the evolution of use of the TDR website, the number and origin of visitors to the site is constantly monitored. As expected, current data indicate a lower percentage of visits from developing countries as compared to industrialized countries (8% and 31%, respectively), although over 61% of visits originate from locations that existing technologies cannot identify (Fig. 1). Despite this, the available data demonstrate that the TDR website reaches a broad range of partners, supporting the need for TDR to continue its strong, proactive policy towards DEC scientists.

Visits to the TDR website are increasing over time. In December 2000, the TDR website received approximately 70 000 pageviews¹ – almost twice as many as the previous year. The overall trend is an increasing number of visits over time. A proactive policy aims to reduce the information gap between scientists in disease endemic countries and those in industrialized countries.

¹ For this analysis, any static HTML document is considered a page. This does not include graphic images (.gif .jpg etc), audio clips, dynamically generated pages, etc. Pageviews represent the number of 'pages' requested only. This number also excludes hits to the site generated by search engine robots. Numbers were generated using Webalizer version 2.0 (www.webalizer.com).



Figure 1. TDR Website: Pageviews by user category (April–December 2000)



TDR Website: www.who.int/tdr
tdr-scientist list: To subscribe, send an email to majordomo@who.ch and type the following in the body of the message: *subscribe tdr-scientists*

As to whether the TDR website is reaching its target audiences or not, Chagas disease may be quoted as an example. Whereas more than 10% of hits to information on Chagas disease are from endemic countries (South and Central America, Mexico), only 4% of hits to non-Chagas disease information are from these countries, indicating that we are reaching one of our target audiences (scientists in DEC's).

CONTACT WITH R&D PARTNERS

TDR is helping to increase day-to-day interaction with its researchers by improving their access to email facilities. In 1999-2000, TDR had contact with: R&D partners in connection with prioritizing research in tuberculosis, lymphatic filariasis, and dengue; control managers in connection with operations research (training, proposal development, surveillance); drug and vaccine developers in order to promote the use of good practices in drug and vaccine trials.

TDR is helping to increase day-to-day interaction with its researchers by improving their access to email facilities. TDR also has contact with R&D partners in order to perceive the needs for research and to provide research advice and guidelines. Examples from 1999-2000 include contacts made with a range of partners for purposes of clarifying research needs and generating research guidelines, contacts made with control managers for purposes of operations research, and contacts made with drug and vaccine researchers.

Contact with R&D partners: Internet connectivity

Throughout the last decade, TDR has encouraged and financially supported its researchers in accessing email facilities. This has greatly increased the day-to-day interaction between TDR and its partners, and also facilitated a growing network of scientists who are now able to communicate in an effective and relatively inexpensive manner. In the mid/late-1990s, with the full-scale introduction of the World Wide Web and improved communication capabilities in DEC's, TDR shifted its support to developing local infrastructure in selected institutions. This included providing hardware and installing Internet connection, allowing high speed data transfer capability and greater access, by larger numbers of users, to the Web. With better facilities in developing countries and increased access to the information highway, TDR's current efforts are focused on how best to access the information through providing training on the *Internet for research*. This training now stands alone, in an abridged format, in most TDR-supported workshops on research methods. Of interest is the fact that it is now rare for any application to come to TDR without an email address – electronic applications are fast becoming the norm.



Contact with R&D partners: research guidelines

TUBERCULOSIS: *Preparation of guidelines and information*

WHO/TDR, through the Global TB Research Initiative, monitors global research activities across the whole range of research. To date there have been two meetings, in association with the US National Institutes for Health (NIH) and other major investors in TB research, to identify gaps in the global research agenda and recommend ways to fill them.² The third meeting will take place in 2002.

