



Making health
research work for
poor people

PROGRESS 2003-2004

Tropical Disease Research



UNICEF/UNDP/
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Special Programme for
Research and Training in
Tropical Diseases (TDR)

TDR/GEN/05.1

Making health research work for poor people

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*Compiled and edited
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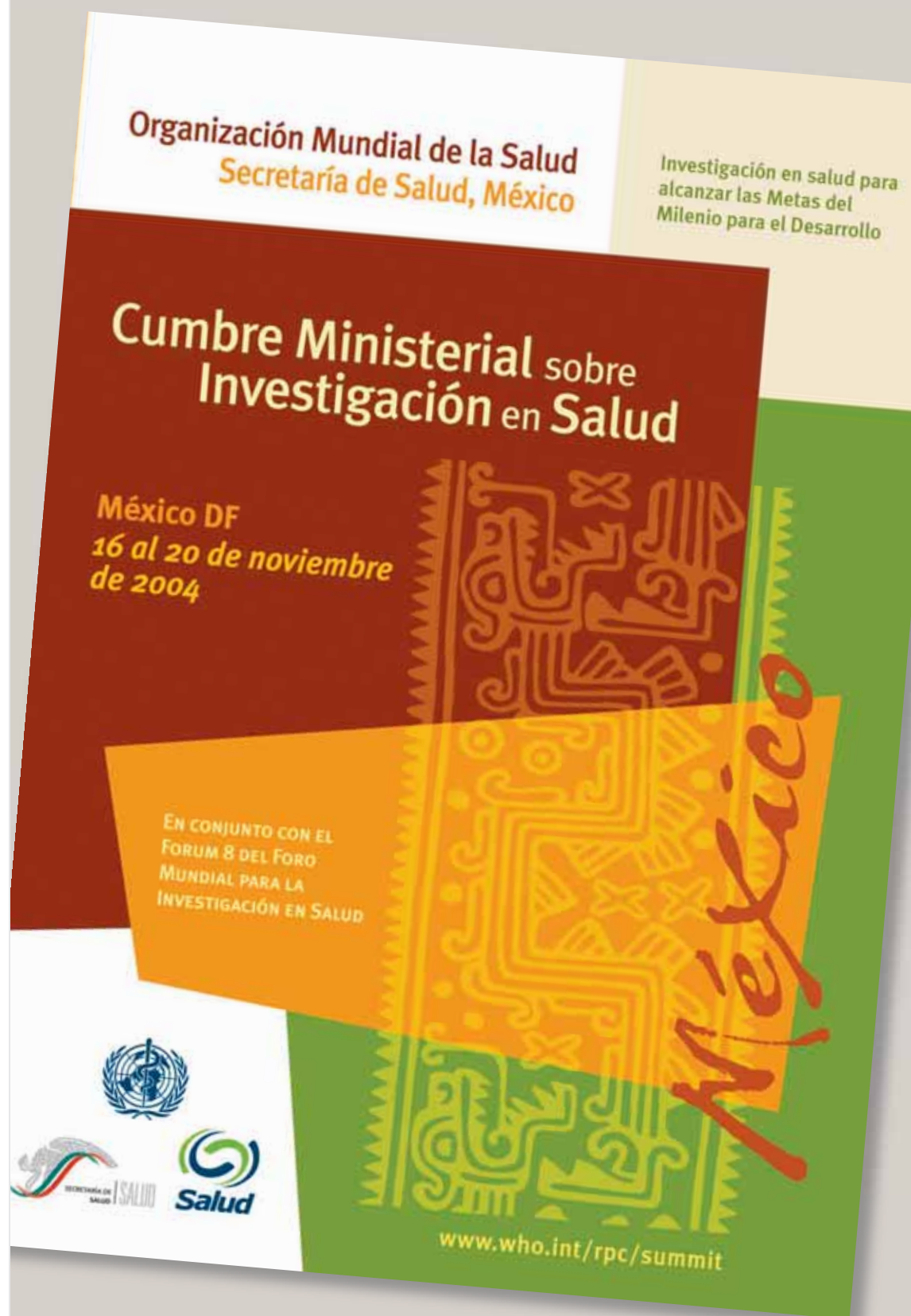
*This report represents
the combined efforts of
many TDR staff, all of
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It is critical that tropical disease research is responsive to the needs of people afflicted by the diseases and that the knowledge generated by research is translated into practical outcomes wherever possible.



Ministerial Summit on Health Research, Mexico, 2004.

Message

Cultivating a research culture for health and development

The links between health research and development are becoming increasingly prominent in the global health debate. It is critical that tropical disease research is responsive to the needs of people afflicted by the diseases and that the knowledge generated by research is translated into practical outcomes wherever possible. TDR continues to play a critical role in this area, as shown by the achievements outlined in this report.

Two events occurred in 2004 that demonstrate the seriousness with which we in WHO view research as vital to improved health: the Mexico Summit for Health Research, and the establishment of the Commission for Intellectual Property and Innovation in Health (CIPiH).

The Mexico Summit held in October 2004 was a milestone meeting that recognized and prioritized more than ever before the commitment of WHO to globally promote and support an effective health research agenda. It highlighted the need to place research within the context of health system needs, while at the same time recognizing the power of biomedical innovation to influence health. The link between health and innovation, and hence research, is also encapsulated in the Commission on Intellectual Property and Innovation in

Health, due to report in 2005. Both events demonstrate a solid link between research, stronger health systems, and the control of disease.

TDR's long history of combining cutting-edge scientific research with the delivery of practical solutions in the fight against tropical diseases is one of WHO's success stories, shared with TDR's other co-sponsors.

TDR has achieved this record by combining research with capacity-building activities, and linking biomedical with social research, to ensure that research is not limited in people's minds to the development of a pharmaceutical intervention. Instead, research can be taken further to provide evidence and knowledge to assist and inform the sustainable delivery and integration of new tools. The challenge for TDR is to undertake this work in a manner that also helps develop sustainable research capacity in developing countries.

We must work towards establishing a research culture in health – a culture that sees both research and control activities as integral components of improved health outcomes and as partner activities in a common health system.



Dr Jong-Wook Lee
WHO Director-General



Third meeting of the Commission on Intellectual Property Rights, Innovation and Public Health, Brazil, 2004.



Intermittent presumptive treatment for malaria in pregnant women. Besides a tetanus injection (as here), patients are given a medical examination, antimalarial tablets, and counselling about HIV/AIDS. Especially in sub-Saharan Africa, malaria, TB and many other diseases are increasingly being viewed within the context of a high-HIV background.

Foreword

One of the major developments in the area of infectious diseases over recent years has been the drive to develop a more integrated approach to healthcare interventions. This goes hand in hand with the development paradigms of sector-wide approaches and re-emphasis on operating from within strengthened health systems. Especially in sub-Saharan Africa, TB, malaria and many other diseases are increasingly being viewed within the context of a high-HIV background (and concomitant disease), while recent discussions about how best to approach the control of other neglected diseases are leading to concepts around integrated approaches, e.g. to helminthic infections. TDR's broad base of activities across many diseases lends itself to having a significant impact on research to inform optimized integrated approaches to disease control in close collaboration with national programmes.

Within the context of WHO and TDR's other co-sponsors, UNICEF, UNDP and the World Bank, there has been increased consolidation of collaboration and support for TDR. The official welcoming of UNICEF as a co-sponsor of TDR at the end of 2003 represented a landmark in TDR's history, signifying the increasing relevance of TDR research to the provision of evidence on issues associated with implementation of tools and methodologies, and corroborating the relevance of research in the area of innovation and tool development.

The 2003-2004 biennium has been a mix of consolidation and transition for TDR. Throughout this period, TDR has continued to deliver success in an international environment of change in infectious diseases research, most notably highlighted by the increase in consortia, public-private partnerships and non-governmental organizations established over the last five years. This success has occurred in diverse areas such as trypanosome genomics, malaria drug development, diagnostics development, implementation research for malaria and the more neglected tropical diseases, and sustainable capacity building and best practices.

TDR has also maintained its activities to promote sustainable capacity building as well as research that encourages innovation and new ideas, approaches and tools (such as drugs, vaccines and diagnostics) to tackle diseases that are primarily associated with poverty.

Finally, although this is a report of activities for 2003-2004, we must look to the future. In the world we live in, the only constant is change. TDR has shown itself to be highly adaptable and responsive in the past. With continued support and advice from its partners and stakeholders we are confident that such responsiveness will ensure TDR's continued success and relevance for tropical diseases research.



Dr A. Asamoah-Baah

Assistant Director-General

*WHO Communicable Diseases programme,
and Special Programme Coordinator*



TDR research has also led to the concept of home management of malaria.

Introduction

It is an honour and a privilege to provide this introduction to the 2003-2004 biennial report as Director of TDR, and to follow on in a line of succession from Ade Lucas, Tore Godal and Carlos Morel, to whom so much is owed.

TDR has a long and proud history of achievement based on its engagement with scientists globally. One aspect of its appeal to partners and stakeholders has been its emphasis on both 'use-inspired' research to deliver new tools, methodologies and strategies to fight tropical diseases, and on strengthening and utilizing research capabilities in countries afflicted by these diseases. A second aspect of its appeal has been to include both scientists and health professionals in its review processes and its agenda and priority-setting exercises.

Past examples of TDR successes include working with industry to develop: multi-drug therapy for leprosy, ivermectin for control of onchocerciasis, and, more recently, miltefosine for treatment of visceral leishmaniasis. Building on concepts put forward by scientists, TDR has helped coordinate large multicountry studies to provide evidence in support of policy for use of: fumigant canisters for control of triatomine bugs responsible for transmission of Chagas disease; insecticide-treated bednets for prevention of malaria transmission by mosquitoes; and artemisinin combination therapy for the treatment of malaria. As mentioned in more detail in this report, TDR-sponsored research has also led to the concept of home management of malaria and community-directed interventions, e.g. for the distribution of ivermectin as part of onchocerciasis control at the periphery of the healthcare system.

Underpinning all of this has been the continuous attention paid to individual and institutional capacity building. Many alumni of TDR are now in positions of authority and influence, either as scientists of international repute or as contributors to national and international programmes. Many institutions have gained international standing with the help of TDR support. Increasingly in recent years, additional attention has been paid to issues of building capacity for best practice such as good clinical practice, ethical review and project management. Much of this has been generated through the creation of networks and partnerships and, in some cases regional forums, to drive the activities. These partnerships are increasingly being led by southern investigators and southern institutions.

Consolidation of 2000-2005 strategy

The last biennial report focused attention on the development of a new results-oriented strategy for TDR. This was described through a matrix structure (Figure 1, next page). One axis of the matrix focused on defined functional activities i.e. basic and strategic research to generate new knowledge, product R&D to produce new tools, implementation research to produce new methods, and strategies for integration into healthcare systems. The other axis of the matrix focused on TDR's ten target diseases.

In the last report we focused on our results in terms of functional activity. In this report we focus on the output by disease to demonstrate the flexibility of perspective allowed by the matrix system.

Partnerships are increasingly being led by southern investigators and southern institutions.

Figure 1
TDR strategic emphases matrix.

TDR Strategic Emphases Matrix		TDR Diseases: Category I (Emerging and uncontrolled diseases)				TDR (Control strategies)
		African trypanosomiasis	Dengue	Leishmaniasis	Malaria	
New Basic Knowledge	New and Improved Tools	New and Improved Methods	New and Improved Strategies and Policies	New Basic Knowledge	New and Improved Tools	New and Improved Methods
New Basic Knowledge	New and Improved Tools	New and Improved Methods	New and Improved Strategies and Policies	New Basic Knowledge	New and Improved Tools	New and Improved Methods
New Basic Knowledge	New and Improved Tools	New and Improved Methods	New and Improved Strategies and Policies	New Basic Knowledge	New and Improved Tools	New and Improved Methods
New Basic Knowledge	New and Improved Tools	New and Improved Methods	New and Improved Strategies and Policies	New Basic Knowledge	New and Improved Tools	New and Improved Methods

- Ridley RG. Research on infectious diseases requires better coordination. *Nature Medicine*, 10, 2004, 1-4.
- Ridley RG. Communicable diseases: a research perspective. In: *Global Forum update on research for health 2005*: 80-83. Geneva, The Global Forum for Health Research.

Furthermore, we do not view the research priorities bulleted within the disease areas as isolated activities. Rather we see them as fitting into several streams of research that are driving ultimately to an objective that will have a health impact and meet a need of disease control. These streams are highlighted within the different sections. The concept of streaming is being developed further.

In looking ahead to further refinement of TDR strategy, it should be noted that the matrix as currently represented does not refer to research capacity building or other cross-cutting issues including research activities that span multiple diseases. A complementary view of how research transitions from basic research to interventions incorporated into health systems is provided in figure 2.^{1,2} Incorporating cross-cutting issues into the matrix analysis of TDR's strategy is a challenge that is currently being addressed.

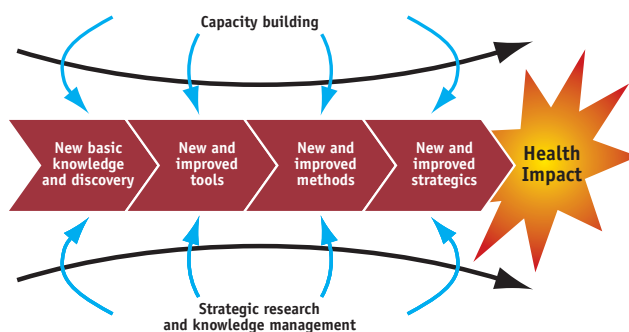





















Figure 2
Transitioning of TDR research.

TDR Diseases: Category 2 (Data available but disease burden persists)		TDR Diseases: Category 3 (Control strategy proven effective, disease burden falling and elimination planned)			
Schistosomiasis	Tuberculosis	Chagas disease	Leprosy	Lymphatic filariasis	Onchocerciasis
<ul style="list-style-type: none"> Bioinformatics and applied genomics for identifying targets for drugs, vaccines and diagnostics Pathogenesis (host-pathogen interactions) focusing on reproductive health issues and immunological aspects of co-infection Socioeconomic impact and methodology for burden of disease assessment 	<ul style="list-style-type: none"> Bioinformatics and applied genomics for identifying targets for drugs, vaccines and diagnostics Impact of health sector reform, globalization and inequality of access 	<ul style="list-style-type: none"> Bioinformatics and applied genomics for identifying targets for drugs and elucidation of pathogenesis and risk factors Genetic and entomological studies on vectors (e.g. mechanisms of resistance, adaptation to ecological changes) 	<ul style="list-style-type: none"> Bioinformatics and applied genomics for identifying targets for diagnostics of infection with <i>Mycobacterium leprae</i> Pathogenesis of nerve reactions Social and behavioural constraints for leprosy elimination 	<ul style="list-style-type: none"> Bioinformatics and applied genomics for identifying targets for drugs Prevalence/reversibility of disease manifestations after treatment, especially in children 	<ul style="list-style-type: none"> Bioinformatics and applied genomics for identifying targets for drugs Understanding ivermectin-resistance mechanisms 
<ul style="list-style-type: none"> Discovery and development of new drugs Evaluate safety and efficacy of existing drugs that are potentially anti-schistosomal Review of vaccine research and development Assess technical and use profiles of available diagnostics 	<ul style="list-style-type: none"> Diagnostic test development: detection of disease, rifampicin resistance, latent infection Discovery and development of new drugs 	<ul style="list-style-type: none"> Discovery and development of new drugs Clinical research on proposed prognostic markers of disease 	<ul style="list-style-type: none"> Rifampicin susceptibility test development Development of a test for infection with <i>M. leprae</i> Development of tools for early diagnosis and treatment of leprosy reactions 	<ul style="list-style-type: none"> Discovery and development of macrofilaricidal drugs or drugs to permanently inhibit microfilariae production Further development and evaluation of diagnostics for drug(s) target 	<ul style="list-style-type: none"> Discovery and development of macrofilaricidal drugs or drugs to permanently inhibit microfilariae production Development of diagnostics for surveillance Development of ivermectin resistance test 
<ul style="list-style-type: none"> Field evaluation of existing diagnostics Rapid assessment method for prevalence of intestinal schistosomiasis Optimization of praziquantel (alone or in combination with artemisinins or mefloquine) 	<ul style="list-style-type: none"> Establishment of role of fixed-drug combinations (FDCs) and evidence base for public health use Development of evidence base for effectiveness of TB preventive therapy in high HIV prevalence areas 	<ul style="list-style-type: none"> Development of methods for control of non-domesticated vectors Insecticide effectiveness and the emergence of vector resistance Evaluation of vector detection tools in low density transmission areas Evaluation of non-conventional diagnostics 	<ul style="list-style-type: none"> Development of shorter universal treatment regimens 	<ul style="list-style-type: none"> Assessment of efficacy and safety of albendazole combinations 	<ul style="list-style-type: none"> Field evaluation of diagnostics for surveillance 
<ul style="list-style-type: none"> Development of strategies for sustainable control and surveillance in different endemic regions, including improved communication strategies 	<ul style="list-style-type: none"> Analysis of approaches to use of antiretrovirals in high HIV-prevalence areas for prevention of primary and secondary TB 	<ul style="list-style-type: none"> Improved strategy for control of anti-intestinal tritomonas Development of strategies for control of expansion of infection within the Amazon region New indicators for control programmes Identification of determinants of effective implementation for <i>Trypanosoma cruzi</i>-safe blood programmes 	<ul style="list-style-type: none"> Development of strategies for integration of existing therapy (MDT) into general health services Modelling the impact of MDT on transmission 	<ul style="list-style-type: none"> Development of evidence-based guidelines for elimination strategies using available drug combinations Development of improved drug delivery strategies, including advocacy strategies Development of sustainable strategies for management of lymphoedema and genital-urinary complications 	<ul style="list-style-type: none"> Development of strategies for sustainable drug delivery under Onchocerciasis Control Programme in West Africa (OCP) and African Programme for Onchocerciasis Control (APOC) Feasibility and cost-benefit of onchocerciasis elimination with ivermectin Development of rapid mapping strategies for low bur

www.who.int/tdr/grants/strategic-emphases

October 2002

Continued high quality research and capacity building output

A strategy is only as good as the output and impact it generates. The past biennium saw several significant advances generated through TDR-sponsored research and capacity building have major impact. Although these are described in more detail within the document, I would particularly like to highlight:

Malaria

- The extension of labelled use of Coartem to children as small as 5 kg, enabling the drug to be better utilized within the most 'at risk' group of malaria patients (i.e. very young children).

- The registration of Lapdap as a new antimalarial agent.
- The development of a strategy for home management of malaria that is now being implemented in many countries and is viewed as a strategically important component of many applications to the Global Fund to Fight AIDS Tuberculosis and Malaria.

Onchocerciasis

- The establishment of a methodology to rapidly determine where it is safe to use the routine strategy of community-directed treatment with ivermectin, and in which areas special precautions are required because of the risk of severe adverse reactions due to high in-

A strategy is only as good as the output and impact it generates.

fection by another parasite, *Loa loa*. Previously, ivermectin distribution was restricted in much of central Africa due to lack of information on the distribution of loiasis.

Lymphatic filariasis

- Data from long-term TDR-sponsored studies on mass drug administration have demonstrated that, in many settings, we need more than the anticipated four years of treatment to interrupt disease transmission. This has caused a re-evaluation of the strategy to eliminate lymphatic filariasis.

Human African trypanosomiasis

- TDR has convened a consortium of organizations that has led to an international effort to fully sequence the tsetse fly genome, with potential benefits for tsetse control.

Sexually transmitted diseases – syphilis

- TDR's entry into sexually transmitted disease diagnostics is starting to have a major impact on public health. The validation of several point-of-care tests and their placement on the WHO procurement list have provided a level of quality assurance for the products and increased uptake. Their role in ad-

ressing congenital syphilis in newborns is being urgently addressed in several countries.

Strategic and discovery research

- In addition to the more directed and immediately 'control applicable' achievements mentioned above, TDR continues to engage in and promote innovative upstream research that can generate the new ideas and approaches of the future.
- Within this context, social economic and behavioural research continues to make a broad impact across the work of the Programme.
- As well as provision of project funding, strategically directed research activity is promoted through focused workshops and the creation of focused networks of investigators.

Capacity building through 'best practice' networks

- Continued attention to research capability strengthening remains at the heart of TDR activities, through project grants, establishment of short courses, and promotion of networks.
- Capacity building for malaria research through engagement with the Multilateral Initiative for Malaria continues to have a significant impact.
- Increased efforts are being made to more fully integrate research capacity building into all our research activities as indicated in much of this report.
- Particularly noteworthy innovative achievements worthy of highlighting include the 'best practice' networks:
 - The TDR-assisted Strategic Initiative for Developing Capacity for Ethical Review (SIDCER) continues to devel-

At a workshop in Entebbe. The Forum for African Medical Editors (FAME) is beginning to have an impact.