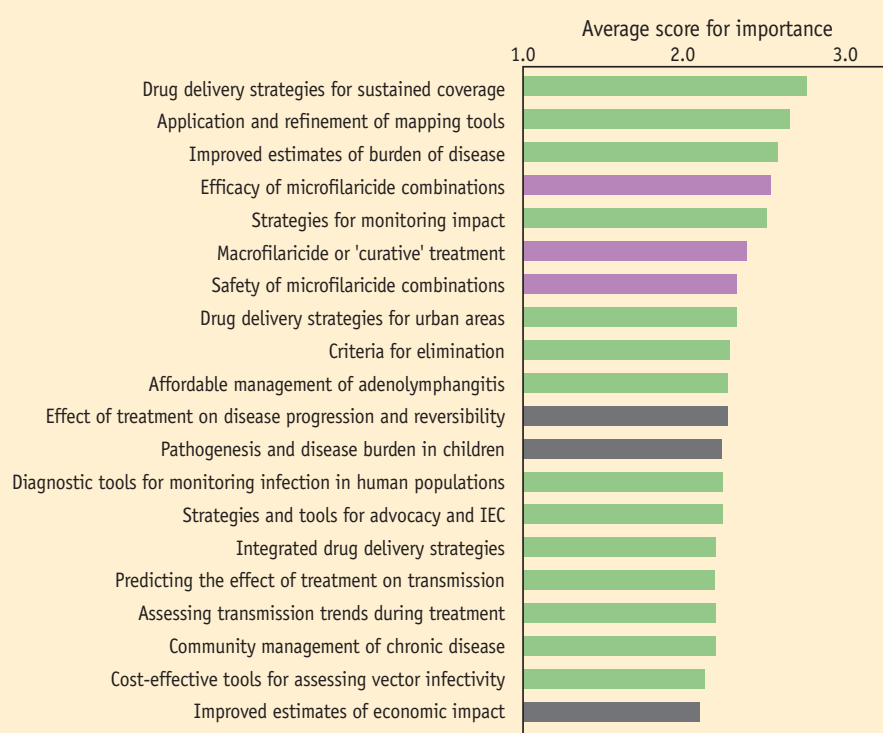
The overall goal is to increase support for TB research. The meetings provide a forum for debate on the research needs of communities and control programmes in high TB burden areas and corresponding research priorities, summarizing the current status of TB control and defining control programmes' research needs in relation to gaps in knowledge and effectiveness of available tools and strategies. The accountability of the several public/private partnerships recently established in TB research will be addressed in future meetings.

FILARIASIS: *Priority setting for research needs*

In 2000, a list of research needs in filariasis control, compiled in the World Health Organization (WHO), was mailed around the world to experts in filariasis research and control for their comments, additional needs, and ranking according to importance for filariasis elimination. Many of the responses came from workers in filariasis endemic countries, and the poll has been very important for developing the TDR lymphatic filariasis workplan.

The top twenty priorities which emerged are shown in Fig 2.

Figure 2. Top twenty research needs for filariasis elimination



Topics covered by workplan of:

- TDR Task Force on Filariasis Intervention Research
- TDR Product Development
- Not covered by TDR

Key to scores:

- 0: not important
- 1: important
- 2: very important
- 3: top priority

² Reports from both meetings are available at: www.who.int/tdr/diseases/tb/gtri.htm



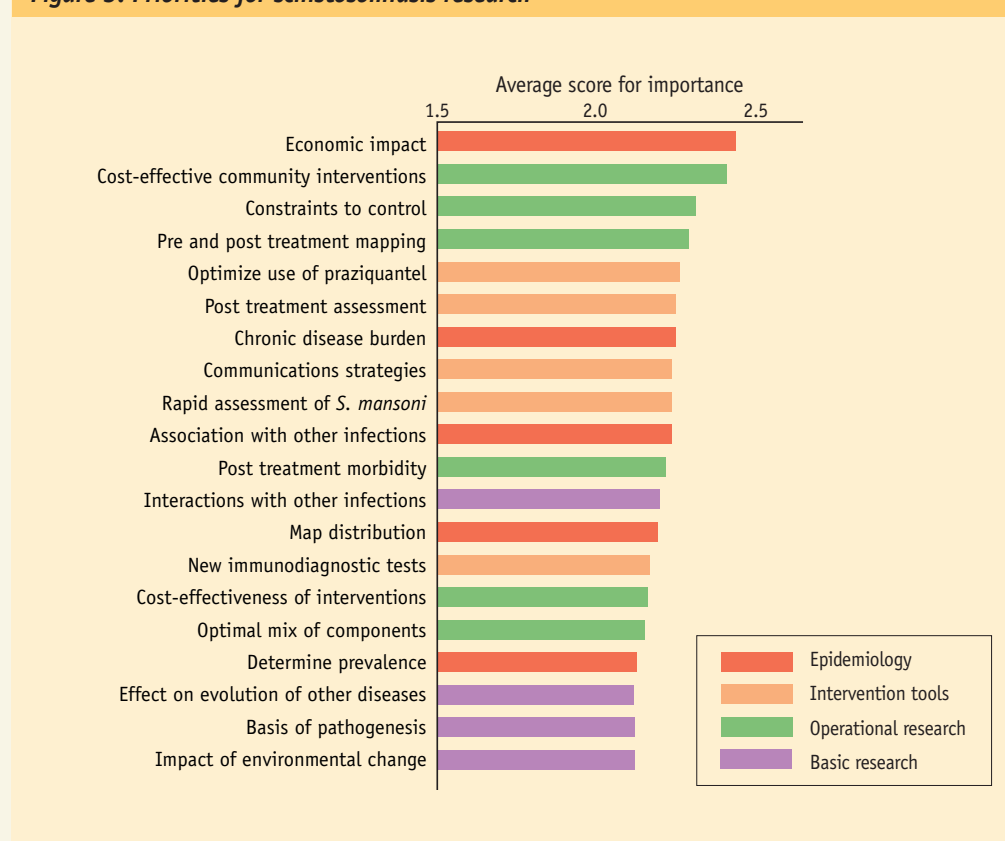
TDR is already addressing many of these needs. TDR Product Development is testing combinations of microfilaricides and searching for a macrofilaricide. The Task Force on Filariasis Intervention Research is addressing drug delivery strategies, strategies for elimination, methods and criteria for monitoring and evaluation, community-based management of chronic disease, and methods of mapping. Since most of these issues overlap with the research needs for onchocerciasis control, this Task Force covers both diseases.

SCHISTOSOMIASIS: *Priorities for research*

In assessing possible priorities for schistosomiasis research, scientists and public health experts were asked to list what they consider are the five priorities. Based on the responses, a questionnaire with 55 questions, in four major areas, namely, epidemiology, intervention tools, operational research and basic research, was formulated and distributed to 249 experts, with 95 returns.

The results of the questionnaire survey are given in Fig. 3. The score was based on the scale 0 to 3, 3 being the highest and preferable. Given the assumption that tools are available to control

Figure 3. Priorities for schistosomiasis research



schistosomiasis, as evidenced by the success in a number of countries, it would follow that the primary research issues to be addressed involve control issues. In this regard, measurement of the economic impact of control is ranked highest, possibly suggesting that this could provide the impetus for schistosomiasis control. The other issues ranked highly concern resolution of obstacles to implementation of control measures. This may reflect the need for implementation research to bridge the gap between the bench and the field as noted in other fora. The responses also suggest that there are gaps in understanding the epidemiology of schistosomiasis in endemic areas as evidenced by the rank of questions on quantifying and assessing the infection and disease.

DENGUE: *Research needs*

Research needs in dengue prevention and control, and the directions that TDR research should take, were the subject of a Scientific Working Group (SWG) meeting in April 2000,³ following the inclusion of dengue in the TDR disease portfolio in June 1999.

The SWG recommended that research efforts be focused on reducing the mortality and morbidity caused by dengue haemorrhagic fever (DHF), with TDR focusing on:

³ Dengue SWG report available for download from: www.who.int/tdr/publications/publications/dengue-swg.htm



WHO/TDR/GRUMP

International trade in tyres, which create a perfect breeding ground for mosquitos, has hastened the spread of dengue.

- Pathogenesis of DHF, including cellular and humoral immunology, factors that predict the onset of DHF, and viral virulence.
- Entomology, including research on molecular/genetic methods to reduce populations of the mosquito vector, *Aedes aegypti*, and transmission of the four dengue viruses.
- Social, economic and behavioural research, and implementation research, to develop community-based mosquito control strategies and identify appropriate behaviour change with regard to mosquito control.
- Developing new diagnostic tools and new treatment approaches.
- Accelerating development of current vaccine candidates.
- Building capacity in all areas of dengue research.

The SWG also made recommendations concerning priorities for other players in the field of dengue research.

Contact with control managers: operations research

MALARIA: *Asian collaborative training network*

The Asian Collaborative Network for Malaria⁴ is a regional 11-country effort to improve training and communication on malaria. The members jointly develop and organize international training courses, and support a communications network for information exchange. ACTMalaria capitalizes on the experience, expertise, and resources of the member countries, recognizing the similarity of many malaria control problems in south-east Asia and that malaria exists across borders. TDR has collaborated with this group since its inception in 1996, initially providing financial support for students participating in ACTMalaria activities. Recent support has been extended to help develop curricula in drug policy and health communications. These are additional to the existing training programme of malaria control.

TUBERCULOSIS: *Proposal development workshop*

To initiate operations research in support of tuberculosis control in the Eastern Mediterranean region, TDR organized a proposal development workshop in collaboration with the International Union Against Tuberculosis and Lung Disease (IUATLD) and the WHO Eastern Mediterranean Regional Office (EMRO). Over a two-week period in June 2000, 22 participants from 11 member states developed five multi-country research protocols. The protocols were subsequently submitted to the EMRO-TDR small grants programme, where three, involving six countries – Djibouti, Egypt, Iran, Iraq, Pakistan and Somalia – were recommended for funding.

⁴ ACTmalaria:
www.actmalaria.org



SCHISTOSOMIASIS: Asian network for research surveillance and control

Following on from an international symposium on schistosomiasis japonicum held at the Jiangsu Institute of Parasitic Diseases, China, in September 1998, TDR agreed to support a network for research, surveillance and control of Asian schistosomiasis. The network links investigators from China and the Philippines and permits an ongoing and efficient exchange of information. In addition to a forum for discussion, the network set up an English language website (<http://www.rnas.org/>) in China for the global dissemination of information.