Credit: WHO/TDR/Certain





op and have impact. Based on operational guidelines published by TDR, self-sustainable regional forums have been established around the world and in several countries there have been resulting improvements in legislation on the subject of clinical studies and their ethical review.

- A second network is starting to have a major impact, namely the Forum for African Medical Editors (FAME). Through convening several meetings of interested parties, a self-sustainable forum has been developed that has led to the publication of guidelines and an enhancement of quality and citation of African medical journals.

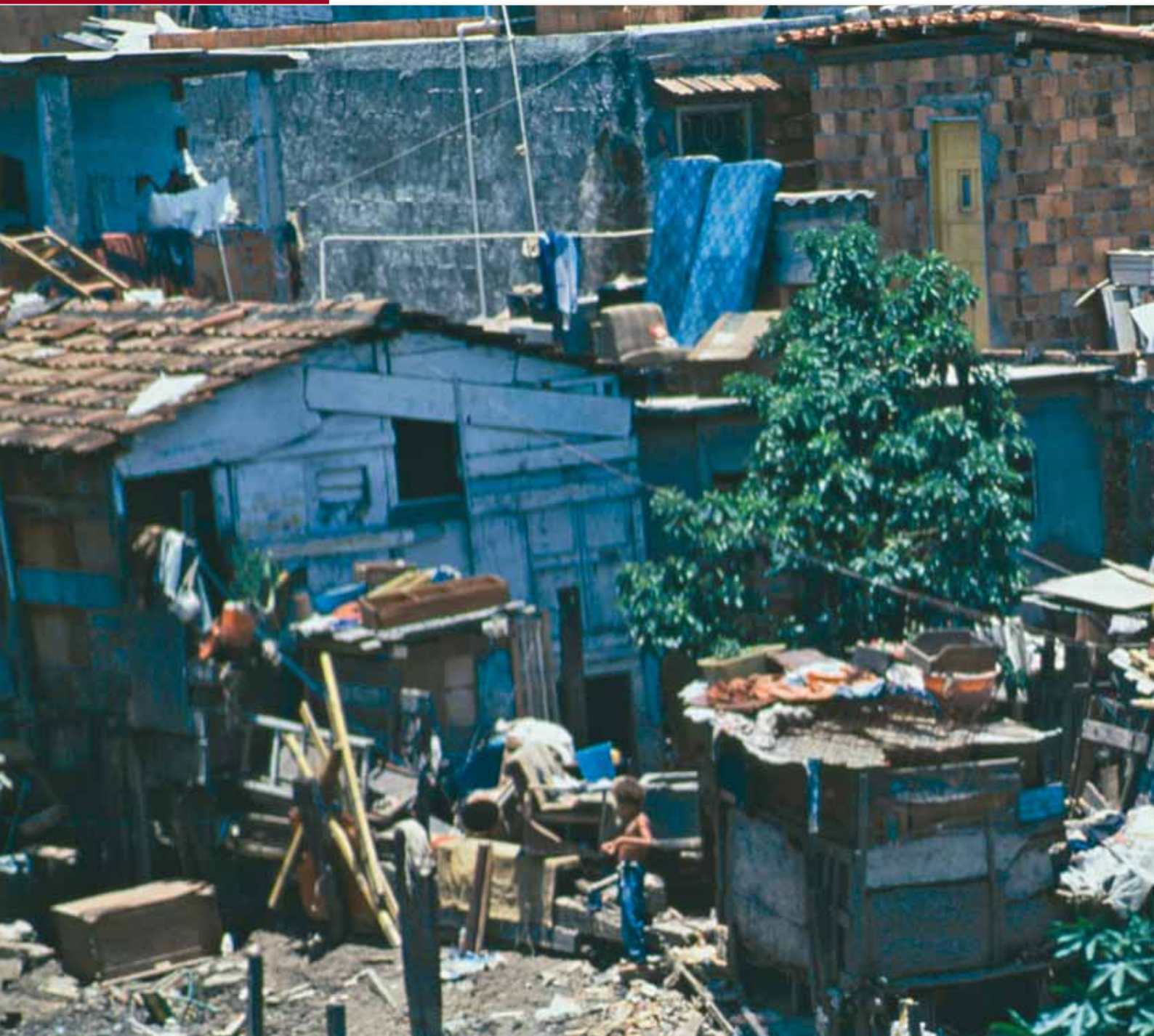
Some additional statistics

- TDR engaged with 1038 research partners in 2003-2004. Of these, over 76% were from developing countries.
- TDR-sponsored research accounted for 426 research publications in 2003-2004. Of these, over 52% had first authors from developing countries.

These figures, available to us due to the development of our 2000-2005 strategy and concomitant monitoring and evaluation of our outputs, indicate very powerfully our commitment to research capacity building and developing country stakeholder participation in health research.

FERCAP – the Forum for Ethical Review Committees in Asia and the Western Pacific – is a forum for developing capacity for ethical review in Asia.

Credit: WHO/TDR/Karbwang



The link between health and human development and the alleviation of poverty has never been so well recognized.

Credit: WHO/TDR

Looking to the future

TDR is a Special Programme co-sponsored by UNICEF, UNDP, the World Bank and WHO. It is governed through a Board of the co-sponsors and 27 government representatives. It is truly a global,

intergovernmental programme that aims to respond to the global need to fight a set of tropical diseases associated with poverty.

Much of the attention of the international health and development community



Research is seen as a vital link to delivering on health and development goals.

Credit: WHO/TDR

is currently focused on the Millenium Development Goals. The link between health and human development and the alleviation of poverty has never been so well appreciated or respected, and research is increasingly being seen as a vital link to delivering on health and development goals.

However, as we link our research into health and development objectives, we should never lose sight of the power of 'innovation' in research, the power to create a totally new paradigm for health control through a technological breakthrough. Such breakthroughs can be pharmaceutical in nature, e.g. an effective vaccine would revolutionize malaria control, or they may be methodological in nature, e.g. through novel approaches to disease management, or they may even be organizational and managerial in nature, e.g. through the creation of new partnerships, structures and interfaces.

TDR is in a unique position. It is placed within WHO at the heart of the UN's special technical agency with responsibility for health. Because of this, it is linked to the structures and organizations dealing with the health concerns in developing countries on a day-to-day basis. TDR understands the health needs and concerns of poor populations. At the same time, it is linked through its scientific and

research mandate to global research expertise in tropical diseases research. It is multidisciplinary, transcends the single-disease approach of many organizations, and addresses issues beyond the biomedical including in social, economic and behavioural research.

Innovation and the vision to address the big issues and concerns of international health research within the context of resource-constrained health systems and communities will rely on insights gained from multidisciplinary expertise, experience and approaches. Through its multiple partners, stakeholders and scientific collaborators, TDR offers a powerful mechanism that can help both to conceptualize research strategies of relevance to disease control and implement them from an end-user perspective.

TDR's challenge in the coming years is to generate the vision and organization that can work with partners to deliver on this promise.

Geneva, May 2005

Dr. Rob Ridley
Director TDR

A young girl with the facial signs of post-kala azar dermal leishmaniasis (PKDL). Whether miltefosine can be used to treat PKDL is currently being assessed.

Credit: WHO/TDR/Crump



Leishmaniasis

More than 12 million people in 88 countries are known to be infected with leishmaniasis, but the true burden remains largely hidden. Two million new cases – 1.5 million of cutaneous leishmaniasis, 500 000 of the visceral form of the disease – occur annually, but declaration of the disease is compulsory in only 32 countries and a substantial number of cases are never recorded.

Leishmaniasis is a disease of poverty, and its victims are among the poorest. In India, a country with a high leishmaniasis burden, 88% of leishmaniasis patients have a daily income of less than US\$ 2, poor socio-economic environment and low educational level; they live in either remote rural areas or poor suburbs. There is social stigma associated with the deformities and disfiguring scars caused by some forms of leishmaniasis, and disease-related disabilities impose a great social burden, hampering productivity and socio-economic development.

Leishmaniasis presents a spectrum of clinical manifestations. The visceral disease is particularly prevalent in Bangladesh, India, Nepal, Sudan and Brazil. These countries together account for 90% of the global visceral leishmaniasis (VL) burden. Malnutrition is a well-known risk factor in the development of this form of leishmaniasis, and epidemics flourish under conditions of famine, complex emergency, and mass population movement. The cutaneous disease is particularly prevalent in Afghanistan, Algeria, Brazil, Iran, Peru, Saudi Arabia and Syria, which together account for 90% of the global cutaneous leishmaniasis (CL) burden. Though far less lethal, epidemics of the cutaneous

form are of particular concern in some countries and difficult to control. Other manifestations include post-kala-azar dermal leishmaniasis (PKDL), which can follow recovery from a VL infection and occurs in India and Africa (mainly in Sudan and Kenya). Mucocutaneous leishmaniasis (ML), which can follow cutaneous leishmaniasis and is endemic in Mexico and Central and South America, produces lesions which can lead to extensive and disfiguring destruction of the mucous membranes of the mouth, nose and throat cavities.

More than 20 species of *Leishmania* can infect humans, and other species are emerging, especially in association with HIV/AIDS. Thirty species of sandfly have been incriminated in transmission of the disease. In some areas, leishmaniasis is a zoonotic infection involving various animal reservoirs, while in other areas humans are the sole reservoir of infection, making vector and reservoir control costly and often impractical.

It is planned to eliminate visceral leishmaniasis (i.e. to eliminate the disease as a public health problem) from the Indian subcontinent by 2015. The tools under discussion for this include vector control (by insecticide spraying and impregnated bednets), rapid diagnostic tests for active case detection, and the new drugs miltefosine and paromomycin (see below). A vaccine for leishmaniasis would also be a boon for global disease control, but no effective vaccine is yet on the market. During 2003-2004, TDR continued its support for research on a number of these tools, as described below.



A doctor watches as a young boy in hospital takes a capsule of miltefosine, the first oral treatment for leishmaniasis.

Credit: WHO/TDR

Towards improved clinical management

Diagnosis

VL is ideally diagnosed by demonstrating the parasite in aspirates of spleen, bone marrow, or lymph nodes. But this method - aspiration of tissue - is unsuitable for use in field settings. Through TDR and its partners, three simple non-invasive serological diagnostic tests to detect VL are being evaluated:

- The freeze-dried direct agglutination test (DAT), a serological test that detects antibodies.
- The rK39 dipstick, a serological test based on recombinant leishmanial antigen, which is being tested for use in active case detection, and is under consideration for use in the elimination programme on the Indian subcontinent.
- A latex agglutination urine test. This test detects antigens, and would provide an ideal alternative to detection of antibodies in immunocompromised patients, particularly with the increasing number of HIV co-infected cases and especially in advanced cases where immune response is impaired.

Field evaluation of the tests is being carried out in a multicentre study. Three trials, in Ethiopia, Sudan and Kenya, are nearing completion; two trials, in Nepal and India, are ongoing. The trials will determine whether the sensitivity and accuracy of the tests are sufficient for control programmes.

Treatment

Miltefosine, the first oral treatment for visceral leishmaniasis, is being developed in close collaboration between the Indian Government, Zentaris and TDR.³ Miltefosine is potential first-line treatment for elimination of kala-azar (VL) on the Indian subcontinent. The drug was first

registered for use in VL in India in 2002, and later (November 2004) registered in Germany. It is now produced in both countries. TDR is facilitating extension of its registration to other disease-endemic countries. Phase IV clinical trials have been completed in Nepal, where registration is expected in 2005. A protocol has been developed for Phase III trials in Brazil and Ethiopia; the trials are expected to be completed by 2007. The chances of showing the drug to be effective and safe are thought to be high.

The efficacy and safety of miltefosine are also being assessed in Indian patients for treatment of PKDL. This manifestation of leishmaniasis occurs as a skin eruption after healing of visceral leishmaniasis (VL). PKDL, for which there is no established effective treatment, is a source for VL transmission. A protocol for Phase II trials has been developed, and preparations are under way at the trial sites, in anticipation that label extension could be obtained in India by 2008. The teratogenic effects of miltefosine seen in animals, however, mean the drug cannot be used in pregnant women; there is also a worry that resistance might develop to the compound.

Paromomycin (an off-patent aminoglycoside antibiotic used in humans as an oral formulation for enteric protozoa and as a topical formulation for Old World CL⁴) is being developed as a potential alternative or second-line therapy for elimination of VL on the Indian sub-continent. There is a propensity for rapid development of resistance to the compound due to its long half-life.

Paromomycin is being developed as an injectable formulation, in partnership with the Institute for OneWorld Health, to treat antimony-resistant *L. donovani* cases. A phase III trial of the injectable formulation, to determine safety and efficacy in patients of 12 years and over in comparison with amphotericin B (currently a main

3 Bhattacharya SK et al. Efficacy and tolerability of miltefosine for childhood visceral leishmaniasis in India. *Clinical Infectious Diseases*, 2004, 38(2):217-221.

4 Asilian A et al. Treatment of cutaneous leishmaniasis with aminosidine (paromomycin) ointment: double-blind, randomized trial in the Islamic Republic of Iran. *Bulletin of the World Health Organization*, 2003, 81(5):353-359.



It is planned to eliminate visceral leishmaniasis from the Indian subcontinent by 2015.

Credit: WHO/MEDIA

Ultimately ways of reaching visceral leishmaniasis patients with full and adequate treatment will be defined.

alternative drug which is toxic and expensive), has been completed in India. In all, 667 patients were recruited at four trial centres by June 2003. The trial concluded in November 2004 and the data are now being analysed to determine cure rates six months after treatment. Preliminary results suggest paromomycin is safe and has a good initial cure rate. The product will be submitted to the regulatory authorities in India in 2005 and regulatory approval could be obtained by 2006.

Delivery

As a continuation of the miltefosine studies in India, and to help expand diagnosis and treatment, studies to develop cost-effective strategies for delivery of new drugs and diagnostics against VL are planned to take place in Bihar, India.

Preparations for these studies (call for letters of interest, proposal selection, protocol development) have been completed; field work has yet to begin. It is hoped that national clearance for the studies will be obtained by early 2005.

The studies will first describe health-seeking behaviour, and the direct and indirect costs of provision of diagnosis and treatment, as well as policy related to this, in Bihar. Ultimately ways of reaching VL patients with full and adequate treatment will be defined. In this way, leishmaniasis can be used as a model for drug delivery by health systems. This project relates to the new initiative by countries of the South-East Asia Region to eliminate VL in the region.

Towards a vaccine

Over the past 20 years or so, TDR has supported research on vaccines made of whole killed parasites (first generation vaccines). Clinical trials showed some of these to be safe and immunogenic, and have more recently been aimed at demonstrating their efficacy. The most immunogenic formulations (of *L. major*) contain alum and BCG as adjuvant; they are known as alum-precipitated autoclaved *Leishmania major* (ALM) plus BCG.⁵ During 2003-2004, alum-ALM+BCG was tested as a therapeutic vaccine for PKDL. Preliminary results of these hospital-based studies in the Sudan suggest the vaccine to be safe and efficacious; efficacy was seen in terms of shorter duration of treatment and less recurrence.

A trial investigating the efficacy of alum-ALM+BCG via live *Leishmania* challenge (initiated in Iran during the previous biennium) was completed in 2003. However, the effectiveness of live challenge as a method of evaluating vaccine candidates requires further evaluation. A separate phase 3 study of efficacy of a killed *L. amazonensis* vaccine in Colombia was completed in 2003. Results did not support efficacy of the vaccine for prophylaxis in volunteer Colombian soldiers.

During 2003-2004, TDR assisted in preparations for developing a second-generation vaccine based on a purified recombinant *Leishmania* fusion protein (containing portions of three different antigens, and formulated with the adjuvant mono-phosphoryl lipid A in squalene oil). The development plan includes trials for prophylactic and therapeutic application in Sudan, India and South America and is now being driven by the Infectious Diseases Research Institute (IDRI, USA).

During the biennium, TDR supported pre-clinical vaccine discovery research, including studies on chimeric genes containing the A2 protein, for use as an amastigote-specific vaccine against visceral leishmaniasis, and on a DNA vaccine – GP63 and GP46 given as VR1012 plasmid constructs with or without alum – against *Leishmania mexicana*. These constructs showed some efficacy as well as cross-protection between *L. mexicana* and *L. donovani*, but alum had little effect on the development of lesions. Protective immune responses to *L. infantum* induced by cysteine proteinases are being evaluated in separate studies. Using a model system for evaluating potential vaccine candidates against visceral leishmaniasis, the infectivity of metacyclic promastigotes in BALB/c mice was enhanced by promastigote secretory gel (PSG) from the midgut of infected sandflies.

TDR also supported studies to increase the efficacy of vaccines through the use of adjuvants. Coupling the OprI lipoprotein from *Pseudomonas aeruginosa* with a *Leishmania* antigen (CGp63) was shown to constitute an appropriate adjuvant to include in vaccines against diseases in which type 1 immune responses are important for protection. Superiority of COOHgp63 (a truncated 32-kDa version of the 63-kDa major cell surface glycoprotein gp63) over gp63 was demonstrated.

New knowledge

Further to its earlier support for analysis and mapping of the *Leishmania* genome, and based on the knowledge gained, TDR continues with postgenomic activities on this parasite.

Both parasite and host factors are being studied for their roles in pathogenesis and virulence. Ongoing work includes molecular characterization of leishporin,

Thirty species of sandfly have been incriminated in the transmission of leishmaniasis.

Credit: WHO/MEDDIA



5 Kamil AA et al. Alum-precipitated autoclaved *Leishmania major* plus bacille Calmette-Guerrin, a candidate vaccine for visceral leishmaniasis: safety, skin-delayed type hypersensitivity response and dose finding in healthy volunteers. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 2003, 97:365-368.

a pore-forming protein of *Leishmania amazonensis*, with a view to investigating the role of this protein in the parasite's virulence and pathogenesis; and functional and biochemical characterization of the putative *Leishmania* telomeric proteins La Rpa-1 and LaRbp38 with a long-term view to disturbing the telomeric chromatin of *L. amazonensis* as a means of arresting parasite growth. The role of the host's apoptosis (programmed cell death) mechanism in disease progression and healing is another topic;⁶ enhanced death of T-lymphocytes, for example, could contribute to spleen enlargement in VL, or to induction and healing of lesions in CL.

Studies of the immune mechanisms underlying CL and ML, and the markers involved with resistance or disease progression, include one on T-cell receptor usage in CL, and another on the role of innate immunity (macrophages, dendritic cells, and neutrophils) in the pathophysiology of *L. major* infection, using a congenic mouse model.

Potential parasite targets for interventions (diagnostics, drugs, vaccines) that are under study include kinesins (motor proteins associated with microtubules) and *Leishmania* telomeric proteins. Methods of diagnosis are particularly needed for PKDL, so TDR researchers are looking for parasite determinants and prognostic markers for development of PKDL. Changes in protein expression in drug-resistant and drug-sensitive *L. donovani* infections are also being examined.

In a comparative genomics (proteomics) approach, the *L. braziliensis* and *L. major* genomes are being compared in silico, in an analysis being carried out in disease-endemic countries. Proteins secreted by promastigotes are being identified. High sequence divergences between the two species are suggested, which might be re-

lated to fundamental aspects of parasite biology and host/parasite interaction.

Building research capacity

As part of its capacity strengthening mandate, TDR encourages research that will allow transfer of relevant technologies to disease-endemic countries. In the case of leishmaniasis, geographical information systems (GIS) and routine culturing techniques were introduced to an institute in Sudan as part of a study which began to produce information about drug resistance. Methods including kDNA polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) profiles, and gp63 n-acetyl glucosamine-1-phosphate transferase (NAGT) PCR RFLP, are now established in the Institute of Endemic Diseases in Sudan through a study aiming at better taxonomy of Sudanese *Leishmania* isolates.

The miltefosine studies on the Indian subcontinent are increasing capacity in clinical data management and good clinical practice (GCP). TDR Research Capacity Strengthening (RCS)-supported activities in preparation for leishmaniasis vaccine development in South America and Sudan included a trial monitoring workshop, a data management workshop, data management training and software evaluation, and GCP training. Other outcomes of research supported by RCS during the biennium included demonstration of the utility of the mariner transposition system in trapping genes, identifying their subcellular location, and studying drug resistance. In another study, characterization of the four clinical forms of leishmaniasis reported from Sudan showed that VL, PKDL and ML are all caused by the *L. donovani* complex, while the cutaneous leishmaniasis isolates were all characterized as *L. major*.



A report of the Scientific Working Group on Leishmaniasis was published in 2004.