Contact with drug and vaccine developers: good practices

To achieve successful registration of new drugs and vaccines for tropical diseases, the component studies must comply with current standards for quality, reliability and integrity of data, and protection of public health. National regulations require that internationally accepted rules, i.e. good manufacturing practice (GMP), good laboratory practice (GLP) and good clinical practice (GCP), are followed in the respective stages of the development and life cycle of a drug product. All biomedical research must also comply with established international guidelines concerning ethical and scientific review of the research, and all patients involved in the trials must be provided with full information and give their informed consent to participate.

Good laboratory practice

In order to address quality standards for non-clinical safety testing of potential products, the introduction of GLP quality standards in test facilities of developing countries was seen as urgent. Training workshops were organized in 1999-2000 as a means of transferring GLP expertise and knowledge to DEC's – at the start of this work, facilities and expertise for GLP were virtually non-existent in these countries. So far, four workshops have been held in Africa, Asia and Latin America, as part of TDR technology transfer activities, to introduce scientists of DEC's to the concepts and requirements of GLP. Participants at the workshops included people already involved in

R&D of drugs and vaccines, in managerial or professorial positions in laboratories and universities – chemists, pharmacologists, toxicologists, pathologists, and immunologists. The aim of the workshops is to enable the participants to produce quality, reliable, reproducible and valid data; apply GLP concepts in their various laboratories to produce quality data; and use the data in support of registration or market authorization. Following the initial GLP workshops in the different regions, some of the original participants have conducted similar workshops in their home countries to help build up the needed capacity for conducting preclinical trials according to good practices.

Because participants at the workshops were willing to pioneer the initiation of GLP concepts in their own laboratories, a general GLP teaching manual was prepared for induction courses – *Good laboratory practice training manual*, TDR/PRD/GLP/00.2. This manual can be used by anyone interested in introducing GLP in their laboratory; it will ensure that all induction courses have the same content.

An SWG on GLP issues was set up. It convened in 1999 and 2000 to discuss how to present the TDR/WHO position on GLP. The requirements for upgrading developing country laboratories involved in research and development (R&D) were examined at the meetings, at which experts in international GLP guidelines and representatives from developing countries participated.

During the discussions it became clear that, although the introduction of GLP quality measures may be impeded by the difficulty of obtaining adequate resources (e.g. facilities, equipment, trained personnel) or the instability of the infrastructure (e.g. water or electricity supply) in DEC's, investments in GLP quality standards would result in tangible returns. From the deliberations of the SWG, it became clear that:

- demonstrated compliance with GLP will become a prerequisite for clinical testing and for drug registration in developing countries, especially if drug products are to be exported to countries other than the country of origin.





- it is essential to avoid the co-existence of two or more international regulatory GLP standards for non-clinical safety testing.
- guidance is needed for the implementation of GLP.

With such considerations in mind, adopting the *Revised OECD principles of good laboratory practice* as the officially endorsed WHO regulation in the area of non-clinical safety testing was seen as the most rational way forward.

At the SWG meetings, it was agreed that, in order for DEC to benefit from GLP quality standards as covered by the Organization for Economic Cooperation and Development (OECD), there is a need to address also the quality of biomedical basic research not included in the OECD Principles. It was recommended that two documents be developed from the proceedings of the meeting: one addressing the quality of research data in the regulated area, and the other addressing this issue in the non-regulated area. The document addressing quality issues in biomedical research in general (discovery studies, studies on proof of concept, studies to establish pharmacodynamics effect and mechanisms of action, etc.) will first be produced as a draft, for wide circulation and comment.

Good clinical practice

In parallel with the activities to transfer GLP skills and technology, TDR has been promoting good clinical practice (GCP) in disease endemic countries. In collaboration with the Joint United Nations Programme on HIV/AIDS (UNAIDS) and Pasteur Mérieux Connaught (PMC-France), workshops were conducted in Africa, Asia, the Eastern Mediterranean and South America, to train physicians and scientists from many disease endemic countries in GCP to become GCP monitors for drug and vaccine trials. Clinical investigators were trained for TDR trials in India, Gabon, Côte d'Ivoire, Zambia, Thailand, Tanzania, Ghana.

Participants in the workshops were introduced to the concepts of product discovery and



TDR is working hard to ensure that workers in disease endemic countries are conversant with good practices.

development, clinical trials (planning, design, conduct) and ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) GCP. The document *Standard operating procedures for clinical investigators and clinical monitors* (TDR/TDP/SOP/99.1)⁵ was studied during the workshops, and there was hands-on field work – assessing potential trial sites for carrying out clinical trials and undertaking actual monitoring visits. Following the initial good practice workshops in the different regions, the workshops have become self-replicating. Each year, refresher courses are held for TDR monitors, to keep them up to date with the latest developments, particularly as regards regulatory, ethics, and patents issues.