6 Eidsmo L et al. The contribution of the Fas/FasL apoptotic pathway in ulcer formation during *Leishmania major*-induced cutaneous leishmaniasis. *The American Journal of Pathology*, 2005, 166(4):1099-1108.



Mobile team performing the card agglutination test for trypanosomiasis (CATT) while investigating sleeping sickness in the Democratic Republic of the Congo. The CATT is a useful test for *T. b. gambiense* infection, but no comparable diagnostic procedure exists for *T. b. rhodesiense*.

Credit: WHO/H. Bower

Human African trypanosomiasis

The prevalence of human African trypanosomiasis (HAT) rose steadily after the 1960s, but is now on the wane. WHO estimates that 300 000 to 500 000 people are affected, but there are no accurate figures.

The nature of this disease is a challenge. HAT occurs in two forms (chronic and acute), in two different stages (early and late), and is fatal unless treated. Epidemics develop if there is no intervention. *Trypanosoma brucei gambiense*, found in central and West Africa, causes chronic infection; a person can be infected for months or years without obvious symptoms, which emerge only when the disease has reached the late stage. *T. b. rhodesiense*, found in southern and East Africa, causes acute infection that emerges after a few weeks; it is more virulent than *T. b. gambiense*. Domestic and wild animals are known to be a major reservoir of *T. b. rhodesiense*, but the role they play as reservoir for *T. b. gambiense* is not clear.

The major challenges faced by control are inadequate resources, inadequate surveillance, and inadequate knowledge of the disease; lack of effective diagnostics; drugs that are costly and/or cause adverse reactions; population movements; and agro-ecological changes that alter the tsetse habitat and increase contact between humans and the tsetse fly, vector of the disease.

HAT has a major impact on the health and development of large numbers of marginalized people, and is coincident with much of the world's most acute poverty. The infection contributes to

poverty more through its effects on livestock than through its effects on humans. In animals, African trypanosomiasis causes an estimated economic loss of US\$ 4.5 billion each year. Presence of the tsetse fly effectively limits meat and dairy production across vast tracts of land, and prevents the use of draught animals, limiting productivity and contributing to poverty.

In its bid to make research work for poor people, TDR supports research on drugs, diagnostics, and vector control, as well as capacity strengthening for research on HAT.

New drugs and treatment regimens

Current treatment for HAT is problematic, especially for patients with late-stage disease and nervous system involvement. The available drugs cannot be taken orally and are generally toxic. Reports of treatment failure are increasing. Pentamidine (five-day regimen) and suramin are used for early-stage disease, while melarsoprol (very toxic with 5-15% encephalopathy; increasing resistance) and intravenous eflornithine are used for late-stage disease. Eflornithine is only effective for *T. b. gambiense* infection; for late-stage *T. b. rhodesiense* infection, there are no alternative drugs when melarsoprol has failed. Eflornithine use is increasing and the drug is currently being donated by Sanofi/Aventis, but it remains expensive to manufacture.

The challenges faced in drug development include poor access to patients (due to low prevalence of disease, poor diag-

Testing for symptoms of sleeping sickness with mother and child patients in a rural clinic.

Credit: WHO/H. Bower

Poor access to patients is one of the challenges faced by control programmes. This trypanosomiasis clinic is in a remote area: Maluku, Democratic Republic of the Congo.

Credit: WHO/H. Bower



nosis, long follow-up, political instability), lack of funds, lack of infrastructure for clinical trial sites, lack of personnel, and lack of pharmaceutical partners, so there is slow progress in trials of existing products.

Drugs being developed for early-stage disease

An oral anti-trypanosomal formulation has been requested by control programmes for human use. Berenil is widely used in animal trypanosomiasis by the intramuscular route and has some advantages (broad profile, low price, range of manufacturers), but available data on its use in humans are old so new studies are required. An oral formulation is currently being assessed in pre-clinical studies. Progression of this development will depend to some extent on the progress of another compound, DB289, belonging to the same chemical series. The activity of DB289 was confirmed in animal models with TDR support; it is now being developed independently of TDR and is currently in Phase II trials.

The efficacy and safety of short-course (three-day) pentamidine treatment are being established and compared with the standard five-day regimen. The pharmacokinetics of pentamidine were described only after the five-day dosing regimen had long been in use; it is thought likely that drug levels will achieve the same trypanocidal activity in three days. A clinical trial involving 400 HAT-positive patients, whose selection will require screening of 30 000 individuals, is to take place in Angola.

Drugs being developed for late-stage disease

A route for synthesizing eflornithine for use in an oral formulation has been selected, and manufacturers have been identified. Safety and efficacy studies (Phase II studies) are expected to start in 2005. The aim is to evaluate the clinical utility of oral eflornithine, and to register the formulation in France.

TDR is also reviewing studies on the efficacy of nifurtimox, which is normally used for Chagas' disease, but might also be effective against HAT, including late-stage disease caused by either *T. b. rhodesiense* or *T. b. gambiense*. The possibility of testing the efficacy of a combination of nifurtimox and intravenous eflornithine is also being assessed; clinical studies will start soon.

Towards improved diagnosis

The card agglutination test for trypanosomiasis (CATT) is useful for screening of *T. b. gambiense*, but there is no comparable test for *T. b. rhodesiense* infection. Correct diagnosis and staging (determining whether the infection is in the early or late stages) is, however, critical for effective management and treatment. The current staging test involves lumbar puncture, a cumbersome procedure not suitable for the field. Diagnostics for HAT is a priority area for TDR, and TDR is currently supporting two lines of work.

Firstly, surface-enhanced laser desorption/ionization (SELDI) technology is being investigated. This mass spectrometry technique analyses protein patterns (changes in abundance, structure, or function), which can indicate pathological change in serum prior to development of clinical symptoms. SELDI has been shown to have the potential to provide a sensitive and specific test for HAT.

The second line of work is to develop and evaluate a dipstick test suitable for diagnosing the infection. TDR is currently supporting one project on target identification and another on the development and evaluation (in a Phase II trial) of a single format lateral flow test.

The management of individuals who are serologically positive (by the CATT) but parasitologically negative is controversial,

but there is anecdotal evidence they later develop unmistakable HAT. A study to estimate the risk of developing overt HAT among serologically suspected cases began in Cameroon in late 2003. This study incorporates the lessons learnt from earlier investigations and is under review at the time of writing.

Vector control

Vector control based on insecticides, targets and traps will be important in the control of African trypanosomiasis for the foreseeable future, and one main line of TDR research is to develop sustainable community-based strategies for tsetse control. Mass trapping using insecticide- or attractant-impregnated traps was used extensively in the past, and is an efficient method of control. However, lack of funding meant it was not sustained. In 2004, TDR published a review of traps and targets for tsetse and HAT control.⁷

With a view to future vector control, TDR is supporting a molecular entomology approach. The objectives are to generate knowledge, by 2009, on molecular and genomics aspects of the tsetse (*Glossina*) fly vectors in order to develop tools to genetically transform them, to identify tsetse genes responsible for disrupting trypanosome growth, and to develop methods to spread selected genes in wild tsetse fly populations.

Studies that TDR is supporting include those aiming at understanding the genetic basis of vector competence in natural populations. Examples of studies on tsetse-trypanosome interactions include looking at the role of a lectin-trypsin complex in the gut of the fly, and at the role of anti-microbial immune peptides in the killing of trypanosomes in the tsetse fly. This work will provide a foundation for manipulating and initiating control of tsetse populations.

One main line of TDR research is to develop sustainable community-based strategies for tsetse control.

⁷ Kuzoe F, Schofield CJ. *Strategic review of traps and targets for tsetse and African trypanosomiasis control*. Geneva, TDR, 2004 (TDR/IDE/TRY/04.1).



Grading coffee. Rural populations are most at risk of sleeping sickness, especially where their work takes them into areas such as forest edges where they may be exposed to tsetse flies, the vectors of sleeping sickness parasites. Credit: WHO/TDR/Mark Edwards

- 8 • Genoscope, France
 • The Institute for Genomic Research (TIGR), USA
 • Sanger Center, United Kingdom
 • Institut de Recherche pour le Développement (IRD), France and Côte d'Ivoire
 • The South African National Bioinformatics Institute (SANBI), South Africa
 • The Kenya Agricultural Research Institute (KARI), Kenya

- 9 Data from midgut and salivary gland EST libraries from GeneDB at: www.genedb.org/genedb/glossina/

- 10 Lemerrier G et al. A pyrophosphatase regulating polyphosphate metabolism in acidocalcisomes is essential for *Trypanosoma brucei* virulence in mice. *The Journal of Biological Chemistry*, 2004, 279(5):3420-3425.

An International *Glossina* Genomics Initiative (IGGI), composed of funding agencies, sequencing and research centres,⁸ was mobilized by TDR and launched in January 2004. By February 2005, this consortium had generated useful data about the genome size (550 Mbp on average) of four *Glossina* species (including *G. p. palpalis* and *G. m. morsitans*) and produced several thousands of bacterial artificial chromosome (BAC) and expressed sequence tag (EST) libraries, which will be used for cloning, physical mapping, assembly and annotation of the genome sequence.⁹ The availability of the *Glossina* genome will provide substantial opportunities for identifying new targets and developing new control tools.

New knowledge

In addition to genomics applications to HAT vectors (described above), TDR is supporting a variety of genomics studies on the parasite itself.

Identification and validation of targets for use in high-throughput screening for drugs, vaccines and diagnostics for HAT

is one line of research. For example, transgenic parasites expressing proteins such as green fluorescent protein (GFP) and luciferase have potential for high-throughput screening, so drug-sensitive and drug-resistant parasites transfected with reporter genes (e.g. those for GFP and luciferase production) are being assayed for their usefulness in drug screens. A workplan was developed in September 2004 to network researchers using transfections and genomics technology. In other studies, kinesins (motor proteins associated with microtubules) and the acidocalcisome, which has a role in polyphosphate metabolism and is not present in mammalian cells,¹⁰ are being examined as potential drug targets in *T. brucei*.

The hierarchy of expression of variant surface glycoprotein (VSG) genes in *T. b. rhodesiense* is under study as a potential basis for a diagnostic test, and might also have potential as a staging test.

The mechanisms by which trypanosomes penetrate the brain in the mammalian host, and the possibly critical role of chemokines in this process, are being investigated. This work could lead to a novel method of staging the infection. Other foci of TDR basic research include the significance of livestock as a reservoir for gambiense sleeping sickness in NW Uganda, and drug discovery (see p. 80-81).

Building research capacity

There is a particular dearth of scientists working on HAT, as exemplified by 2003 figures for the global number of publications on HAT: 182, of which 17 first authors were from DEC countries, including 11 from Africa. In 2003, a proposal on how to involve researchers from endemic countries was reviewed in TDR, and a decision taken to devote one RCS institutional capacity project to building capacity for



Mass trapping using insecticide or attractant-impregnated traps is an efficient method of control.

Credit: WHO/TDR/Crump

Tsetse fly traps can be an extremely effective method of reducing the tsetse menace.

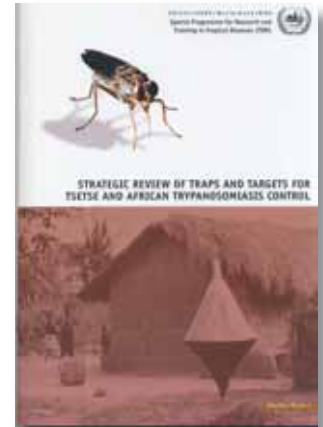
Credit: WHO/TDR/Crump

HAT. A special initiative for capacity strengthening in HAT was started, and three applications were received following a call for proposals.

The TDR Research Steering Group proposed that this special initiative be managed as a network, with one coordinating institute. The Trypanosomiasis Research Centre (TRC, the former Kenya Trypanosomiasis Research Institute or KETRI), Kenya, was identified as coordinating agency in July 2004. TRC will work closely with five other institutions to take advantage of their cutting-edge technology

and training potential, and will coordinate the development of a proposal for research capacity building for HAT to be submitted to TDR for consideration by its Research Strengthening Group in 2005. The initiative will focus on highly endemic countries e.g. Angola, Democratic Republic of the Congo, but take into account other areas where the disease is endemic.

Individual TDR training grants are supporting, for example, the search for anti-trypanosomal compounds in medicinal plants.



TDR published a review of traps and targets for tsetse and trypanosomiasis control.



Triatomine bugs, the vectors of Chagas' disease parasites, live in cracks and crevices in the walls and ceilings of poorly built houses.

Credit: WHO/TDR

Chagas' disease

About thirteen million people living in Central and South America are currently estimated to be infected with *Trypanosoma cruzi*, the parasite causing Chagas' disease. About 25% of those infected show disease symptoms, which can vary widely depending on the parasite strain, the individual infected and the duration (acute or more long-term) of the infection. It is estimated that 25 to 30% of chronically infected patients will eventually suffer from irreversible damage to the heart and digestive tract, resulting in some 14 000 annual deaths and causing considerable morbidity.

The disease can be transmitted in three ways: by the bite of bloodsucking triatomine insect vectors, by blood transfusion, or by congenital transmission. In countries of the Southern Cone of South America (Argentina, Bolivia, Brazil, Chile, Paraguay, Uruguay), the main vector species is domiciliated and lives in or around human housing; in Central America, Mexico, and regions of the Andean countries and Amazon basin, the vector species live both in dwellings and in uninhabited areas. In line with these differences in vector behaviour, control measures – insecticide treatment of housing, plus mandatory screening of donated blood – have been largely successful in eliminating transmission of *T. cruzi* in many areas where the vectors are domiciliated, but not elsewhere. Overall, the annual incidence of new cases is estimated to have fallen from 700 000 – 800 000 in the 1980s to around 200 000 today.

However, Chagas' disease remains a serious problem. It disproportionately affects poorer people, especially those living in rural areas and in poor-quality housing, where the vectors find convenient refuges

in cracks and crevices. Poverty also limits patients' access to treatment, whose costs in many countries are high. Health systems in most endemic countries are such that the socioeconomic costs of the disease are entirely borne by the patient. In some countries, availability of the drugs most commonly used for treatment is limited. Current drugs (benznidazole and nifurtimox) can cure at least 50% of patients if administered during the acute stage of the disease, but they are not effective against the chronic stage of the disease once damage to heart and digestive tract starts to occur. The pathogenesis of the disease is not well understood, and methods to assess its progression and cure are not well developed.

Although the numbers of affected individuals are falling, maintenance of this trend depends on continued surveillance and intervention where necessary. Research on new intervention methods, strategies and policies is now (since 2000) managed by the Pan-American Health Organization (PAHO), with an emphasis on control of non-domiciliated triatomines and interruption of vectorial transmission. TDR continues to carry out research on improving treatment and investigating the basic biology and pathogenesis of the disease. TDR's portfolio and strategy concerning Chagas' disease will be reviewed and reassessed by a forthcoming scientific working group (SWG), to be held in 2005.

Towards improved treatment for chronic disease

TDR is currently funding two projects aimed at evaluating the clinical use of new serological tools to assess cure and



A triatomine bug: vector of Chagas' disease.

Credit: WHO/MEDDIA

Substandard living conditions in shanty towns expose the inhabitants to a wide variety of diseases. Poor quality housing is a prime habitat for the vector of Chagas' disease.

Credit: WHO/TDR/Mark Edwards



11 Urbina JA, Docampo R. specific chemotherapy of Chagas disease: controversies and advances. *Trends in Parasitology*, 2003, 19(11):495-501.

12 Amaya et al. The high resolution structures of free and inhibitor-bound *Trypanosoma rangeli* sialidase and its comparison with *T. cruzi* trans-sialidase. *Journal of Molecular Biology*, 2003, 325:773-784.

13 Menezes CA et al. Phenotypic and functional characteristics of CD28+ and CD28- cells from chagasic patients: distinct repertoire and cytokine expression. *Clinical and Experimental Immunology*, 2004, 137(1):129-138.

14 Schijman AG et al. Aetiological treatment of congenital Chagas' disease diagnosed and monitored by the polymerase chain reaction. *Journal of Antimicrobial Chemotherapy*, 2003, 52:441-449.

progression of the disease. Protocols have been developed for a multicentre clinical study to assess the value of benznidazole in treating patients with chronic infection before irreversible tissue damage occurs. These plans are being reviewed by a project development team before their proposed implementation. Of several thousand compounds screened during the biennium for potential anti-*T. cruzi* activity in vitro, none was more promising than the triazoles studied during the previous biennium.¹¹ Further development of triazoles for Chagas' disease depends on identification of an interested pharmaceutical partner.

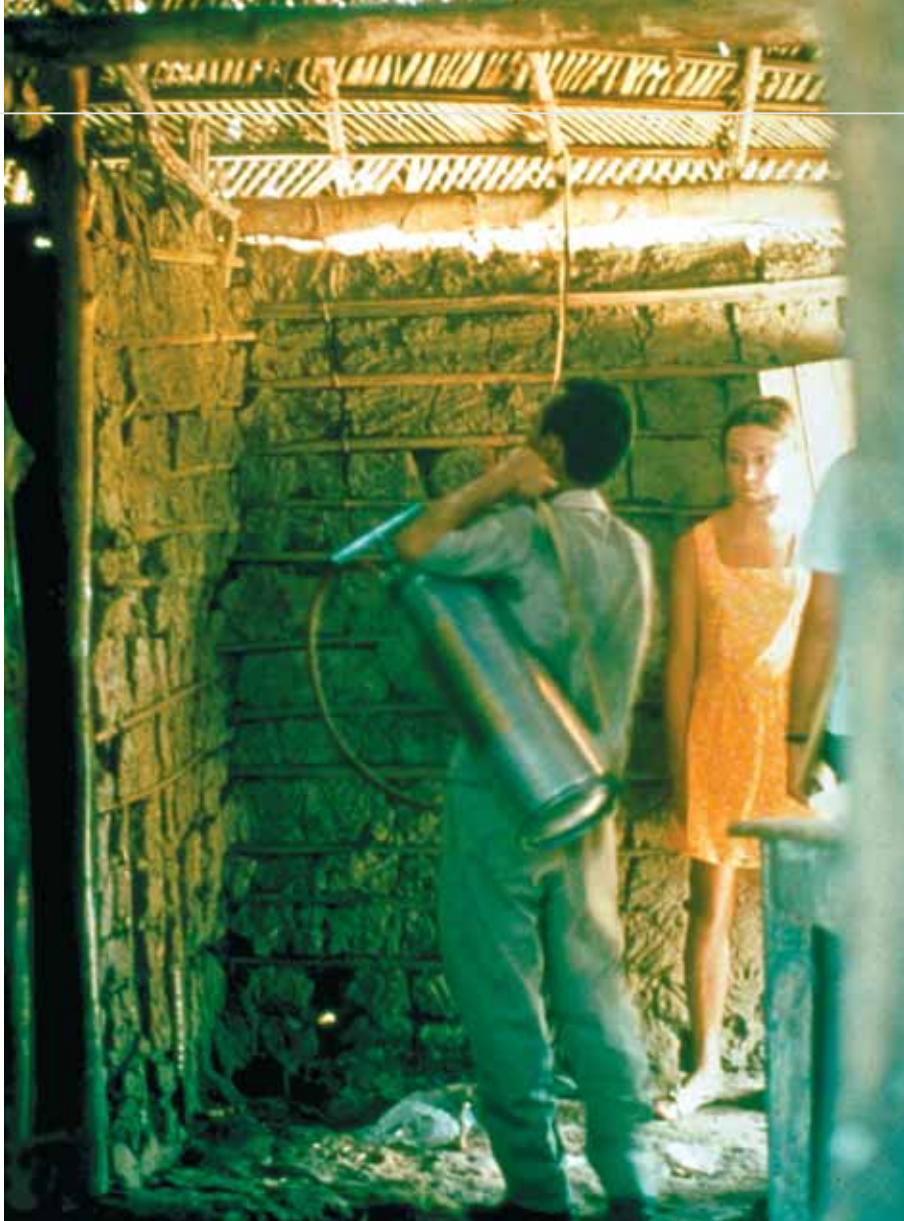
New knowledge

TDR continued to conduct research on the roles of autoimmunity, and individual host and parasite-specific factors, in pathogenesis of the disease, especially of its chronic phase. Factors being studied include GPI-mucins, the lysosomal phos-

pholipase A1, and the parasite trans-sialidases,¹² which induce specific CD8-positive (CD8+) T-cell immune responses. Parasite load in heart tissues is correlated with disease severity, and inversely correlated with the number of T cells producing interferon-gamma. Results from one study suggest that CD8+ cells, particularly those lacking CD28, are the most likely effector cells eliciting tissue pathology, while CD4+ cells play a regulatory role in the disease.¹³

Results from ongoing investigations into the role of parasite burden and molecular constitution of parasite strains in the incidence of congenital transmission of Chagas' disease will be of direct clinical relevance to the handling of congenital infections. The results will feed into development of a tool for early diagnosis of infection in pregnant women and newborns.¹⁴

Basic research on parasite biology included initiation of a *T. cruzi* proteomics



Insecticide treatment of housing is useful for eliminating transmission of Chagas' disease in areas where the vectors are domiciliated.

Credit: WHO/MEDDIA

A comprehensive proteome map will provide an important tool for future work.

initiative. A comprehensive proteome map will provide an important tool for future work on such topics as drug resistance, virulence, and cell signalling, and will likely yield data essential for development of diagnostics and other practical applications. Other basic research on parasite biology includes work on apoptosis, and studies of the biosynthesis of cruzipain, galactofuranose, kinesins and oligopeptidase B.

Novel effective therapeutics are needed for trypanosome infections. Studies focusing on elucidating the structure of a key enzyme – sialidase – in the parasites that cause Chagas' disease and African

sleeping sickness have made possible a better understanding of the roles of this enzyme in transglycosylation and other activities. Results of the studies include description of the 3-D structures and modes of action of *Trypanosoma rangeli* sialidase and *T. cruzi* trans-sialidase.^{15, 12} The studies provided valuable information on the enzymes as potential drug targets and an opportunity for rational design of novel inhibitors that could be developed for potential therapeutic applications. A project on the differential expression of virulence factors and human infection by the main parasite lineages of *T. cruzi* is ongoing.

15 Buschiazzi et al. The crystal structure and mode of action of trans-sialidase, a key enzyme in *Trypanosoma cruzi*. *Molecular Cell*, 2002, 10:757-768.



A mother holds her young daughter who has erythema, puffiness, and petechiae over her body, all signs of dengue haemorrhagic fever.

Credit: WHO/TDR/Crump

Dengue

The global burden of dengue viral infections has increased at least four-fold over the last three decades. The primary vector, the mosquito *Aedes aegypti*, has spread throughout the tropics. An estimated 50 million dengue infections now occur annually in over 100 countries, particularly in South-East Asia, the Americas, and the Western Pacific islands. Life-threatening complications such as dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS) are more likely to occur when individuals who are already immune to one of the four dengue virus serotypes become infected with another virus serotype. About 500 000 cases of DHF occur annually and about 19 000 dengue-related deaths were reported in 2002.

The reasons for the recent rise in number of dengue infections are not fully understood. It is likely that increased population mobility and poor living conditions, resulting from increased urbanization and unplanned urban growth, are important associated factors. Poverty in urban areas contributes to vector spread by providing an abundance of mosquito breeding sites, particularly water storage containers in and around houses; this makes it difficult for under-funded health services to keep the vector population at low levels and to detect and control epidemics in their early stages.

There is no specific treatment for dengue, but appropriate clinical case management can save many lives. No dengue vaccine is available. Clinical trials of several vaccine candidates are planned, but the threat of complications due to immune enhancement is a serious obstacle to development of any vaccine that does not generate long-lasting protection against the four serotypes. The WHO Initiative

for Vaccine Research (IVR) has now taken over from TDR work on guidelines for dengue vaccine trials and support of vaccine development.

Thus, control of the disease depends heavily on measures taken to combat the vector and prevent the spread of epidemics, plus early diagnosis and improved case management of patients. The Scientific Working Group on Dengue, at its meeting in 2000,¹⁶ recommended that TDR's strategic emphases for dengue research should include improving case management and treatment guidelines, developing new diagnostics, creating new knowledge relevant to vector control and pathogenesis, as well as establishing new and validated indicators for entomological surveillance.

Towards improved vector control

New methods of identifying and targeting the most productive vector breeding sites are needed for better vector control. A multicountry project to determine the utility of counting *A. aegypti* pupae in water containers as a method for monitoring relevant breeding sites was recently completed; the findings will be published in 2005. The project was based on the recommendations of a commissioned report¹⁷ on methods of monitoring breeding sites, and a workshop held on the subject in 2003. The results showed that it is possible to identify, through the pupal survey method, the most productive types of water containers which can be targeted for control (see fig. 3). The efficacy of this approach is now being tested in a new multicentre study.



16 Scientific Working Group on Dengue. Meeting report, 3-5 April 2000. Geneva, WHO/TDR, 2000 (TDR/DEN/SWG/00.1).

17 Focks DA. A review of entomological sampling methods and indicators for dengue vectors. Geneva, TDR, 2003 (TDR/IDE/Den/03.1).

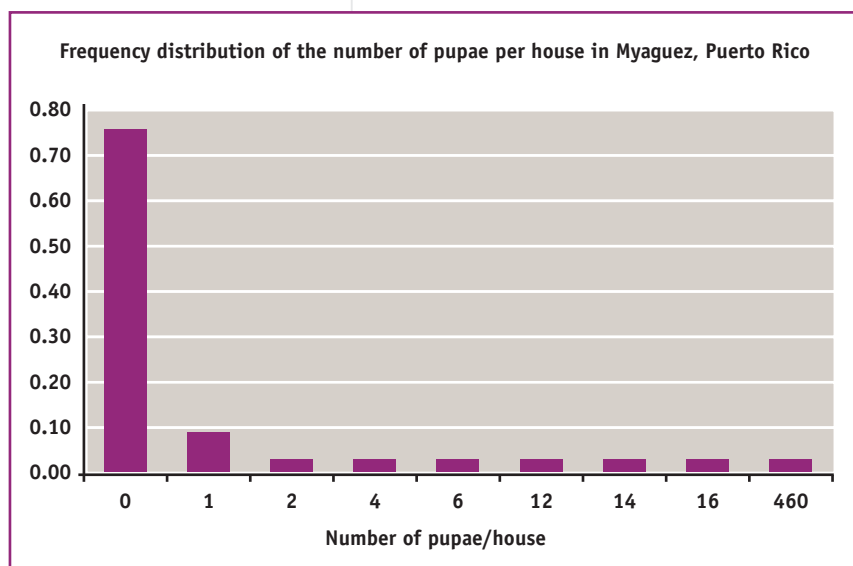


Figure 3

Frequency distribution of *Ae. aegypti* pupae per house (note that one house had 460 pupae). The efficacy of a new approach, in which the most productive types of water container are targeted for control, is being tested in a multicentre study.

From: Focks DA, 2003. *A review of entomological sampling methods and indicators for dengue vectors*. Geneva, TDR, 2003 (TDR/IDE/Den/03.1).



Dengue haemorrhagic fever (DHF) is a life-threatening complication of dengue virus infection. This young girl has erythema and petechiae (small purple spots in the skin caused by internal bleeding) on the face, and red, swollen lips, all signs of DHF.

Credit line: WHO/TDR/Crump

18 Parks W, Lloyd L. *Planning social mobilization and communication for dengue fever prevention and control*. Tunis, World Health Organization Mediterranean Centre for Vulnerability Reduction, 2004 (WHO/CDS/WMC/2004.2, TDR/STR/SEB/DEN/04.1).

In collaboration with WHO's Mediterranean Centre for Vulnerability Reduction (WMC), TDR contributed to a step-by-step guide on social mobilization for dengue control.¹⁸ TDR's Steering Committee on Strategic Social, Economic and Behavioural Research is providing the major coordinating input for interdisciplinary projects on vector ecology and its relation to biological and social aspects of disease transmission and control. This programme is supported by the Canadian International Development Research Centre (IDRC) and is focused on two studies being carried out in Brazil and Colombia, whose full results will be published in 2005.

SDR also funded several mosquito genome-based research projects that are potentially relevant to vector control. Work on completion of the *A. aegypti* genome and refinement of vector transformation techniques continued, leading to stable transformation of refractory *Aedes* mosquitoes. Other achievements can be found on pages 82-83.

Towards improved case management

Effective management of dengue patients requires rapid diagnosis. Current diagnostic tests are of variable quality, and their performance and accuracy have not been validated. Tests based on viral genome detection are complex and expensive. At a joint meeting held with the Pediatric Dengue Vaccine Initiative in October 2004 (proceedings to be published in 2005), product characteristics for dengue diagnostic tests for different indications were defined, an inventory of existing tests was drawn up, and a TDR-led strategy for dengue test development and evaluation was presented. The establishment of laboratory networks in South-East Asia and Latin America, and field trials of the performance of selected tests, are now in preparation, and plans for facilitating the development of new tests with higher performance characteristics are being developed.



Covering storage jars with a net. Unless covered properly, such jars provide ideal breeding places for the *Aedes* mosquitoes which transmit dengue.

Credit: WHO/TDR/Crump

At this meeting, dengue clinicians and epidemiologists discussed how best to classify and treat dengue cases according to their severity, and concluded that a multicentre prospective clinical study is needed to consolidate the current dengue case classification and to better identify early warning signs of severe dengue across regions, age groups and nutritional levels. A research protocol for validating and implementing optimized treatment guidelines was further developed; this multicentre study will be funded by the INCO programme of the European Commission with complementary funding from TDR.

Building research capacity

The vector control projects mentioned above had strong capacity strengthening components. In addition, two training courses in vector genomics for investigators from disease-endemic countries were organized at centres in Mali and Tanzania.



Carrying out pupal surveys.

Credit: WHO/TDR/Kroeger





Mass drug administration in a village: a health worker places albendazole and DEC tablets in the hand of a young boy.
Credit: WHO/TDR/Crump

Lymphatic filariasis

About 120 million people worldwide are thought to be infected with the parasitic worms that cause lymphatic filariasis, although this number is subject to much uncertainty as the distribution of the disease is still not well mapped in certain regions, particularly of Africa. About 40 million of those infected are disfigured and severely incapacitated by the disease. Lymphatic filariasis is not fatal, but is one of the leading causes of long-term permanent disability, accounting for the loss of some 5 million disability-adjusted life years (DALYs) annually. While the incidence of filariasis has been falling in some countries, notably China, it has been stable or rising over the last decade together with increasing population and urbanization in India and Africa, where the majority (over 75%) of those affected live.

The parasites that cause lymphatic filariasis are *Wuchereria bancrofti* (in 95% of cases), which is mainly transmitted by mosquitoes of the genus *Culex* (in India) or *Anopheles* (in Africa), and *Brugia malayi* or more rarely *B. timori*, which are mainly transmitted by *Mansonia* mosquitoes. Immature parasites (microfilariae) are taken up in the insects' blood meals, and develop into infective forms that can enter human skin during another feeding session. These forms mature and circulate in the lymph and blood systems, finally lodging as adult worms (macrofilariae) in afferent lymphatic vessels. The pathology of the disease is not fully understood, but blockage of lymphatic vessels is an important contributing factor, typically producing painful, disfiguring swelling (lymphoedema leading to elephantiasis) of limbs, breasts, or genitals in cases of chronic infection. In some endemic communities, up to 10% of adults can suffer from elephantiasis, with an even higher percentage being

affected by less obvious internal damage to kidneys and the lymphatic system.

Lymphatic filariasis mainly affects poor communities, both urban and rural, because its transmission is favoured by crowding, lack of bednets and screens for houses, inadequate sanitation, and the presence of standing water which provides mosquitoes with breeding sites. Also, the disease itself is a strong impediment to socioeconomic development. It is typically acquired in childhood, but its chronic complications develop in adults, who may become physically incapacitated or stigmatized, so that they lose the opportunity to marry and raise a family whose members could provide palliative care for affected persons.

Control of the disease depends, first, on preventing its transmission by drug treatment and taking measures against mosquitoes, and second, on alleviating its symptoms, mainly by the application of hygiene and treatment of local secondary infections that commonly affect areas of the body with inadequate lymphatic circulation. A single dose of diethylcarbamazine (DEC), or ivermectin (in areas where onchocerciasis is also prevalent), combined with albendazole can reduce blood microfilarial levels to such low levels that transmission from treated patients is unlikely or greatly reduced for at least a year. Thus, in theory, it should be possible to eliminate the disease from an endemic community if the entire 'at-risk' population could be treated once a year for a period that is long enough to keep microfilarial levels below the transmission threshold for at least the reproductive lifespan of the adult worm – until recently believed to be about 4 to 6 years but now thought to be longer. In practice, how-

ever, several important issues need to be resolved before the disease can be eliminated from a major endemic area. Chief among them are the number of annual treatments and degree of coverage (percentage of the population actually receiving effective treatment) required for elimination, and the dependence of these parameters on endemicity levels and the nature of the vector/parasite complex involved. Elimination programmes also need appropriate procedures and criteria for monitoring progress and evaluating their cost-effectiveness.

TDR is a partner in the Global Programme to Eliminate Lymphatic Filariasis (GPELF), which was founded in 2000 with the dual aims of stopping the spread of infection (i.e. interrupting transmission) and alleviating the suffering of affected individuals. A main focus of TDR's research during the biennium has been to investigate the impact of mass administration of anthelmintic drug combinations on filarial infection and transmission at several sites with different parasite/vector complexes and levels of endemicity. TDR also supported studies aimed at improving drug delivery to urban populations, at developing sustainable strategies for management of disease symptoms (lymphoedema), and at the discovery of new drugs (macrofilaricides) that could advance elimination of the disease, or drug combinations that would allow combined treatment of filariasis together with other diseases.

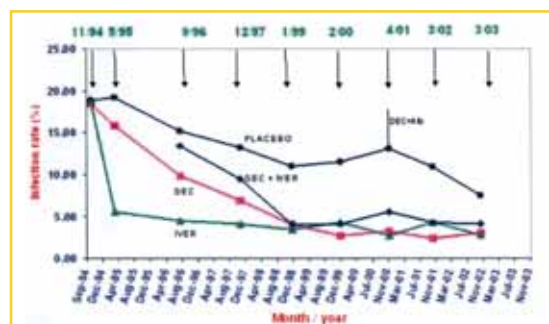
Mass drug administration strategies for disease elimination

The safety and efficacy against lymphatic filariasis of the drug combination DEC and albendazole was studied in a randomized controlled trial in India that showed the drug combination to be as safe as DEC alone, and that both drugs were adequately absorbed. However, in this trial there was no evidence of greater efficacy of the combination at 12 months follow-up.¹⁹ Mass drug administration (MDA) strategies that use different drug combinations with the aim of eliminating transmission from communities where the disease is endemic are now under trial in large field studies at five separate sites, two in India and three in Africa. The studies with the albendazole combinations started in 2001/2002, but a large trial in Pondicherry, India, involving over 30 000 people, has been under way since 1993, starting with a comparison between DEC and ivermectin alone, and continuing with the addition of a DEC/ivermectin and later a DEC/albendazole combination.²⁰ The results show that infection rates and morbidity were reduced by all treatments, but not to levels sufficient to interrupt transmission: after five treatment cycles, vector infection rates had dropped from 20% to 2–4%, but remained stable at this level through another four treatment cycles (Fig 4).

19 Kshirsagar NA et al. Safety, tolerability, efficacy and plasma concentrations of diethylcarbamazine and albendazole co-administration in a field study in an area endemic for lymphatic filariasis in India. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 2004, 98(4):205-217.

20 Ramaiah KD et al. The impact of six rounds of single-dose mass administration of diethylcarbamazine or ivermectin on the transmission of *Wuchereria bancrofti* by *Culex quinquefasciatus* and its implications for lymphatic filariasis elimination programmes. *Tropical Medicine and International Health*, 2003, 8(12):1082-1092.

Figure 4
Impact of mass drug administration on vector infection rate.





A vector control study in India resulted in a revised estimate of the mean lifespan of *Wuchereria bancrofti*. Here a researcher collects *Toxorhynchites splendens* larvae at the Vector Control Research Centre in Pondicherry.

Credit: WHO/TDR/Chandran

The difficulties in completely interrupting transmission in this study can be at least partly explained by the fact that, in such MDA programmes, not all community members receive the drugs and, of those who do, not all consume them as recommended. During MDA in Orissa, India, DEC could be distributed to an estimated 76% of members of rural communities but to only 45% of urban communities, and follow-up investigations showed that over one third of those who received the medicine did not actually consume it.²¹ The reasons for the unexpectedly low rates of compliance found in these studies are complex: baseline data for a new study to develop more effective drug delivery strategies for urban areas suggested that elimination of filariasis was not felt as a high-priority need, especially among high-income groups in the community.²² In a separate study in Tamil Nadu, specific advocacy for drug consumption was shown to improve compliance, but not enough to reach coverage levels that would ensure elimination of transmission. Computer simulations with the model

Lymphasim, using realistic estimates of treatment coverage, indicate that 6 to 10 rounds of treatment may be required to achieve elimination of filariasis infection and transmission. Application of the model to data from a vector control intervention study in Pondicherry, India, resulted in a revised estimate of the mean lifespan of *W. bancrofti* of 10 years.²³ Lymphasim was initially developed for *Culex*-transmitted filariasis in India but is now being modified for Africa, where both vector competence and infection patterns in the human population have been shown to be fundamentally different.^{24, 25}

The African version of the model will use data from additional trials that are under way at three sites in Africa, where the effects of MDA with DEC/albendazole (Kenya) and ivermectin/albendazole (Ghana, Mali) are being studied under conditions of different endemicity and vector/parasite complexes. A scientific working group on lymphatic filariasis, to be convened in May 2005, will examine the preliminary results of all relevant trials

- 21 Babu BV, Kar SK. Coverage, compliance and some operational issues of mass drug administration during the programme to eliminate lymphatic filariasis in Orissa, India. *Tropical Medicine and International Health*, 2004, 9(6):702-709.
- 22 Ramaiah KD et al. Situation analysis in a large urban area of India, prior to launching a programme of mass drug administrations to eliminate lymphatic filariasis. *Annals of Tropical Medicine and Parasitology*, 2005, 99(3):243-252.
- 23 Subramanian S et al. The dynamics of *Wuchereria bancrofti* infection: a model-based analysis of longitudinal data from Pondicherry, India. *Parasitology*, 2004, 128(5):467-482.
- 24 Boakye DA et al. Vector competence, for *Wuchereria bancrofti*, of the *Anopheles* populations in the Bongo district of Ghana. *Annals of Tropical Medicine and Parasitology*, 2004, 98(5):501-508.
- 25 Stolk WA et al. Meta-analysis of age-prevalence patterns in lymphatic filariasis: no decline in microfilaraemia prevalence in older age groups as predicted by models with acquired immunity. *Parasitology*, 2004, 129(5):605-612.

Mass drug administration in a Samoan village: a village elder helps a young mother give DEC and albendazole tablets to a young child.

Credit: WHO/TDR/Crump



to date and consider whether and how MDA strategies can achieve elimination of filariasis.

Morbidity management and research capacity strengthening

During the biennium, TDR supported two studies whose aim was to compare different strategies (community, family, or individual-based) for lymphoedema management. These were carried out in Nigeria and Mali. Both showed that family-based approaches were more acceptable and effective, in terms of clinical outcome, cost and likely sustainability, than community-based strategies. A workshop was organized by TDR Research Capability Strengthening (RCS) in late 2003 to draw up plans for further research in this area. However, lack of funding is currently preventing these

promising initial results from being followed up by studies on a larger scale or in different countries.

Strategic research and development of a macrofilaricide

A social research study²⁶ described the development, implementation, and value of support groups for women with lymphatic filariasis. Based on an interdisciplinary framework, the study integrated perspectives of medical anthropology and social epidemiology to demonstrate the relevance and applicability of a chronic-disease support-group model for tropical disease control in a developing country. Based on this experience with lymphatic filariasis, support groups were seen to offer a cost-effective intervention for chronic diseases; after adaptation to local settings, interventions were more effective.

26 Coreil J, Mayard G, Addiss D. Support groups for women with lymphatic filariasis in Haiti. *Final Report Series in Social Economic and Behavioural Research No. 2*, 2003 (TDR/STR/RP/03.1).

TDR continued to support research towards the development of new tools for filariasis control based on the *B. malayi* genome sequence, which has recently been completed,²⁷ and on the growing sequence data available from *W. bancrofti*. TDR-funded laboratories increased the numbers of compounds screened each year against helminths, and the anthelmintic activities of several promising compounds are currently being investigated, as described in more detail in the section dealing with strategic research on onchocerciasis (pages 48-49). The strategy recommended by TDR for screening new compounds for anthelmintic activity against molecular targets, also described in the section on onchocerciasis, should be equally applicable to filariasis.

Support groups were seen to offer a cost-effective intervention for chronic diseases.

Research has shown that women's support groups can provide significant benefits for lymphatic filariasis patients and help to ease their suffering.

Credit: WHO/TDR/Crump



27 Whitton C et al. A genome sequence survey of the filarial nematode *Brugia malayi*: repeats, gene discovery, and comparative genomics. *Molecular and Biochemical Parasitology*, 2004, 137(2):215-227.