Standard operating procedures (SOPs) of good clinical practice have been applied to TDR-supported trials, i.e. to trials of oral miltefosine, paromomycin, malarone, fosmidomycin, eflorni-

⁵ SOPs available for download from: www.who.int/tdr/publications/publications/sop.htm



thine, artemether for schistosomiasis, an AMA-1 malaria vaccine trial, and combination trials in onchocerciasis and lymphatic filariasis.

Strengthening ethical review

The workshops in GCP highlighted the need for ethical guidance when conducting trials in DECs. So, in collaboration with SmithKline Beecham Biologicals (now GlaxoSmithKline), TDR helped run two seminars in 1999 to evaluate the current status of ethical review procedures in Asia, the Western Pacific and Africa, and define ways to contribute to the development of the ethical review process in these regions. Most countries in these regions were found to have institutional ethics committees but not to have recommended procedures for constituting institutional review boards. Participants recommended, amongst other things, providing operational guidelines for forming ethics committees and review boards, establishing a forum for members of the different ethics committees to exchange ideas etc. and providing continuous training on International Committee on Harmonization (ICH)/GCP to ethics committees at national level.

Following the recommendations, TDR produced *Operational guidelines for ethics committees that review biomedical research* (TDR/PRD/ETHICS/2000.1).⁶ These guidelines will enable local ethics committees develop their own specific review procedures needed to ensure the patient is not exploited. Implementing the standard informed consent procedures – whereby each patient receives an explanation of what the trial is about and gives his/her consent to take part in the trial – presents one of the biggest difficulties in conducting clinical trials in developing countries. In fact, few patients can fully understand all the details about the study they are participating in, and careful review by the ethics committee is one of the most effective measures for this. The guidelines have been widely distributed, and within six months of publication had been translated into ten languages (English, French, German, Laotian, Filipino, Russian, Spanish, Thai, Turkish, Vietnamese), the translations having been financed by various intergovernmental agencies, governments, industry.

Another result of the recommendations was that, to foster improved understanding and implementation of ethical review of biomedical research, different fora were set up: the Forum on Ethics Committees in Asia and Western Pacific (FERCAP) countries, Foro Latino Americano de Comités de Ética en Investigación en Salud (Latin American Forum of Ethics Committees in Health Research – FLACEIS), Pan African Bioethics Initiative (PABIN).

As to training, an annual course is now being offered in research ethics by Thammasat University, Thailand, as part of its regular activities. The University of Bergen, Norway, is a partner in this, and the agreement will enable Master's and Ph.D. training in research ethics. These capacity building efforts are also linked to a three-year project funded by the European Commission which has the aim of developing course modules in research ethics. These course modules will be field tested and used in regional courses, allowing synergy between the different efforts.

⁶ Ethics document available for download from: www.who.int/tdr/publications/publications/ethics.htm



Resources for Research

FINANCE AND RESOURCES

In covering technical activities for 1999-2000, this programme report spans the two budgetary biennia of 1998-1999 and 2000-2001. In 1998-1999, TDR's governing body approved a budget of US\$62.245 million. In the current biennium, 2000-2001, TDR is operating with an approved Joint Coordinating Board (JCB) budget of US\$73.913 million and a Special Fund for Artesunate of US\$6.5 million. Thus there has been a substantial increase in the approved budget. See Table of financial contributions, pages 88-89 for contributions to TDR.

The TDR trust fund mechanism

At the heart of the smooth functioning of TDR is the TDR Trust Fund, which acts as a large pool of funds made up from specific donor contributions. A Memorandum of Understanding agreed by the donors, as to the manner in which funds can be contributed, ensures that the Trust Fund operates in a manner best suited to the advancement of research and training in tropical diseases. The result is a higher level of flexibility within an agreed framework.

To ensure that donor bodies are satisfied with the implementation of the programme, both scientifically and financially, a series of technical and financial reporting measures exists. One of the principal technical measures in place is the annual Scientific and Technical Advisory Committee (STAC) meeting which reviews scientific and technical matters. As to financial reporting, programme expenditures according to the approved budget and planned activities are presented annually for review and approval by the JCB.

Source of funds

TDR is a Special Programme, co-sponsored by the United Nations Development Programme, World Bank and World Health Organization. Although the budget level is approved by the JCB, actual funding received depends on the individual contributors.

TDR has a secure level of funding from its co-sponsors, while other donors can pledge firmly in writing, or contribute as and when they wish without commitment. This results in a loose relationship between an approved programme budget, secure level of funding, and expected but unconfirmed contributions. The impact on TDR is that its technical and scientific implementation has to be managed carefully against funds available throughout the year. This is a particular challenge when the approved budget represents a significant increase compared to the previous biennium, which is the case for 2000-2001.

Current funding situation

The past four biennia have seen continued slow reduction in the amount of donor income, but the year 2000 has shown the first sign of reversal of this trend. An income of US\$30.2 million has been received, and an income figure of US\$58 million is forecast for the biennium 2000-2001.