Community-directed distributors (CDD) preparing to dispense ivermectin tablets from a central distribution point in their village.
Credit: WHO/APOC/TDR/Crump

Onchocerciasis

Onchocerciasis is not itself a fatal disease, but it can have very severe consequences if left untreated: they include disfigurement, severe itching, skin depigmentation, and most devastatingly, vision impairment and eventual blindness. The great majority (99%) of the 37 million people thought to be infected live in 30 countries in sub-Saharan Africa. Of these, over a quarter of a million are blind, and twice that number suffer from various degrees of less severe but still debilitating visual impairment. Visual impairment and blindness account for 40% of disability-adjusted life years (DALYs) associated with onchocerciasis. The other main clinical manifestation, accounting for 60% of DALYs, is skin disease with severe itching. The relative importance of ocular and skin complications varies with the parasite strain involved; blindness tends to predominate in savannah areas and skin disease in forest areas.

Onchocerciasis can have important socio-economic consequences. For example, fear of blindness has led to depopulation of fertile river valleys of the West African savannah, greatly diminishing agricultural production and increasing poverty and famine, while disfigurement can hinder social integration. The socioeconomic importance of the disease was the main reason for creation of the Onchocerciasis Control Programme in West Africa (OCP) in 1975.

Control operations under OCP were originally based on killing the larvae of *Simulium* blackflies, which transmit the parasite (*Onchocerca volvulus*), by spraying insecticides over the blackfly breeding sites. But with the donation of Mectizan® (ivermectin) by Merck & Co. Inc. in 1987, control operations changed from exclusive

vector control to larviciding combined with ivermectin treatment or, in some areas, to ivermectin treatment alone. OCP was very successful; it was officially closed in December 2002 after the disease had been eliminated as a public health problem from all but one of the participating countries.

Building on the knowledge and experience gained in OCP, a second programme – the African Programme for Onchocerciasis Control (APOC) – was launched in 1995 to combat the rest of Africa's river blindness. Operations in APOC countries are nearly exclusively based on treatment with ivermectin, as vector control is rarely cost-effective in these countries. The communities in disease-endemic areas are treated with one dose of ivermectin per year, which is very effective at killing larval parasites (microfilariae).

While it kills larvae, however, ivermectin does not eliminate adult worms from the body, or prevent them from producing new microfilariae during their lifespan (estimated as up to 14 years). As long as blackflies are present, onchocerciasis can continue to be transmitted and regular ivermectin treatment is necessary for its control. In addition, ivermectin can produce very severe side-effects if administered to patients that are heavily infected with another parasitic worm, *Loa loa* (acute inflammatory reactions caused by the sudden death of large numbers of worms can be life-threatening); guidelines for rapidly identifying communities where high intensity of *Loa loa* infection occurs were produced in 2002.²⁸ Finally, there are fears that *O. volvulus*, like some related parasites of livestock, may develop resistance to ivermectin, thus jeopardizing the entire control programme.

28 *Guidelines for rapid assessment of Loa loa*. TDR/IDE/RAPLOA/02.1

***[Results suggest]
that community-
based treatment
of onchocerciasis,
lymphatic filariasis,
schistosomiasis
and intestinal
helminths can be
safely integrated.***

29 Homeida M et al. APOC's strategy of community-directed treatment with ivermectin (CDTI) and its potential for providing additional health services to the poorest populations. *Annals of Tropical Medicine and Parasitology*, 2002, 96:93-104.

30 Remme JH. Research for control: the onchocerciasis experience. *Tropical Medicine and International Health*, 2004, 9(2):243-254.

TDR's current research is directed, first, towards developing sustainable strategies based on ivermectin use for control of the disease, focusing on the integration of ivermectin delivery with other community-based interventions, the development of rapid procedures for mapping and surveillance of the disease, and diagnostic procedures for detecting the appearance of ivermectin-resistant *O. volvulus* in communities, and on analysis of the feasibility, cost and benefits of eliminating onchocerciasis transmission and infection from endemic foci in Africa. A second line of research is directed towards the discovery of new drugs (macro-filaricides) that can kill or sterilize adult *O. volvulus* worms.

Improved ivermectin strategies

Community-directed interventions and drug combinations

The strategy of community-directed treatment with ivermectin, developed by TDR, has proven very successful in oncho-

cerciasis control. Over 30 million people are now treated annually with ivermectin and communities have responded enthusiastically to the concept of community-directed intervention in which they themselves are in charge of planning and implementation. Because of this success, there is growing interest in using this approach for the integrated delivery of interventions against other diseases.²⁹ The board of the African Programme for Onchocerciasis Control, which includes the ministers of health of 19 African countries, requested TDR to undertake the research needed to provide the evidence base for such an integrated approach. Following an extensive consultative process, a multicountry study on community-directed interventions was launched in 2004.³⁰ The interventions included in the study range in complexity from vitamin A supplementation and insecticide-impregnated nets for malaria to DOTS treatment for tuberculosis and home management of malaria. Nine multidisciplinary study teams from five African countries are undertaking the study, covering a total of 45 health districts. The first results are expected by July 2006. In the

A health worker leaves the district health centre with boxes of ivermectin tablets on the back of his motorcycle. He will deliver the tablets to the local health post, from where community-directed distributors will collect them.

Credit: WHO/APOC/TDR/Crump



meantime, a pilot study in Uganda has already demonstrated that integrated community-directed treatment of onchocerciasis, schistosomiasis and intestinal helminths in feasible and more effective than delivery through the current, separate programmes for these diseases.³¹

Because of this move towards integrated delivery of community-based interventions, TDR has been supporting studies on the safety of co-administration of different anthelmintics. An important result is the finding that co-administration of praziquantel, albendazole and ivermectin or diethylcarbamazine is safe, suggesting that community-based treatment of onchocerciasis, lymphatic filariasis, schistosomiasis and intestinal helminths can be safely integrated.

A meeting was held to discuss studies on possible alternative treatments that might lower the microfilarial load in patients infected with *Loa loa*, and thus reduce their risk of developing adverse reactions after subsequent ivermectin treatment. A study of the efficacy and safety of loiasis treatment with albendazole is planned to start in 2005.

Tools for surveillance and mapping

Onchocercal microfilariae are readily detected in small skin biopsies (skin snips), but the procedure is invasive and time-consuming. TDR is collaborating with a pharmaceutical partner to develop an alternative diagnostic test that uses transdermal delivery technology to apply diethylcarbamazine to the skin, and the presence of a mild local reaction to microfilarial death produced by the drug, as evidence of infection. Pilot versions of such a patch were tested in the field during the biennium, but the results suggest that current versions are not yet optimal. The feasibility of increasing the diethylcarbamazine dose per patch is now under study.

A number of genetic changes in parasites associated with multiple treatments have been described. In order to determine their potential value as markers for ivermectin resistance, they will be validated in field studies in areas with more than 15 years of ivermectin treatment.

RAPLOA is a method developed to rapidly assess communities for the presence of high intensity *Loa loa* infection before ivermectin use, and thus minimize the associated risk of severe side-effects following ivermectin treatment.³² This method was validated during the biennium in field trials carried out in the Republic of the Congo and at two sites in the Democratic Republic of the Congo. Results confirmed the validity of the method over a wide geographic area (see Figure 5).

31 Ndyomugenyi R, Kabatereine N. Integrated community-directed treatment for the control of onchocerciasis, schistosomiasis and intestinal helminths infections in Uganda: advantages and disadvantages. *Tropical Medicine and International Health*, 2003, 8(11):997-1004.

32 Takougang I et al. Rapid assessment method for prevalence and intensity of *Loa loa* infection. *Bulletin of the World Health Organization*, 2002, 80(11):852-858.

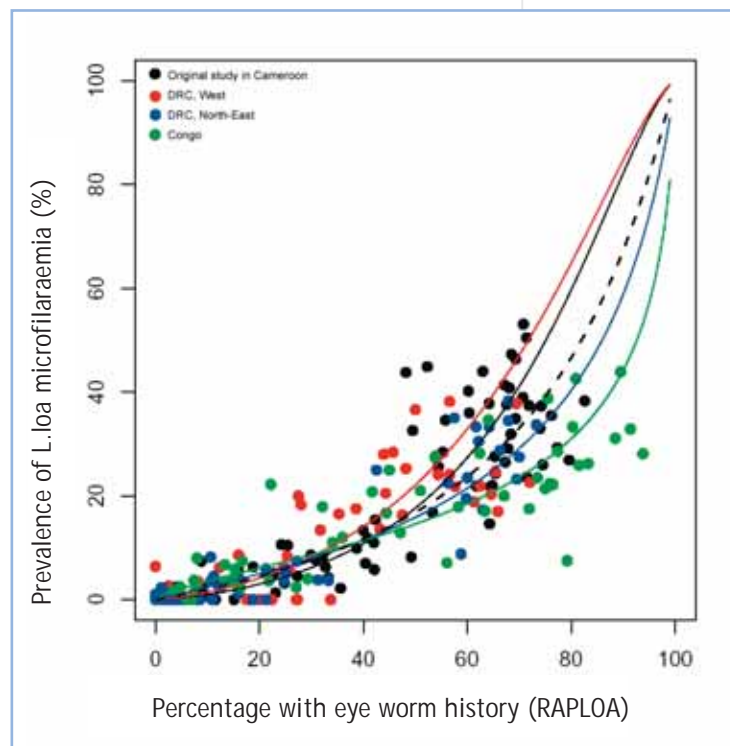


Figure 5
The relationship between RAPLOA and parasitological data on loiasis prevalence is similar in all study sites.



Villagers discuss how to go about distributing ivermectin.

Credit: WHO/TDR/Crump

33 Thomson MC et al. Mapping the distribution of *Loa loa* in Cameroon in support of the African Programme for Onchocerciasis Control. *Filaria Journal*, 2004, 3(1):7.

34 Borsboom GJ et al. Impact of ivermectin on onchocerciasis transmission: assessing the empirical evidence that repeated ivermectin mass treatments may lead to elimination/eradication in West-Africa. *Filaria Journal*, 2003, 2(1):8.

RAPLOA was subsequently accepted by the Mectizan Expert Committee and the APOC Expert Committee, and the ivermectin mass treatment guidelines have now been modified to incorporate RAPLOA. Research now focuses on the development of a rapid mapping method that combines RAPLOA and an environmental risk model for loiasis.³³

Interrupting transmission

Whether onchocerciasis can be eliminated with ivermectin treatment from all endemic foci in Africa is a hotly-debated question. A review of the empirical evidence on the impact of 10-14 years of ivermectin treatment in Africa showed a variable pattern, with significant transmission still ongoing in some river basins while in others transmission may have been interrupted.³⁴ The Gates Founda-

tion has provided funds for a study in five river basins in Mali, Senegal and Guinea-Bissau, where there have been 16 years of treatment with ivermectin and where the prevalence of infection has fallen to very low levels, in order to determine whether treatment can be safely stopped. TDR, the WHO Regional Office for Africa (AFRO), APOC and partners in these countries have designed and developed the protocol for the studies, which are planned to start in 2005.

Development of new macrofilaricides and strategic research

TDR continues to search for a new safe and effective drug that kills or sterilizes adult worms. TDR-supported experiments

in animals previously suggested that moxidectin may be macrofilaricidal (causes death of adult worms). This compound belongs to the same chemical family as ivermectin, although its different pharmacokinetic properties may increase its anthelmintic efficacy. A tablet formulation of moxidectin was developed by Wyeth, and Phase I clinical trials were completed during the biennium. The data were encouraging and support conclusions from pre-clinical toxicity studies that moxidectin has the safety profile required of a drug for onchocerciasis control. Wyeth and TDR jointly formulated a development strategy that was discussed with regulatory authorities in the UK, Ghana and France. The first study of subjects infected with *O. volvulus* awaits the outcome of further discussions with regulatory authorities.

During the biennium, the protocols used for TDR-funded screening of new types of compound for anti-onchocercal activity were revised to increase throughput and reliability of testing. Two classes of compound (novel tetracyclines and cyclo-depsipeptides) not related to the ivermectin-moxidectin family showed promising activity in vitro and in vivo. These classes are being further investigated in collaboration with pharmaceutical partners (Paratek, Pfizer, Bayer, Meiji). At present, the screening of new compounds is performed on live parasites, and has therefore a rather limited throughput. Screening on helminth-derived molecular targets, and target validation using RNAi techniques, has many potential advantages and was the subject of a TDR-hosted meeting and report published in 2004.³⁵ The report suggests ways of systematically identifying new drug targets in *Onchocerca* and *Brugia* (which causes lymphatic filariasis) parasites.

Building research capacity

Capacity strengthening was an integral and important part of most of the projects described above. For example, the principal investigator of the original RAPLOA study in East Cameroon provided support with proposal development, study design, and field implementation to the teams from the ministries of health of the Congo and the Democratic Republic of the Congo. The complex clinical trials required to investigate the efficacy of new drug combinations also required the development and training of strong local research teams. A workshop for training in advanced qualitative data analysis was organized in 2004 for the social scientists of the nine multidisciplinary teams of the multicountry study on community-directed interventions; each team was provided with a registered copy of one of the leading computer programmes for qualitative data analysis.

The complex clinical trials required to investigate the efficacy of new drug combinations required the development and training of strong local research teams.

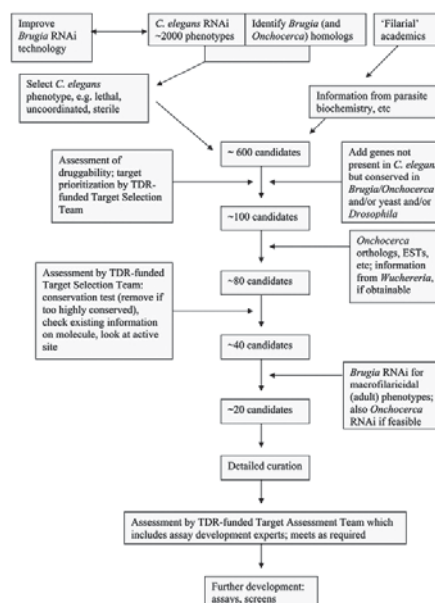


Figure 6
Flow chart for identification and validation of antifilarial drug targets.

From: RNA interference as a means of identifying drug targets for filariasis. Report of a WHO/TDR Scientific Working Group, 2004 (WHO/PRD/RNAi/2004).

35 Behm C et al. RNA interference as a means of identifying drug targets for filariasis: Report of a WHO/TDR Scientific Working Group. Geneva, WHO/TDR, 2004 (WHO/PRD/RNAi/2004)



A doctor examines the distended abdomen of a patient with advanced intestinal schistosomiasis. This form of the disease can be difficult to diagnose in the early stages. *Credit: WHO/TDR/Crump*

Schistosomiasis

An estimated 170 million people in sub-Saharan Africa, and a further 30 million in North Africa, Asia and South America, suffer from schistosomiasis, which is generally associated with rural poverty. The global burden of death and chronic disability is high – perhaps 20 million with severe disease and an estimated 200 000 deaths in 2003 – and may well be underestimated, since schistosomiasis-related conditions such as anaemia and low growth rate may not be recognized as resulting from the disease. Most infections are caused by *Schistosoma mansoni*, *S. haematobium* or *S. japonicum*, with two other species (*S. intercalatum* and *S. mekongi*) contributing less to the case load.

Humans are infected when they enter or come in contact with schistosome-infested water. Schistosomiasis is primarily a disease due to extreme poverty – people get infected because they do not have access to safe water supplies and proper sanitation. The disease is maintained under these conditions because infected people release schistosome eggs in their excreta. After reaching water, the eggs hatch into larvae that infect aquatic snails, where they develop further until they are released as free-swimming immature parasites (cercariae) that can penetrate the skin of human hosts and develop into adult worms. People acquire the infection during the course of routine domestic, agricultural or occupational duties. The adult worms lodge in blood vessels of the intestinal or urinary (for *S. haematobium*) systems. After mating, female worms produce eggs that are deposited in the liver, bladder or other tissues, depending on the infecting species, and are released in excreta to complete the cycle. The manifestations of disease are due to chronic inflammatory reactions induced by the eggs.

Control of the disease currently relies on chemotherapy, either of high-risk groups (e.g. schoolchildren, irrigation workers) at the community level, or of individuals with diagnosed infection. When effective diagnosis and chemotherapy are allied with health education, provision of adequate sanitation and potable water, and snail control, transmission of the disease can be essentially eliminated (as in, for example, Japan, parts of China and Brazil, and the Caribbean islands). In sub-Saharan Africa, in contrast, it is estimated that schistosomiasis is second only to malaria as a cause of morbidity among tropical diseases.

Rapid diagnosis in the field, especially of intestinal schistosomiasis, remains difficult. Current treatment is based mainly on a single drug, praziquantel, which was introduced over 25 years ago. Praziquantel is safe, well tolerated and effective as a single-dose treatment. However, treatment failures have been reported, and it is likely that increasing resistance of parasites to the drug accounts for some of these cases. Oxamniquine can be used as an alternative anti-schistosomal drug, but it is not effective against *S. haematobium*. Repeated infection induces some degree of immunity to the parasite in humans, so an effective vaccine could offer a promising alternative to chemotherapy or be used in conjunction with it,³⁶ but so far no such vaccine is available.

Towards improved treatment

Diagnosis

Intestinal schistosomiasis can be difficult to diagnose, especially in areas of low disease transmission. TDR and its part-

36 Bergquist NR, Leonardo LR, Mitchell GF. Vaccine-linked chemotherapy: can schistosomiasis control benefit from an integrated approach? *Trends in Parasitology*, 2005, 21(3):112-117.

People become infected when they come into contact with schistosome-infested water, as here, where men emptying a fish trap expose themselves to infection. Credit: WHO/TDR/Crump



ners have drawn up protocols for evaluating rapid diagnostic tests for detection of *S. mansoni* and/or *S. haematobium*. The evaluation will be undertaken at four different sites during 2005. Urinary tract infection due to *S. haematobium* is more easily diagnosed, as there is a good correlation between infection and the presence of blood in the urine. This correlation has been validated at the community and district level, and if it can be scaled up, could provide a basis for future extension of community-directed treatment to a national level.

Medication

In most countries, the standard dose of praziquantel is 40 mg/kg per treatment. Because treatment failures have been observed, and in some cases associated with a need for higher drug doses to kill the parasite isolated from the patient, the safety and efficacy of a higher dose of praziquantel are being studied in TDR-supported clinical trials at four sites in Asia, Africa and South America. Drug combinations may also help to improve treatment success rates and prevent the development of resistance. The combination of artemether and praziquantel is being tested in clinical trials in China and Egypt. However, as recommended by a TDR-convened expert committee, use of this combination is not planned in

malaria-endemic areas because of the risk that it might induce resistance to artemisinins in malaria parasites. A protocol for testing a combination of oxamniquine and praziquantel has recently been prepared, and if approved, will be the basis for Phase I clinical trials to start in 2005. A separate proposal to test triclabendazole, an anthelmintic drug that is active against *Fasciola* parasites, in patients co-infected with *Fasciola* and schistosomes is currently under review.

Because praziquantel has been such an effective drug, there has been very little research directed at finding new treatments for the disease, giving rise to the risk that resistance to praziquantel becomes widespread while treatment options remain very limited. In 2003, TDR allocated funds for screening compounds for anti-schistosomal activity to two laboratories. After validation of the screening methods, over 600 compounds were evaluated for their activity against adult worms in vitro; the activities of a few selected compounds, including new synthetic artemisinin analogues, are being further evaluated in infected mice.

Towards a vaccine

Lack of funding severely curtailed TDR's direct involvement in schistosome vaccine development during the past biennium. In 2003, TDR organized a meeting on the future of schistosome vaccine development. The participants recommended that development of the two most advanced vaccine candidates – Sm14 from *S. mansoni*, which has entered a Phase I clinical trial, and Sh28GST from *S. haematobium*, for which a Phase III trial is planned – should continue. TDR contributed to the clinical monitoring of the Sh28GST Phase II trial. At least six other candidates show some degree of efficacy in animal models of schistosomiasis and also merit further attention.³⁶ An electronic network to facilitate communication between scientists working on schistosome vaccines has been set up and linked to the TDR website.

New knowledge

TDR continued to support the schistosome genome network website, and the genomes for *S. mansoni* and *S. japonicum* have been published.³⁷ Many thousands of expressed sequence tags (ESTs) from *S. mansoni* and *S. japonicum* have been characterized.³⁸ Among the gene products identified or better characterized with TDR support during the biennium are phosphoenolpyruvate carboxykinase, an immunogen of *S. mansoni* eggs; Sm-p40, an antigen involved in egg-induced pathology, in which new T-cell epitopes were identified; and several known or novel proteins whose roles in the architecture of the schistosome tegument were clarified. The possible role of human macrophage inflammatory protein 1 α (MIP-1 α) in the pathogenesis of the disease was further investigated.³⁹

The genetic structure of natural *S. mansoni* populations, knowledge of which may

bear on reasons for some treatment failures, is being investigated in an endemic area of Brazil using microsatellite markers. Several studies dealing with the influence of health sector reforms or gender on access to treatment, or social and environmental influences on disease prevalence, were funded in China.⁴⁰ It appears that reforms encouraging user fees in the Chinese health sector have limited access to treatment for poorer people.

Capacity building

Many of the studies mentioned above, and especially those carried out in disease-endemic regions, have a research capacity strengthening component. TDR provided specific support for capacity building to the projects aimed at improving treatment by increasing the dose of praziquantel. After issuing a call for proposals to carry out this work, TDR provided support for developing the selected proposals, including protocols and preparations for scientific, technical and ethical review of the projects, training in good clinical practice and the conduct of clinical trials. The studies will be carried out in Brazil, Mauritania, the Philippines and Tanzania. Support for developing the proposal to evaluate triclabendazole as a potential anti-schistosomal agent was also provided. TDR maintains its close links with the Regional Network for Research, Surveillance and Control of Asian Schistosomiasis, a multicountry partnership which has helped to spread the use of tools such as remote sensing and geographic information systems for schistosomiasis control. TDR, with the Schistosomiasis Control Initiative (SCI), the Schistosomiasis Research Programme (SRP), and the Danish Bilharziasis Laboratory (DBL), is supporting the establishment of another regional schistosomiasis research network in Africa.



www.nhm.ac.uk/hosted_sites/schis

37 www.nhm.ac.uk/hosted_sites/schisto/

www.genedb.org/genedb/smansoni/imdex.jsp

38 McManus DP et al. Schistosome transcriptome analysis at the cutting edge. *Trends in Parasitology*, 2004, 20(7):301-304.

39 Souza AL et al. Potential role of the chemokine macrophage inflammatory protein 1 α in human and experimental schistosomiasis. *Infection and Immunity*, 2005, 72(4):2515-2523.

40 *The International Journal of Health Planning and Management*, 2004, 19(suppl. 1). (Several articles in this special supplement deal with health sector reforms in China.)



This elderly woman has been deserted and lives alone in poverty. Credit: WHO/TDR/Vlassoff

Leprosy

The number of people suffering from leprosy has greatly diminished over the last 20 years, from an estimated 10 million patients worldwide in the early 1980s to about 450 000 at the beginning of 2005. The disease was eliminated as a public health problem from 113 countries during this period. Nevertheless, leprosy is still a feared disease, not only because of the severe deformities that can affect patients, but because of the burdens of social stigma and poverty that it can lay on victims. Patients may be pauperized or reduced to the state of outcasts, particularly in poor, marginalized populations that lack access to treatment and information about the disease. Untreated leprosy can lead to severe, irreversible disfigurement, including skin lesions (depigmentation, extensive nodule formation), damage to mucous membranes, and accumulation of wounds, burns and ulcers where peripheral nerve loss has occurred, for example on the hands, arms and legs. Although leprosy is not in fact especially contagious, fear of contagion contributes to the isolation of victims. The mechanism of transmission of the causative bacterium (*Mycobacterium leprae*) is still unclear: transmission is thought to be via nasal discharge and droplets from the respiratory tract of untreated patients, and perhaps also in some cases via skin contact.

Control and progress towards elimination of the disease is based on early detection and multidrug therapy (MDT) of individual cases. A standard course of MDT (6 months for paucibacillary leprosy and 12 months for multibacillary leprosy) is very effective against *M. leprae*, and neither relapses nor emergence of MDT-resistant strains of the bacterium have been reported. However, progress towards elimination of the disease could be improved by better

case-finding and widening access to MDT with simplified treatment regimens. Possible ways of doing this were examined by a TDR-convened scientific working group at the end of 2002, whose report⁴¹ recommended three approaches to reducing still further the burden of this feared disease: integrating leprosy control services with other general public health measures and extending access to MDT; understanding disease transmission, especially by using rapid diagnostic tests; and investigating ways of preventing nerve damage due to infection.

Towards the integration of leprosy control

Simplifying treatment

A long-term, multicentre study is under way to determine the feasibility and value of introducing a Uniform-MDT protocol for leprosy treatment (currently, different protocols and drug combinations are in use, depending on the clinical stage of the disease). The drugs used for MDT include the dapsone-clofazamine-rifampicin combination. The possibility that the duration of MDT could be reduced to six months is also part of the Uniform-MDT study. Results of this study should be available in 2010.

Integrating services

The issue of integrating leprosy control measures into general public health services was addressed at a TDR-organized workshop held in Brazil in 2004.⁴² The participants identified a number of challenges posed by integration, as well as variables related to failures of leprosy elimination programmes, and developed a framework for a multicentre study in high and low prevalence countries. Additional

41 *Scientific Working Group on Leprosy*. Meeting report, 26-28 November 2002 (TDR/SWG/02)

42 Integrating leprosy control: new challenges for implementation research. *TDRnews*, 2004, 72:4. For report, see: www.paho.org/English/AD/DPC/CD/lep-rio-2004.htm

Research suggested that the activation of TLR2 on Schwann cells contributes to the nerve injury.

- 43 Hussain et al. Leprosy patients with lepromatous disease have an up-regulated IL-8 response that is unlinked to TNF-alpha responses. *International Journal of Leprosy and Other Mycobacterial Diseases*, 2004, 72(1):35-44.
- 44 Oliveira RB et al. Expression of Toll-like receptor 2 on human Schwann cells: mechanism of nerve damage in leprosy. *Infection and Immunity*, 2003, 71(3):1427-1433.
- 45 Krutzik SR et al. Activation and regulation of Toll-like receptors 2 and 1 in human leprosy. *Nature Medicine*, 2003, 9(5):525-532.

studies and funding will be required to determine empirically the relative importance of the different measures needed to integrate leprosy control with other public health measures in different settings.

Improving research capacity

Few entities are today pursuing capacity building for leprosy, it being a disease that is targeted for elimination as a public health problem and that has the tool (multidrug therapy) to achieve this goal. TDR supported two projects important to leprosy elimination in two countries that still have a significant burden of disease. In Brazil, a research group has been established that examines field and laboratory-based techniques for early diagnosis, predictors of progression, and immunopathology of leprosy – all important to the eventual elimination of leprosy. In Myanmar, a research training grant was used to study the prevention of disability by leprosy in the community using a self-care teaching approach – an important study for those not diagnosed in the early stages of the disease.

In 2003, TDR organized a meeting with representatives of the Pan-American health Organization and leprosy disease control coordinators, to discuss how best to develop health sciences research capacity for monitoring leprosy in areas of low disease prevalence – such capacity is especially needed as elimination programmes become more successful in the Americas.

New knowledge

TDR supported several postgenomic research projects on *M. leprae* aimed at developing new diagnostic tests for the disease.⁴³ Other studies focused on a molecule, the Toll-like receptor 2 (TLR2), a pattern recognition receptor of the innate immune system. Research into the contribution of this receptor to nerve damage in leprosy suggested that the activation of TLR2 on Schwann cells contributes to the nerve injury.^{44, 45} The roles of cytokines and alpha-defensins in the pathology of leprosy are also being

A health worker distributes a pack of multidrug therapy to a patient with multibacillary leprosy, and explains how the tablets should be taken. Simplified treatment regimens would help towards eliminating the disease.

Credit: WHO/TDR/Grump





investigated. The numbers of small tandem repeats in *M. leprae* DNA are being used as bacterial strain markers in studies that could throw light on how the disease is transmitted. Other studies on leprosy are mentioned in the chapter on strategic research, pages 79-87.

In addition, in 2003/04, TDR contributed to several organizational meetings leading to the formation of a new global Initiative for Diagnostic and Epidemiological Assays for Leprosy (IDEAL). A major international workshop supported by the Heiser Foundation was held in October 2004 at the Armauer Hansen Research Institute/All Africa Leprosy Rehabilitation and Training Center (AHRI/ALERT)

in Addis Ababa, Ethiopia, and a steering committee was elected to develop and submit several funding proposals designed to support the new initiative.

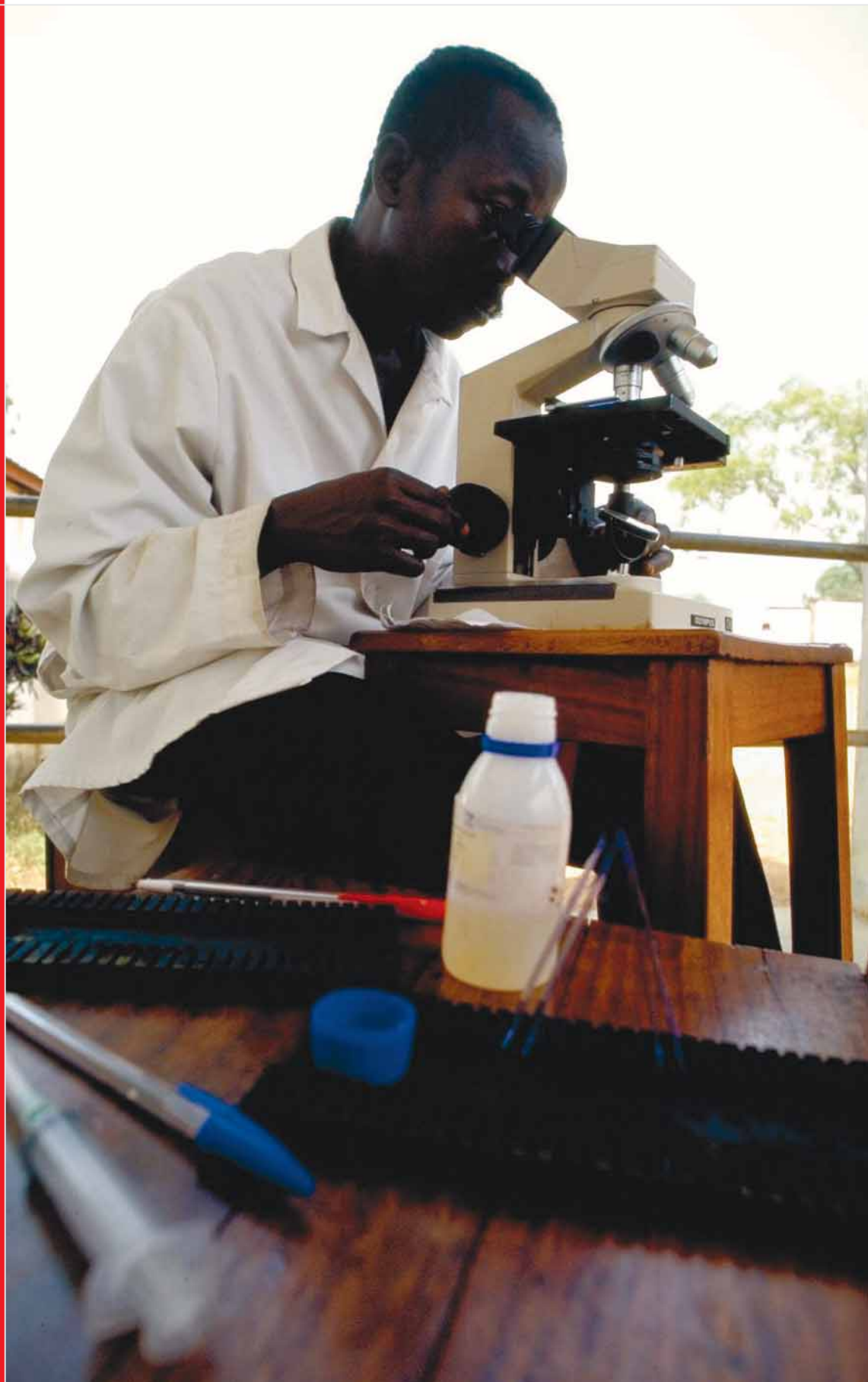


Extending access to multidrug therapy (MDT) is an approach identified to reduce still further the burden of this disease. Here, a village chief sticks an MDT poster to his truck to help inform his remote community.

Credit: WHO/TDR/Crump

Integrating leprosy services into the general health services is a major research challenge. This primary health care centre in India is used as a leprosy clinic: the child was born following a pregnancy in which her mother continued multidrug therapy.

Credit: WHO/TDR/J. Maurice



Sputum microscopy is the most accurate way to diagnose TB.
Credit: WHO/TBP/Davenport

Tuberculosis

In 1993, WHO declared the rising incidence of tuberculosis (TB) a global public health emergency. Since then, the disease has advanced, now causing an estimated 2 million deaths annually. Several inter-linked factors contribute to this progression: first, the spread of the HIV/AIDS pandemic (one third of the approximately 40 million HIV cases worldwide are co-infected with *Mycobacterium tuberculosis*, and for these individuals, the risk of developing clinical TB is about 10% per year); second, poverty and the widening gap between rich and poor (many studies, supported by TDR and other organizations, show that poverty is a major factor determining access to health information, diagnosis and suitable treatment for TB, while, in some poorer countries, the health infrastructure responsible for delivery and surveillance of treatment is threatened with collapse in the face of the epidemic); third, the difficulties of case detection (probably less than 40% of TB cases are detected, partly because current diagnostic methods are slow and cumbersome and an increasing proportion of HIV-infected TB cases present with sputum smear negative disease); and finally, the rising incidence of multidrug resistant (MDR) mycobacteria (for example, the prevalence of MDR-TB was estimated to reach 14.1% in Estonia).

In response to this situation, TDR's portfolio was expanded to include TB in 1998, and TDR is now working together with other organizations in three areas critical to disease control:

- development, evaluation and demonstration of new diagnostic methods, in collaboration with the Foundation for Innovative Diagnostics (FIND, a Bill and Melinda Gates Foundation funded

initiative which spun off from TDR's TB diagnostics initiative in 2003), and the Stop TB Diagnostics Working Group (for which TDR provides the secretariat)

- treatment of HIV/TB co-infected patients, together with the Stop TB and HIV/AIDS departments of WHO
- effective delivery of existing or new drug combinations, with drug manufacturers and partners in countries with heavy disease burdens.

TDR also continues to conduct strategic research on inequalities of access to health information, diagnosis and therapy, and on mechanisms of pathogenesis of the disease, based on increasing knowledge of mycobacterial biochemistry and genetics.

Towards improved clinical management

Diagnostics

A global strategy for diagnosing and treating tuberculosis has been implemented in over 160 countries worldwide. Nonetheless, millions of TB cases are undetected and/or unreported. Progress is irrefutably constrained by the inadequacy of available diagnostic tools. This may in part be due to poor access to diagnostic facilities, however, more rapid and reliable diagnostic methods would almost certainly improve detection rates. Traditional microscopic methods are thought to confirm less than half of patients with active disease, and to be particularly ineffective in cases of HIV/TB co-infection. Detection of multidrug-resistant (MDR) bacteria, which depends on detection of bacterial growth in selected media, is especially

time-consuming due to the remarkably slow growth rate of the TB organism. Between 2001 and 2003, twenty projects aimed at developing novel diagnostic methods were funded under a TDR/FIND Bright Ideas Grants Programme, and, of these, two are now being followed up for development and large-scale field testing. TDR is funding a comparative evaluation in Peru of several existing diagnostic assays for the detection of drug resistance, to be completed in 2005. The findings of this trial will assist in the development of recommendations for appropriate use of these technologies in developing countries. Furthermore, the performance and operational characteristics of 19 commercially available rapid serological tests for tuberculosis are being evaluated using serum specimens from the TDR Tuberculosis Specimen Bank. The Specimen Bank is a repository of reference materials collected from TB suspects and TB patients around the world. Collection sites were expanded to six new centres in different geographic areas in 2004. The TDR TB Specimen Bank and TB Strain Bank are precious resources that facilitate test development

and evaluation, and support proficiency testing in laboratories around the globe.

Shortening treatment

Current treatment consists of a six-month regimen of at least four anti-TB drugs (isoniazid, rifampicin, pyrazinamide, ethambutol), each supplied as individually-packaged drugs. This regime, when correctly followed as a directly-observed treatment 'short course' (DOTS), results in cure rates following diagnosis of over 95%, and is recommended policy in 180 countries. However, less than a third of all TB patients actually receive DOTS, partly because access to treatment may be difficult, but also because compliance with the long and complicated treatment course is often poor. Protocols have been developed for a clinical trial to test the efficacy and safety of fixed-dose combination anti-TB chemotherapy, which should also increase compliance. The trial, which was delayed by difficulties in procuring both single-drug formulations (as comparator) and fixed-dose drug combinations, is now about to commence recruitment and is supported by donations from Lupin pharmaceuticals.

Traditional microscopic methods of diagnosis are thought to confirm less than half of patients with active disease, and to be particularly ineffective in cases of HIV/TB co-infection.

Credit: WHO/TBP/Gary Hampton





Few new anti-TB drugs are likely to become available soon, because of past lack of investment in the field. However, fluoroquinolones such as gatifloxacin have shown promise as anti-TB agents in clinical trials. In partnership with Bristol Myers Squibb and Lupin, TDR is undertaking the necessary pre-clinical studies to allow clinical trials of a gatifloxacin-containing four-drug fixed-dose combination to go ahead in 2005. This would be in collaboration with a European Commission supported clinical study (OFLOTUB) consortium. If successful, this combination would shorten the duration of treatment from six to four months, increasing

patient compliance and cure rates. The experience gained in setting up these trials will help to define the framework for discussions with regulatory agencies on how best to develop and conduct clinical trials of additional new anti-TB drugs.

Antiretroviral therapy for co-infections

Treatment of HIV/TB co-infected patients is challenging. TDR has undertaken a review of strategies for using highly active anti-retroviral therapy (HAART) against HIV/AIDS within TB control settings. A multicentre trial to establish the effects of early HAART in HIV-positive patients

TB cultures: detection of multi-drug-resistant bacteria depends on their rate of growth in selected media and is very time consuming.

Credit: WHO/TBP/Davenport

For TB, X-ray diagnosis is more expensive and less accurate than sputum examination.

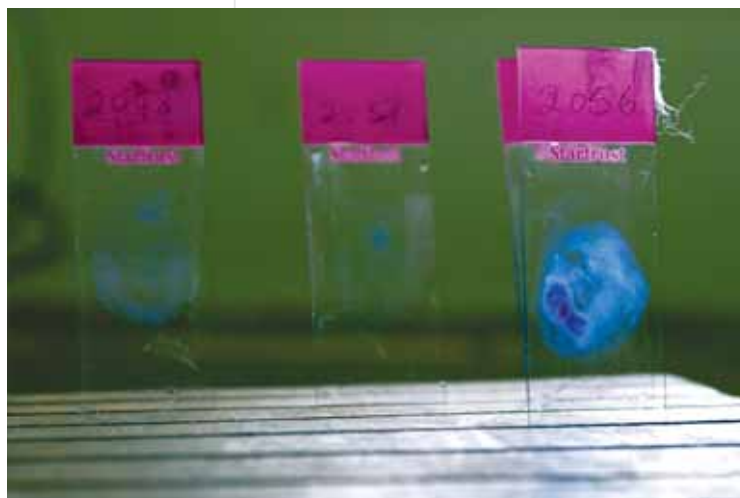
Credit: WHO/TBP/Pierre Viot



46 Weiss MG et al. *Gender and tuberculosis: cross-site analysis and implications of a multi-country study in Bangladesh, India, Malawi, and Colombia*. Unpublished report, September 2004 (in press).

Stained slides of sputum smears ready for microscopy.

Credit: WHO/TBP/Gary Hampton



receiving anti-TB treatment has been planned for 2005. The study will be undertaken within the national TB programmes of Tanzania, Uganda, South Africa and Zambia. In the same context, a strategy framework for implementation and operational research in support of the use of HAART in resource-limited settings is being developed together with the HIV/AIDS department of WHO, UNAIDS and

UNDP, based on consultations with technical partners and national country programme representatives held during 2004.

New knowledge

Gender effects in TB control programmes are particularly important and were investigated in a multicountry study in Bangladesh, India, Malawi and Colombia.⁴⁶ In addition to basic epidemiological assessments of registries and outpatient clinics, this study integrated epidemiological with anthropological frameworks and methods. Registry data showed fewer women were diagnosed with TB, and men were more likely to have problems starting and completing treatment. Delays for women in seeking care often resulted from their responsibilities as family caretakers, and problems accessing health services for men more typically resulted from responsibilities to work and earn a livelihood. Provider delays were also likely to be longer for women. Determinants of de-

layed diagnosis and treatment included cultural factors affecting diagnosis for women, the financial impact, and aspects of stigma related to the disease, gender, and site-specific factors. The emotional impact of tuberculosis was particularly striking. Each study made suggestions for control related to clinical practice, design and data needs of control programmes, and to particular needs for community outreach and health information, with particular attention to provider delay for women and case-holding for men. The cross-site analysis distinguished local priorities and overarching needs for gender-sensitive TB control.