Table 1. TDR income (1992-2001)

Biennium	1992-1993	1994-1995	1996-1997	1998-1999	2000-2001
TDR contributions US\$ million	64.3	56.4	54.4	51.6	58 (forecast)

Should this materialize, TDR would be back to the pre-1994 funding level.

FUTURE FUNDING: REACHING NEW DONORS

Starting in 2000, TDR embarked on a new strategy which involved changes to the technical aspects of the programme, with support from the JCB. The success of the strategy hinges in large part on TDR's ability to increase its funding to allow successful technical implementation in those areas newly incorporated, i.e. in tuberculosis and dengue, the two major diseases taken into the TDR disease portfolio in 1999, and in social, economic and behavioural, diagnostics, and implementation research.



TDR has a three-way approach to arrive at a real growth in funds received: to generate an increased level of contributions from the traditional donor base; to seek out more designated funding from donors; and to diversify the donor type.

1999 and 2000 have shown the first evidence of both new donors for TDR, and increased donations of a designated nature being received by TDR. New donors include Médecins sans Frontières and the Bill and Melinda Gates Foundation. Meanwhile, donors with established track records are showing that they are able to provide funds to the programme of a designated nature on top of their undesignated contributions.

DESIGNATED FUNDING: A CHALLENGE FOR MANAGEMENT

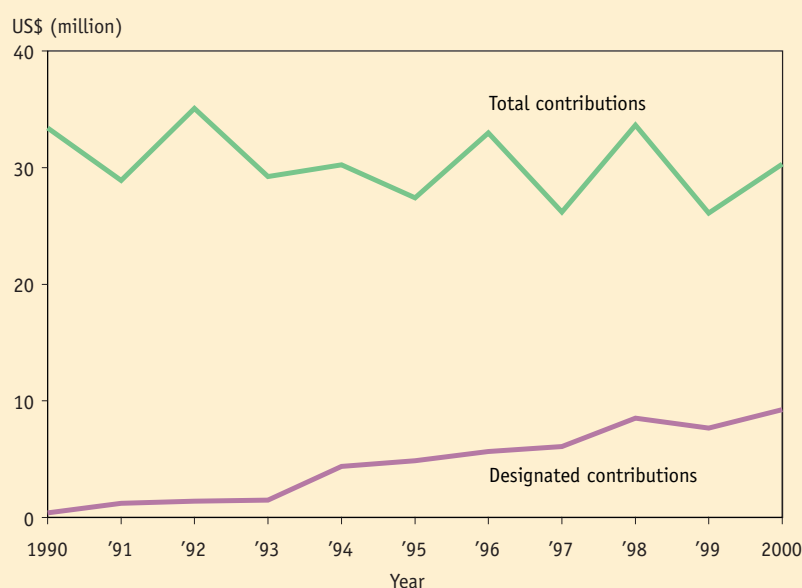
By virtue that TDR operates a Trust Fund, which is in essence an undesignated funding mechanism, donations that are designated are accepted insofar as they complement the programme's technical and scientific objectives. Funds that do not fit the programme's technical profile are not accepted. A further important managerial aspect is that the level of designated funding needs to be capped so as to ensure other technical activities are not eclipsed, as would likely occur with certain 'orphan' tropical diseases that TDR has in its portfolio.

The challenge of managing increased designated donations is particularly difficult in a period of transition such as TDR is currently experiencing. This will be the case until such time that TDR has expanded its income level to a point where increased designations fit well with an undesignated fund base that fully supports the 'orphan' diseases.

There has been a marked progression in designated funding over the last few biennia. In 1996, US\$1.2 million were designated, in 1998 US\$5.8 million, and in 2000 US\$9.0 million. The year 2000 has already seen a designated contribution exceeding that received during complete biennial periods in the past – as in 1996-1997 and 1998-1999, when total designations of US\$6.9 million and US\$8.1 million were received respectively. Fig. 1 indicates the trend over the last decade in designated funding, against a backdrop of relatively stable income.

Immediately following the approval of the TDR strategy for 2000-2005 by the JCB in June 2000, the Programme began wide consultation with the donor group to determine a feasible strategy to increase the income level by the US\$30 million foreseen in the strategy. A resource mobilization strategy will need to address the mechanisms for managing, and the effect of, the anticipated increase in proportion of designated funding.

Figure 1. Trend in designated contributions in the TDR Trust Fund





USE OF FUNDS: PROGRAMME EFFICIENCY BY CONTROL OF BUDGET ELEMENTS

TDR, as a funding programme for research and training, uses a financial measurement to track expenditure types across the biennia. This measure gives TDR stakeholders a clear picture of the spread of use of funds in relation to the categories referred to as 'operations', 'operational support' and 'personnel'. The existing expenditure ratio for these categories is 70:10:20 respectively.