The immune response to mycobacteria is complex. Chemokines are potential markers of immunopathology in pulmonary and extra-pulmonary TB, and their activation in response to vaccine strains of varying virulence is being investigated in patients with different manifestations of tuberculosis. Basic research on mycobacterial biochemistry and genetics continues to provide insight into bacterial metabolism and how new drugs might be selected to inhibit it. Some biochemical pathways (D-alanine biosynthesis, signalling in phagosomes⁴⁷) were better characterized during 2003, as were some of the proteins produced by the TB bacterium that are involved in its survival inside macrophages. Studies of the mycobacterial fbpABC gene regulator and PE-PGRS proteins (some of the which are cell surface constituents involved in interaction of the mycobacterium with the macrophage), as well as comparative gene expression analysis following drug treatment, provided information about potential new drug targets.

Building research capacity

Focused capacity strengthening was part of two TB-related projects during the biennium. One, which started in 2002 and

has progressed well in Kazakhstan, involved a study of the emergence of MDR-TB. Preparations for the clinical trials of four standard anti-TB drugs as a fixed-dose combination in Ethiopia and Nigeria (see above) involved building capacity at the trial sites. Similarly extensive preparations involving a number of good clinical practice (GCP) and good laboratory practice (GLP) compliance workshops have been conducted in Tanzania, Uganda, Zambia and South Africa in advance of the study investigating concomitant use of TB drugs and HAART among HIV-infected TB cases. These two studies have provided both institutional strengthening and improved research capacity within the countries involved in the studies.

TDR's research training programme is currently supporting nine young researchers pursuing their doctoral studies and focusing on important TB issues, such as clinical aspects of tuberculosis including multidrug resistance and nutrition; social science studies including gender issues, improving compliance and health sector response; and the interaction between TB and schistosomiasis. Many of these studies are being conducted in the most resource-poor countries, including Bangladesh, Lao People's Democratic Republic, Myanmar, Timor-Lest and Yemen. Further information on TDR's training programmes can be found on pages 89-95.



The emotional impact of tuberculosis was particularly striking.

47 Anes E et al. Selected lipids activate phagosome actin assembly and maturation resulting in killing of pathogenic mycobacteria. *Nature Cell Biology*, 2003, 5(9):793-802.

A technician at the WHO/TDR tuberculosis specimen bank catalogues tuberculosis samples (saliva, serum and sputum) arriving from hospitals/clinics in developing countries.
Credit: WHO/TDR/Crump



A rural shop where antimalarials are sold. Credit: WHO/RBM/Remme

Malaria

Malaria is one of the most important of the tropical diseases. Over two billion people are at risk of infection, over a quarter of a billion cases are thought to occur annually, and at least a million people die every year as a result of the disease, alone or in combination with other conditions. Most of the fatalities occur in Africa, following infection with *Plasmodium falciparum*, the most virulent of the parasites causing human malaria. The disease is closely associated with poverty. Not only does poverty lead to increased risk of malaria, through inability of individuals to pay for simple preventive measures or effective medicines, or inability of poorly-funded health services to provide them, but malaria is itself a cause of poverty. The disease is estimated to be responsible for an annual loss of around 0.5 to 1% of gross domestic product in countries where it is endemic. Over a period of 25 years, this could represent a loss of around a quarter of a country's gross domestic product. The malaria burden falls particularly heavily on the poor because the direct and indirect costs of a single case often represent a significant portion of a person's income.⁴⁸

Infective parasites are transmitted by mosquito bite. Insecticide-treated bednets (ITNs) can reduce infection rates, but not eliminate malaria from endemic areas. Insecticide resistance of mosquitoes is a growing problem. Young children who have not had time to develop some immunity to the parasite, and pregnant women who are not immune to receptors expressed by *P. falciparum* that allow it to lodge in the placenta, are especially vulnerable to the disease. To be effective, treatment needs to be easily accessible and rapidly administered. Resistance to widely-used antimalarial drugs has been

spreading at an alarming rate in recent years, so policies to prevent or slow the development of resistance, and alternative treatments where resistance is detected, are also needed.

These are not easy obstacles to overcome. Total annual death rates due to malaria have not fallen significantly since the launching of the Roll Back Malaria (RBM) programme by WHO in 1998. TDR, a main provider of research input into RBM, spends almost half of its operational budget on malaria-related projects, and is active in all research areas relevant to the disease, from basic research to formulation of policies and disease control strategies. TDR also works together in a common Task Force with the Multilateral Initiative on Malaria (MIM) to strengthen scientific research on malaria in Africa, and maintains close links with other types of organization involved in malaria research, examples of which are noted where individual projects are discussed below. A well-coordinated, collaborative effort of all those involved in fighting malaria is needed if we are to reduce the burden of disease.

Towards improved clinical management

Two major achievements were documented in the area of product development for malaria in the biennium under review.

Lapdap, composed of chlorproguanil and dapson, was registered as a new treatment for uncomplicated malaria in 2003 as a result of TDR's work with GlaxoSmithKline and partners in developed and developing countries,^{49, 50} with

48 Malaney P, Spielman A, Sachs J. The malaria gap. *American Journal of Tropical Medicine and Hygiene*, 2004, 71 (2 Suppl):141-146.

49 Sulo J et al. Chlorproguanil-dapsone versus sulfadoxine-pyrimethamine for sequential episodes of uncomplicated falciparum malaria in Kenya and Malawi: a randomised clinical trial. *The Lancet*, 2002, 360: 1136-1143.

50 Allouche A et al. Comparison of chlorproguanil-dapsone with sulfadoxine-pyrimethamine for the treatment of uncomplicated falciparum malaria in young African children: double-blind randomised controlled trial. *The Lancet*, 2004, 363: 1843-1848.

funding from the UK Department for International Development (DFID) (see *TDRnews*, 2003, 70:3).

In 2004, regulatory approval was obtained for the use of CoartemR (an artemisinin-based combination therapy or ACT, containing artemether and lumefantrine) in infants and young children weighing down to 5 kg. The approval was based on clinical studies undertaken by TDR in partnership with Novartis and RBM.

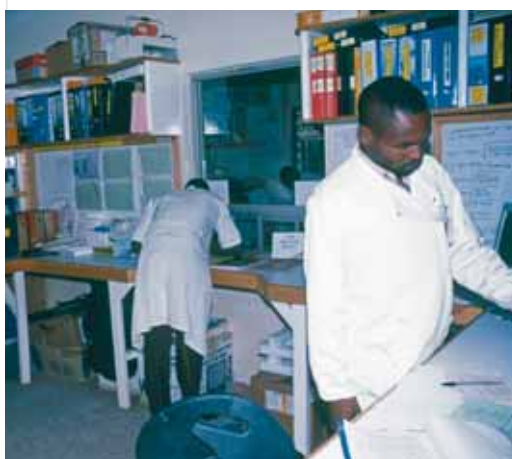
It is important to recognize that improving the situation with respect to malaria treatment requires more than simply the registration of safe and effective new

would be the scaling-up of more effective home management of suspected malaria (HMM). A manual on *Scaling up home-based management of malaria: from research to implementation* was published by TDR in collaboration with RBM and the WHO Regional Office for Africa (AFRO).⁵¹ The adaptation of HMM programmes to use of the ACT Coartem, rather than chloroquine or sulphadoxine/pyrimethamine, is currently a brake on the rapid implementation of ACT-based HMM, as is the shortage of appropriate ACT options other than Coartem. There are understandable concerns about the appropriateness of using ACTs at the community level as the drugs are new, expensive, and lack evidence-based delivery models. TDR is committed to addressing the concerns, which include feasibility, acceptability, effectiveness, cost-effectiveness, compliance, possible need to restrict use to malaria-confirmed cases, possible increase of resistance as a result of un-disciplined use, through implementation research so that ACTs can be made available to communities in a safe, acceptable and effective way.

Since 2003, TDR has funded five projects in three African countries (Ghana, Nigeria and Uganda) to establish the feasibility, acceptability and effectiveness of using ACTs in the context of HMM; the first study was completed in May 2005 in Ghana and a final report will be made available. More studies are planned to start in 2005 in Burkina Faso, Tanzania, Zambia, Benin and Cameroon.

A study of the possibilities of linking HMM with other community-directed interventions (for example, the expanded programme of immunization [EPI], ivermectin treatment, vitamin A delivery) has been started in West Africa.

Successful community-based malaria management requires knowledge of factors



Lapdap trial: a haematology laboratory where blood smears are checked for parasites and clinical samples are kept in deep-freezes.

Credit: WHO/TDR/Crump

drugs. TDR's strategy for improving treatment is based on four types of activity: first, increasing access to and appropriate use of antimalarial drugs; second, improving the management of malaria in high-risk groups (pregnant women and young children); third, combating the rise of drug resistance and understanding its development; and finally, discovering and developing new treatments for the disease.

Access to and appropriate use of antimalarial drugs

The single most cost-effective measure that could be taken to improve treatment

⁵¹ *Scaling up home-based management of malaria: From research to implementation*. Geneva, WHO/TDR, 2004 (WHO/HTM/MAL/2004.1096; TDR/IDE/HMM/04.1).

Also at: http://www.who.int/tdr/publications/publications/home_2004.htm



that influence compliance with anti-malarial treatment. Clear visual instructions for taking the correct doses of Lapdap were designed as a result of studies carried out in Kenya, Tanzania and Malawi by TDR and RBM in partnership with GlaxoSmithKline. The impact of this and other factors on compliance is currently being examined in several countries.

Management of malaria in high-risk groups

Child-bearing women are at particular risk from malaria, and infection with

HIV increases the risk of malaria infections and parasite densities in these patients. A Phase IV clinical trial to examine the safety and efficacy of Lapdap for treatment of uncomplicated malaria in pregnancy is under development. A protocol and plans for a study of the use of Coartem to treat severe malaria in pregnancy have also been drawn up. Proposals for research that will evaluate treatment efforts for childhood malaria and pneumonia at the community level have been developed by six African countries, and await funding for implementation in 2005.

As part of the home management for malaria (HMM) strategy, anti-malarial drugs are made available to vulnerable groups close to their homes through purposely trained community members.

Credit: WHO/TDR/Salako

A community-based drug distributor, part of the home management for malaria (HMM) programme in Zambia.

Credit: WHO/TDR/Pagnoni



comprehensive evaluation of clinical benefit are under way as are studies to establish the optimal strategy for providing access to the drug in real life. These studies will involve 20 000 subjects and are under way in six African countries.

Combating the rise of drug resistance: drug combinations

Development of drug resistance is slowed by using different antimalarial drugs in combination, so it is now recommended policy to introduce new antimalarial compounds as components of fixed-dosed combinations such as Lapdap and Coartem. Proposals have been received to implement an accelerated pharmacovigilance programme following the introduction of Lapdap, including surveillance of resistance as well as safety. Establishing such a pharmacovigilance programme will also be relevant to the introduction of other drug combinations.

The properties of typical artemisinin derivatives (rapid action, gametocytocidal activity, short half-life) make these compounds attractive partners for combination therapy (ACT). TDR is involved in several programmes to study the safety and efficacy of ACTs.^{54, 55} The combination of Lapdap/artesunate (chlorproguanil/dapsone plus artesunate) will be evaluated in Phase III trials in Africa, in partnership with GlaxoSmithKline and the Medicines for Malaria Venture (MMV). Two other fixed-dose combinations, artesunate/amodiaquine (AS/AQ) and artesunate/mefloquine (AS/MQ), are being developed in collaboration with the Drugs for Neglected Diseases Initiative (DNDi). Trials are ongoing in Burkina Faso (AS/AQ) and in Thailand (AS/MQ). A partnership to develop pyronaridine/artesunate with the Korean pharmaceutical company Shin Poong has now been fully transitioned to MMV. A Project in South-East Africa is ongoing to study the long-term impact (including cost-

Following a comprehensive review of the reproductive toxicity, clinical efficacy and safety of the artemisinin derivatives in pregnancy,⁵² WHO, in collaboration with Novartis and the Government of Zambia, embarked upon a collaborative initiative to develop a Pregnancy Register that will provide data on at least 1600 pregnant women exposed to Coartem or sulphadoxine/pyrimethamine (either deliberately or inadvertently) during their pregnancy. Any effects upon development of the child will be monitored in this study.

Rectal artesunate, developed by WHO/TDR in partnership with Knoll/Abbott (for drug substance preparation), RP Scherer and Scanpharm (for drug production), is intended for use as an emergency treatment for severe malaria.⁵³ The work necessary for registration of this drug is largely complete (some data concerning long-term stability of the product are still being collected), and the revised dossier should be submitted to regulatory authorities in 2005. As required for a drug that might be of life-saving benefit where submission has been made for registration on the basis of a surrogate marker of benefit, protocols and clinical trials for

52 World Health Organization. *Assessment of the safety of artemisinin compounds in pregnancy. Report of two informal consultations convened by WHO in 2002*. Geneva, World Health Organization (WHO/CDS/MAL/2003.1094; WHO/RBM/TDR/Artemisinin/03.1).

53 Barnes KI et al. Efficacy of rectal artesunate compared with parenteral quinine in initial treatment of moderately severe malaria in African children and adults: a randomised study. *Lancet*, 2004, 363(9421):1598-1605.

54 Olliaro PL, Taylor WR. Developing artemisinin based drug combinations for the treatment of drug resistant falciparum malaria: A review. *Journal of Postgraduate Medicine*, 2004, 50:40-44.

55 Abacassamo F et al. Efficacy of chloroquine, amodiaquine, sulphadoxine-pyrimethamine and combination therapy with artesunate in Mozambican children with non-complicated malaria. *Tropical Medicine and International Health*, 2004, 9:200-208.

effectiveness) of introducing ACTs, and the principal factors that determine their effective use.

New antimalarial compounds

Compounds with antimalarial activity studied during the biennium as part of TDR's drug discovery programme included the natural product manzamine.⁵⁶ Based on data generated through TDR support, investigators were able to further develop the work through MMV funding. Novel compounds are also being further followed up based on screens against rodent malaria *in vivo*, and screens of compounds against *P. falciparum* *in vitro*. While maintaining the capacity to screen compounds against whole parasites, the Drug Discovery unit has now put more emphasis on screening molecular targets. Several kinases as well as other recombinant enzymes from *P. falciparum* are currently the targets of high-throughput screening campaigns.

Some 30 000 compounds in total have now been tested for activity against malaria parasites under the JPMW programme, established five years ago between TDR, the Japanese Ministry of Health, the Kitasato Institute and 12 (later 14) Japanese pharmaceutical companies. An interesting lead series based on the natural product borrelidin was identified⁵⁷ and is the basis of an application to MMV for further funding. The Malperox project, under which hundreds of synthetic and semi-synthetic endoperoxides (compounds containing an artemisinin-type peroxide bridge) were extensively evaluated, was closed in 2003 because the encouraging results obtained with three separate compound series were also sufficiently promising to be the basis for applications for further support from other organizations. A compound developed from one of these series, OZ277, is now being evaluated by MMV in Phase II clinical trials.

Diagnostics

Malaria is currently diagnosed by microscopy of blood smears. However, many cases of presumptive malaria are treated on the basis of symptoms (fever) alone. TDR is currently assessing the utility of rapid non-microscopic diagnostic procedures for the disease. Rapid diagnostic tests are expected to be useful in predicting and following the spread of epidemics, in monitoring treatment, and in leading to more efficient use of antimalarials. Mathematical models of the effects of introducing such tests have been developed, and detailed plans have been drawn up, in collaboration with the WHO Regional Office for the Western Pacific, to ensure the quality of the tests through a network of malaria reference centres.

Rapid detection of drug-resistant malaria is important. TDR-supported work has validated the use of simple, inexpensive and field-adapted methods to measure resistance. The development of a tool package for detecting and monitoring resistance, based on *in vitro* drug susceptibility testing and parasite genotyping by the polymerase chain reaction (PCR), is nearing completion. This research has already been useful for the revision of WHO guidelines on resistance-monitoring policy.

Towards prevention

The effectiveness of insecticide-treated bednets (ITNs) in preventing malaria was demonstrated in previous work funded by TDR. Currently, the possibility of integrating provision of ITNs and advice on their use with other community-directed interventions, e.g. HMM or ivermectin treatment, is the subject of a large-scale study in West Africa. The importance of an integrated approach to malaria control was shown by a TDR-funded study that demonstrated the cost-effectiveness of the combined use of ACT,



Lapdap trial: a researcher takes blood from a vein in the arm of an infant who has malaria and is taking part in the trial.

Credit: WHO/TDR/Crump

56 Rao KV et al. New manzamine alkaloids with activity against infectious and tropical parasitic diseases from an Indonesian sponge. *Journal of Natural Products*, 2003, 66(6):823-828.

57 Otaguro K et al. *In vitro* and *in vivo* antimalarial activities of a non-glycosidic 18-membered macrolide antibiotic, borrelidin, against drug-resistant strains of Plasmodia. *The Journal of Antibiotics*, (Tokyo), 2003, 56:727-729.

Management of malaria in a high-risk group. This pregnant woman is having her blood pressure checked. As well as antimalarial tablets, she will be given a medical examination, counselling about HIV/AIDS, and a tetanus injection.

Credit: WHO/TDR/Crump



insecticides and good case management in Natal.⁵⁸

58 Muheki C, McIntyre D, Barnes KI. Artemisinin-based combination therapy reduces expenditure on malaria treatment in KwaZulu Natal, South Africa. *Tropical Medicine and International Health*, 2004, 9(9):959-966.

59 IPTi partnership:

- Swiss Tropical Institute
- London School of Hygiene and Tropical Medicine
- Unidad de Epidemiología y Bioestadística, Barcelona
- US Centers for Disease Control
- TDR
- Funding: the Bill and Melinda Gates Foundation

60 Pan W et al. Fusion of two malaria vaccine candidate antigens enhances product yield, immunogenicity, and antibody-mediated inhibition of parasite growth in vitro. *The Journal of Immunology*, 2004, 172:6167-6174.

Starting in 2000, a multicentre clinical trial was undertaken by TDR and partners (Ifakara, Tanzania; Swiss Tropical Institute; Unidad de Epidemiología y Bioestadística, Barcelona; National Institute of Medical Research, Tanzania) to establish whether prevention of malaria through intermittent preventive treatment (IPT) with an anti-malarial drug was as efficient in preventing clinical malaria or anaemia as daily treatment for four months with iron supplementation. Encouraging preliminary results led to the planning of several trials to establish the benefit of IPT in different countries of Africa. These trials are being undertaken by the recently-formed IPTi consortium.⁵⁹ If IPT administration is integrated into the EPI programme it will be important to establish in advance that IPT has no adverse influence on infants' immune responses to the EPI vaccines. This is being done at

present, led by RBM in collaboration with other members of the Consortium.

Lack of funding led to severe restriction in TDR's activities in vaccine research and development, in particular for malaria, during the biennium. However, pending the availability of funds, TDR's policy is to continue supporting strategic research that could impact on vaccine discovery, such as surrogate markers of protection, as well as some projects directed towards characterization and validation of candidate vaccine antigens. Some development projects that were supported by TDR at the start of the biennium are now being managed by IVR. The most advanced of these concerns the PfCP-2 vaccine candidate, a hybrid protein combining parts of two *P. falciparum* blood-stage antigens, which was successfully tested in a Phase I trial in Shanghai.⁶⁰ This project is now obtaining significant resources from the Malaria Vaccine Initiative. Other projects taken over by WHO/IVR concerned the

P. falciparum blood-stage antigens MSP1.42, EBA-175 and MSP-1-19, which are still in pre-clinical development. The RTS,S/SBAS2 vaccine candidate, whose development had previously received TDR support, is now being studied in Phase II clinical trials in Mozambique.