'Operations' is a category used for the funding of research, training, and provision of technical information, guidelines etc. by the programme, such as projects in disease endemic countries or scientific workshops and training. 'Operational support' is a category used to track costs associated with travel and meetings, while 'personnel' is used to measure staffing costs. See Figure 2, Budget by programme area 1999-2000 and Figure 3, Budget by disease 1999-2000.

Figure 2. Budget by programme area 1999-2000

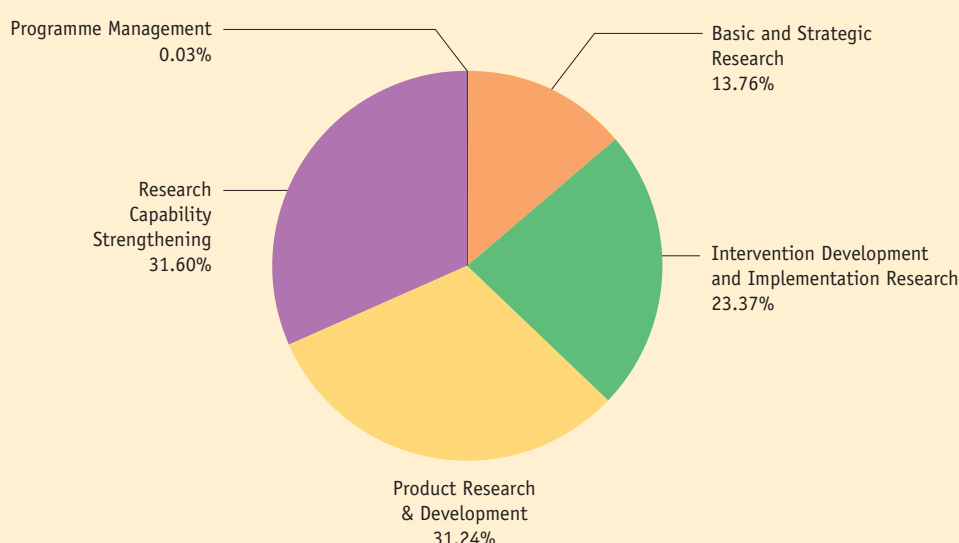
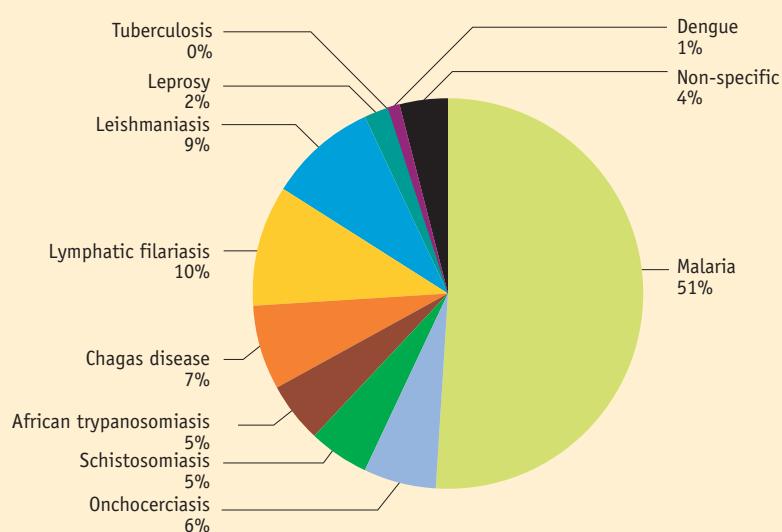


Figure 3. Budget by disease 1999-2000





Financial Contributions

UNDP/WORLD BANK/WHO
Special Programme for Research and Training in Tropical Diseases (TDR)
Contributions to TDR (in US\$ up to 31st December 2000)

CONTRIBUTOR	Total: 1974-1995	1996	1997	1998	1999	2000
African Development Bank Group	2,255,461	0	0	0	0	0
Arab Fund for Economic & Social Development	330,205	0	0	0	0	0
Asta Medica	0	0	0	0	42,979	0
Australia	8,512,751	1,207,153	696,240	588,150	623,228	624,265
Austria	593,008	0	0	0	0	0
Bahamas	500	0	0	0	0	0
Bayer AG (FRG)	10,000	0	0	0	0	0
Belgium	10,429,942	928,606	835,185	830,601	768,266	818,193
Brazil	100,000	0	0	0	0	0
Cameroon	79,182	0	0	0	0	0
Canada	21,373,729	1,065,693	1,014,493	937,500	952,381	945,946
China	710,000	55,000	55,000	55,000	55,000	0
Cuba	27,089	0	0	2,000	0	0
Cyprus	239	0	0	0	0	0
The former Czechoslovakia	34,965	0	0	0	0	0
Denmark	50,123,186	5,778,337	2,483,307	2,485,028	1,149,409	3,158,747
Edna McConnell Clark Foundation (USA)	1,025,000	0	0	0	0	0
Finland	2,810,104	0	0	0	0	0
Ford Foundation (USA)	20,000	0	0	0	0	0
France	5,757,729	266,152	0	166,945	0	135,030
Gates Foundation	0	0	0	0	0	2,000,000
Germany	21,645,993	1,003,464	730,290	643,138	901,295	733,384
Global Forum for Health Research	0	0	0	0	250,000	0
Greece	304,173	0	0	0	0	0
Gulbenkian Foundation (POR)	25,000	0	0	0	0	0
India	447,853	23,055	50,481	0	24,758	25,104
International Amateur Athletic Federation	0	1,000	0	0	0	0
International Development Research Centre (CAN)	3,210,540	72,595	306,531	61,768	39,880	59,376
International Federation of Anti-Leprosy Associations	2,167,007	89,459	86,888	23,737	0	14,457
Iran (Islamic Republic of)	10,000	0	0	0	0	19,970
Iraq	5,000	0	0	0	0	0
Ireland	314,310	157,000	156,340	141,210	126,160	100,000
Israel	6,500	0	0	0	0	0
Italy	6,293,116	0	33,222	87,209	100,000	178,623
Japan	1,870,000	350,000	300,000	150,000	600,000	500,000
Leprosy Trust Board (NZ)	109,445	0	0	0	0	0



UNDP/WORLD BANK/WHO
Special Programme for Research and Training in Tropical Diseases (TDR)
Contributions to TDR (in US\$ up to 31st December 2000)

CONTRIBUTOR	Total: 1974-1995	1996	1997	1998	1999	2000
Luxembourg	1,312,140	385,480	418,060	475,007	531,960	522,882
MacArthur Foundation (USA)	6,000,000	154,000	190,000	36,000	0	0
Malaysia	70,000	25,000	0	25,000	0	75,000
Médecins Sans Frontières (France)	0	0	0	0	0	50,000
Mexico	151,953	0	20,000	10,000	10,000	10,000
Netherlands	23,499,140	1,755,996	1,772,434	1,793,018	1,294,268	1,568,137
New Zealand	168,179	52,980	0	82,125	37,853	40,510
Niger	2,252	0	0	0	0	0
Nigeria	515,373	0	0	0	0	0
Nippon Foundation (JPN)*	5,940,767	100,000	100,000	100,000	100,000	0
Norway	46,450,630	3,712,500	4,483,298	3,803,211	3,231,939	2,845,665
OPEC Fund for International Development	890,000	100,000	100,000	0	0	0
Oswaldo Cruz Foundation (BRA)	200,000	75,000	0	75,000	75,000	0
Pan American Health and Education Foundation (USA)	996,980	29,139	6,000	0	0	0
Portugal	22,500	7,500	7,500	7,500	0	0
Rockefeller Foundation (USA)	1,250,000	75,000	0	250,000	600,000	200,000
Romania	1,995	0	0	0	0	0
SANOFI (FRA)	39,216	0	0	0	0	0
Slovakia	1,985	0	0	0	0	0
Sweden	45,809,179	1,419,065	1,963,405	2,564,524	2,360,091	2,431,290
Switzerland	18,223,580	775,194	714,286	709,220	718,954	818,713
Thailand	116,576	19,920	0	40,494	20,436	0
Thrasher Research Fund (USA)	50,000	0	0	0	0	0
Turkey	59,951	0	9,712	5,000	4,773	5,000
United Kingdom	19,242,617	3,271,651	80,645	3,749,667	875,788	3,410,844
United States of America	46,003,912	300,000	2,300,000	3,950,000	150,000	2,800,000
United Nations Development Programme	42,255,208	2,226,200	988,180	1,000,000	500,000	500,000
Wellcome Trust (UK)	25,000	0	0	0	0	0
World Bank	49,440,000	3,800,000	2,500,000	3,000,000	3,000,000	2,500,000
World Health Organization	23,441,816	1,008,000	1,008,000	1,132,300	1,183,300	1,178,240
WHO Regional Office for Africa	0	0	250,000	0	0	0
African Programme for Onchocerciasis Control (APOC)	0	0	400,000	0	1,980,000	700,000
Onchocerciasis Control Programme	0	0	0	0	275,000	320,976
Roll Back Malaria	0	0	0	0	0	1,000,000
Miscellaneous	33,891	1,175	15,147	3,089	2,248	7,350
TOTAL CONTRIBUTIONS FOR TDR	472,816,867	30,291,314	24,074,644	28,983,441	22,584,965	30,297,702

*Formerly Japan Shipbuilding Industry Foundation