New knowledge

Dihydrofolate reductase (DHFR) enzymes have served as valuable targets for antimalarials, although the often rapid development of resistance to inhibitors of the enzymes underscores the need for better understanding of the enzymes' characteristics and roles. The Steering Committee on Pathogenesis and Applied Genomics (PAG) provided support for research on dihydrofolate reductase (pfDHFR) of *P. falciparum*, which included development of synthetic genes, generation of mutants resistant to inhibitors and structural based approaches for understanding antifolate binding to the enzyme. Crystallization and characterization of the component enzyme that resulted from the studies provided the opportunity to develop a novel screening system for identification of new inhibitors and a better understanding of the enzyme and resistance to inhibitors.⁶¹ In another project, non-active site regions of the *P. falciparum* dihydrofolate reductase-thymidylate synthase enzyme are being explored as possible inhibitor targets.⁶²

Proteome analysis was used to investigate the resistance of *P. falciparum* to aminoquinoline drugs. In another proteomic analysis of *P. falciparum*, parasite proteins expressed in various life cycle stages were identified. The data identified 714 proteins in schizonts and trophozoites, 931 in gametocytes, and 645 in gametes.⁶³ In all, 1300 unique proteins were identified. While 27% of proteins in all stages were identified, 35% of game-

toocyte proteins, 41% of trophozoites/schizont proteins, and 15% of gamete proteins were specific to their respective stage. Of the new proteins with transmembrane domains, 200 provide potential vaccine candidates.

In an innovative clinical project, one of the major features of pathogenesis in *P. vivax* infection – paroxysms – is being studied. Parasite products in patient plasma that are active during *P. vivax* paroxysms are being chemically characterized, and their antigenic nature investigated.⁶⁴ Further examples of work on malaria pathogenesis, can be found on pages 79-80.

Interrupting development of the malaria parasite in the mosquito, and hence interrupting malaria transmission, comes under the purview of the Steering Committee on Molecular Entomology. The research undertaken exploits advances in molecular biology and genetics. Much of the work on *Anopheles* mosquitoes has been paralleled on *Aedes* mosquitoes (which transmit dengue), and is described on pages 82-83.

Several effector genes (immune response genes) that could be targeted to inhibit the growth of malaria parasites in the mosquito have now been identified. They comprise serine protease (SP), phospholipase A2, C-type lectin genes, leucine rich-repeat immunogenes, trypsin, chymotrypsin, lipophorin and chitinase⁶⁵ genes. Some of these effectors have been successfully used to develop gene constructs to block pathogen development with an average 85% blocking effect. However, this level still needs improvement to ensure 100% blockage of transmission and also to minimize the risks of development of resistance to a given type of blockage.

Social and health systems research related to malaria continues to be addressed by TDR's Steering Committee on Social,

61 Sirawaraporn et al. Mutational analysis of *Plasmodium falciparum* dihydrofolate reductase: the role of aspartate-54 and Phenylalanine 223 on catalytic activity and antifolate binding. *Molecular and Biochemical Parasitology*, 2002, 121:185-193.

62 Yuvaniyama J et al. Insights into antifolate resistance from malarial DHFR-TS structures. *Nature Structural Biology*, 2003, 10:357-365.

63 Lasonder E et al. Analysis of the *Plasmodium falciparum* proteome by high-accuracy mass spectrometry. *Nature*, 2002, 419:537-542.

64 Karunaweera ND et al. The paroxysm of *Plasmodium vivax* malaria. *Trends in Parasitology*, 2003, 19:188-193.

65 Fengwu Li et al. An anti-chitinase malaria transmission-blocking single chain antibody as an effector molecule for creating a *Plasmodium falciparum*-refractory mosquito. *Journal of Infectious Diseases*, 2005 (in press).

A boy dismantles a bednet in the compound of his home. The nets are erected outdoors so that people sleeping in the open are safe from mosquito bites. Credit: WHO/TDR/Crump



66 Heggenhougen HK, Hackethal V, Vivek P. *The behavioural and social aspects of malaria and its control: An introduction and annotated bibliography*. Geneva, TDR, 2003 (TDR/STR/SEB/VOL/03.1)

67 *International Journal of Health Planning and Management*, 2004, 19:S1

68 Zeidan A et al. The impact of user fee exemption on service utilization and treatment seeking behaviour: the case of malaria in Sudan. *International Journal of Health Planning and Management*, 2004, 19:S95-S106.

69 Espino F, Beltran M, Carisma B. Malaria control through municipalities in the Philippines. *International Journal of Health Planning and Management*, 2004, 19:S155-S166.

70 Tana S. *Inequity of access to malaria treatment in times of economic crisis and health sector reform: A case study of Kulonprogo district, Yogyakarta Special Province of Indonesia*. Yogyakarta, 2003 (ISBN 979-97585-0-5).

71 Macer, D. Ethical, legal and social issues of genetically modified disease vectors in public health. *Special Topics in Social, Economic and Behavioural Research*. Geneva, TDR, 2003 (TDR/STR/SEB/ST/03.1).

Economic and Behavioural Research. In 2003, TDR published a monograph and annotated bibliography on social science aspects of malaria and its control.⁶⁶ The review covers a wide range of issues relevant to understanding malaria transmission dynamics and designing malaria interventions on the basis of social science evidence, including disease perceptions, bednet usage and acceptance, community participation, the impact of human mobility, gender and equity issues.

Following the recommendations from a TDR scientific working group meeting in 2000, social research activities continue to focus on policy and health systems factors in malaria control, with relevance to impact on policy, strategy and public health action. Six malaria-specific studies carried out in Sudan, Nigeria, Uganda, Tanzania and the Philippines and addressing health financing and decentralization issues were published in 2004, in a TDR-sponsored special issue on health sector reform and tropical diseases.⁶⁷ For example, an experimental study carried out in Sudan substantiated the dramatic impact of user fee exemptions on increasing service utilization and appropriate health seeking among

children under the age of five and pregnant women.⁶⁸ A case study carried out in the Philippines illuminated the challenges faced by municipalities with the mandate of decentralized malaria programme management.⁶⁹ Several studies were initiated on the performance and dynamics of malaria control programmes in changing health systems, on malaria-related care-seeking in times of economic crisis, political conflict and other fundamental issues affecting access to malaria-related interventions. An investigator-published monograph, published in 2003 on the basis of TDR-sponsored research, presents a rich case study of the dramatic impact of the 1997 economic crisis in Indonesia on equitable malaria control efforts.⁷⁰

The ethical, legal and social implications (ELSI) of health biotechnologies and their development and transfer into resource-poor settings constitute another new programme area in TDR's social research agenda. To open this portfolio, TDR published a review of the ethical, legal and social implications of genetically modified insect vectors.⁷¹

Building research capacity

Much of the research described in this chapter was carried out in malaria-endemic countries, by teams largely based in those countries, whose activities contributed to research capacity strengthening as an integral part of the project. TDR also has a special focus on capacity strengthening for malaria research through the Multilateral Initiative on Malaria (MIM – see also page 92).

The aim of the TDR/MIM Task Force is to develop core groups of African investigators and laboratories to carry out relevant research (towards effective control tools), to provide training, and to develop relevant research questions.

During the biennium, the TDR/MIM Task Force reviewed proposals and funded four centres in Africa to provide training on malaria vector biology and detection of insecticide resistance. Other activities included workshops on protocol development, sustainable research capacity in central Africa, and quality and content of research proposals. Also, with support from MIM partners (the Malaria Research Reference Reagent Resource Centre [MR4] and the MIM Communications network [MIMCom]), common protocols for collecting data were established through the antimalarial drug resistance network.

Two TDR Research Capability Strengthening (RCS)-supported projects aim to discover novel natural products with antimalarial activity. Working with TDR's Drug Discovery unit, laboratories in Kenya and Nigeria have adopted common protocols for in vitro screening of natural products, a measure necessary for them to link productively with other TDR-funded laboratories currently working on screening and evaluation of compounds. Additional research on natural products with insecticidal, repellent or

antimalarial activity was funded by the TDR/MIM Task Force in Kenya and Nigeria. RCS also provided support for researchers from Brazil and Cameroon to undertake high-throughput screening against selected *P. falciparum*-derived molecular targets in a pharmaceutical company environment.

A partnership involving TDR, Roll Back Malaria, and the WHO Regional Office for Africa (MIM/TDR/RBM/AFRO) is promoting research and training in areas with immediate relevance to the implementation of malaria control interventions, strategies and policies. Capacity to produce high-quality data on malaria burden and risk across several countries in Africa is being developed in a multi-country project funded through the MIM/TDR task force. In this project, long-term (4-year) data are being collected on morbidity and mortality trends; the study will be completed by early 2006.

In addition to MIM and RCS support, activities to strengthen capacity in malaria research are supported by all functional areas of TDR. For example, two workshops were held on *Vector genomics and its application* in Mali and Thailand, and centres were established in these countries to provide training in vector genomics.



Participants at a workshop on natural products.



Sexually transmitted diseases

WHO estimates that more than one million new cases of curable, sexually-transmitted bacterial infections (STI) occur worldwide every day. It is estimated that 80-90% of this global burden of STIs occurs in poor and marginalized populations in the developing world where there is poor or no access to diagnostics. There is especially urgent need for improved diagnostics for STIs in HIV-endemic areas as studies in sub-Saharan Africa have shown that STIs are important cofactors in the transmission of HIV infection.

Most STIs cause no or only minor acute symptoms, but undetected infections can have serious consequences that include infertility, pelvic inflammatory disease, cervical cancer, and adverse pregnancy outcomes. In particular, syphilis in pregnancy causes stillbirth, spontaneous abortion, intra-uterine growth retardation or preterm delivery in up to 50% of cases. Congenital syphilis is preventable if infected mothers are identified and treated appropriately by mid-second trimester.

The Sexually Transmitted Diseases Diagnostics Initiative (SDI) was founded in 1990 in response to a widely perceived need to improve care for patients with STIs in resource-limited settings through improved diagnostics. The SDI secretariat has been housed in various agencies since its inception and most recently moved to the World Health Organization, where it is managed out of TDR. The placement of SDI in TDR allows the initiative to benefit from TDR's considerable expertise in product development and evaluation and to exploit synergies in the development of diagnostics for other communicable diseases.

A joint SDI-Wellcome Trust meeting held in 2001 identified evaluating the performance and utility of rapid point-of-care diagnostics for syphilis (caused by *Treponema pallidum*), gonorrhoea (caused by *Neisseria gonorrhoeae*) and genital chlamydial infection (caused by *Chlamydia trachomatis*) as important priorities for SDI. In the meantime, SDI undertook an exercise to map the landscape of needs and opportunities for development of diagnostics for STIs with funding from the Wellcome Trust, the Bill & Melinda Gates Foundation, the United States Agency for International Development (USAID), and the Rockefeller Foundation. The results are published in a 2004 report.⁷²

Diagnostics

As reported in the previous biennium, six rapid diagnostic tests for syphilis were evaluated in eight laboratory sites around the world for their potential public health use in resource-poor settings⁷³ (Box 1). These tests have now been included in the WHO Bulk Procurement scheme, resulting in significant price savings for STI control programmes of UN member states. A second round of laboratory-based evaluation of another three rapid syphilis tests has been initiated. Field trials of the performance and utility of four of the most promising rapid syphilis tests have now been completed at SDI field sites in Tanzania, Haiti, China and Brazil (Box 1). Using data from the field sites, mathematical models have been developed to estimate the impact and cost-effectiveness of different strategies for introducing these rapid tests into control programmes

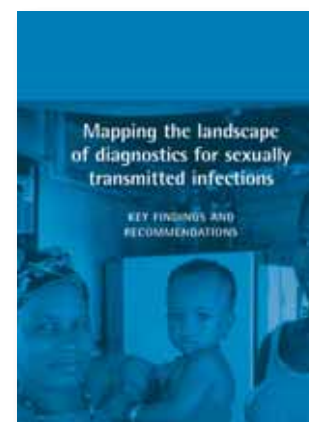
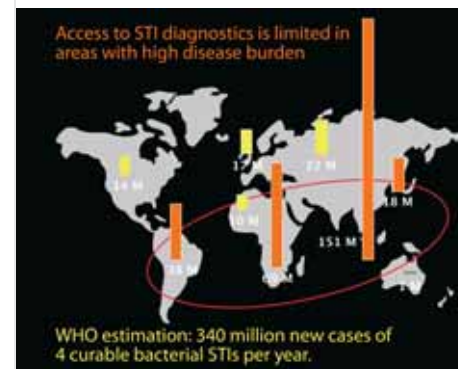


Figure 7
Global burden of disease.



72 Kettler H, White K, Hawkes S. *Mapping the landscape for sexually transmitted infections: key findings and recommendations*. Geneva, TDR (TDR/STI/IDE/04.1).

73 Laboratory-based evaluation of rapid syphilis diagnostics: results from eight SDI sites. *Diagnostics Evaluation Series No. 1*. Geneva, TDR (TDR/SDI/DE/03.1).

Rapid testing in Brazil.



At a workshop in Tanzania, one of the sites where syphilis tests are being evaluated



in different settings. User guidelines are being developed from the results of the modelling in consultation with stakeholders and experts.

In settings with a high prevalence of HIV and funding for Prevention of Mother to Child Transmission (PMTCT) programmes, there is an urgent need to integrate syphilis screening into the HIV prevention programme to avoid the tragedy of babies being saved from HIV only to die from syphilis.⁷⁴ A meeting in Tanzania is planned for 2005 to assess whether and how the use of these rapid tests can be integrated into public health policies, for example by linking HIV and STI testing programmes for expectant mothers.

Three rapid diagnostic tests for genital chlamydial infection and two for gonorrhoeal infection are being evaluated at SDI field sites in Brazil, Benin, China and Madagascar (Box 1). Current ongoing work by SDI includes developing a pre-qualification scheme for diagnostics akin to that for essential medicines, developing strategies for test introduction and sustainable adoption, and finalizing guidelines for the design and conduct of diagnostic evaluations. SDI also has a website⁷⁵ that provides up-to-date information on SDI activities as well as summaries of the latest peer-reviewed publications on STI diagnostics accompanied by expert commentary on the application of these findings in the developing world.



74 Peeling RW et al. Avoiding HIV and dying of syphilis. *The Lancet*, 2004, 364(9445):1561-1563.

75 www.who.int/std_diagnostics/

www.who.int/std_diagnostics/

Industry partners and tests:

• Abbott Determine Syphilis (USA)	syphilis tests
• Becton Dickenson (USA)	syphilis tests
• CKY Biotech (USA)	syphilis tests
• Dienes Diagnostica (Italy)	syphilis tests
• Fujirebio Inc. (Japan)	syphilis tests
• Omega Diagnostics (UK)	syphilis tests
• Pacific Biotech (Thailand)	syphilis tests
• Qualpro Syphichick (India)	syphilis tests
• Standard Diagnostics (Korea)	syphilis tests
• Thermoelectron (USA)	chlamydia and gonorrhoea tests
• Unipath Inc (UK)	chlamydia tests
• Zonda Inc (USA)	chlamydia and gonorrhoea tests

The evaluation (laboratory and/or field) sites:

Africa

- Benin: SIDA-Laval University, Cotonou
- the Gambia: Medical Research Council, Banjul
- Madagascar: Institut Pasteur, Antananarivo
- South Africa: University of Natal, Durban
- the United Republic of Tanzania: National Medical Research Institute, Mwanza

Americas

- Brazil: Alfredo di Matta Foundation, Manaus
- Haiti: Groupe Haitien d'Etudes du Sarcome de Kaposi et des Infections Opportunistes, Port au Prince
- United States of America: University of Alabama, Tuscaloosa

Asia

- China: National STD Center, Nanjing; Peking Union Medical College
- India: All India Medical Research Institute, Delhi
- Sri Lanka: Ministry of Health, Colombo

Europe

- the Russian Federation: Central Institute for Skin and Venereal Diseases, Moscow

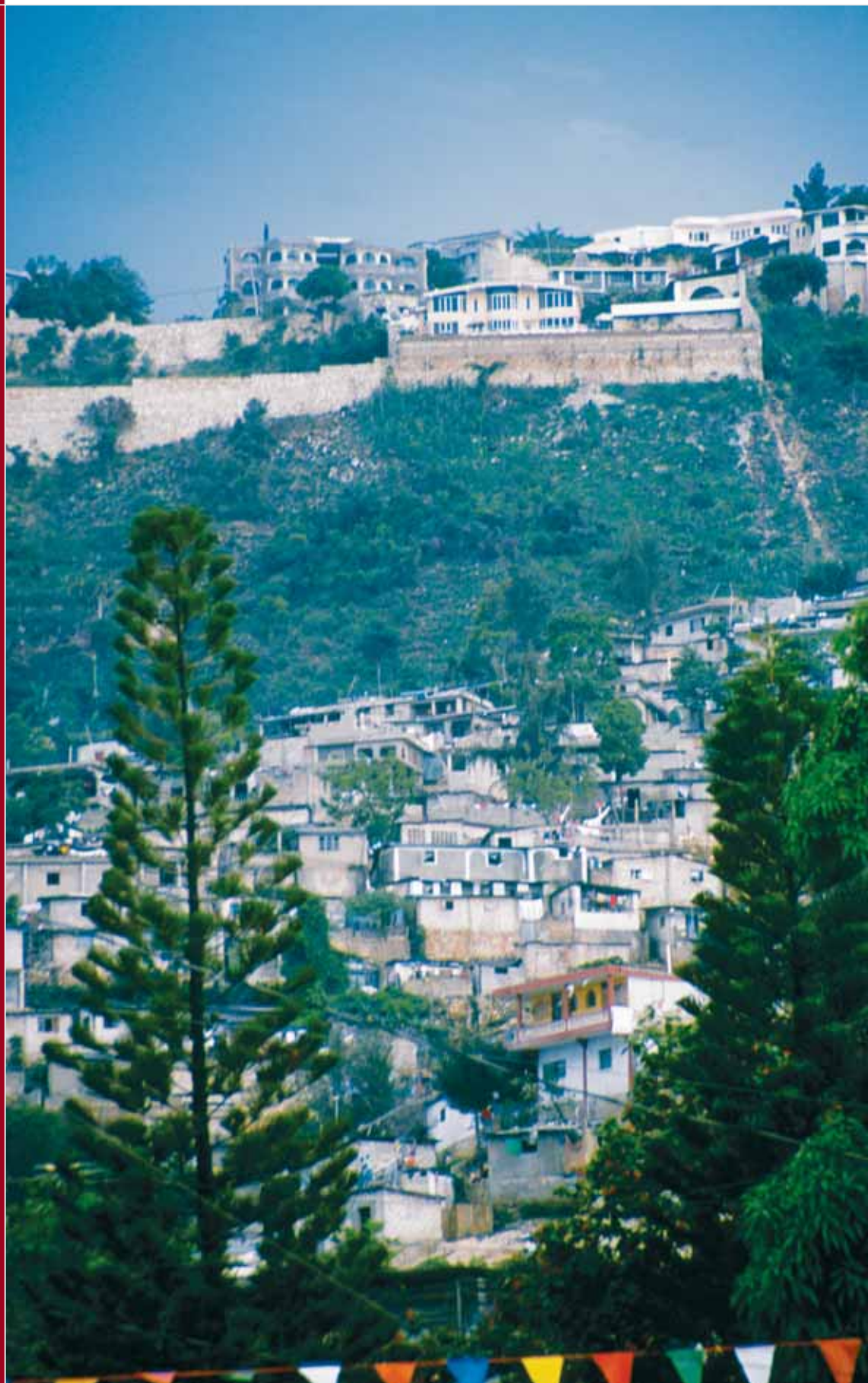
Box 1

Diagnostic tests and the sites where evaluation was or is being undertaken with SDI support.



Good laboratory practice/good clinical practice SDI workshop in China.

... to avoid the tragedy of babies being saved from HIV only to die from syphilis.



Large, expensive villas stand above low-quality housing. The divide between rich and poor is very apparent.

Credit: WHO/TDR/Crump

Strategic research

Tropical diseases continue to pose a variety of unresolved fundamental questions that need to be addressed in order to better strategize and enhance their control. These questions are multi-faceted, wide-ranging and concern both the biological and social realities in which the diseases emerge and persist. How can knowledge about the genetic make-up and ecological niche of a disease vector be used to interrupt the development of pathogens in this vector? What would be the ethical, legal and social implications of the release of genetically-modified disease vectors? How can a deepened understanding of pathogenic processes, e.g. of the progression from dengue fever to dengue hemorrhagic fever, be exploited in disease control and patient management? Which chemical compounds or proteins can be transformed into novel leads for the development of drugs, and candidates for vaccines and diagnostics? How are disease control efforts constrained by social, behavioural, economic and policy factors, and how can new knowledge about these factors be made useful to improve both disease control efforts and overall public health, especially of neglected populations?

These questions illustrate the scope of strategic research in TDR. This research is dedicated to generating new knowledge about the biological, social, economic, health systems, and behavioural dimensions of infectious diseases. On the one hand, such knowledge can lead to elucidation, characterization and validation of innovative targets for drugs, diagnostics, vaccines and novel vector control approaches. On the other hand, it can contribute to disease control strategy by making it better informed and grounded in social science evidence. This strategic research is also linked, and contributes,

to product research and development, implementation research, and capacity building within TDR.

The objectives of strategic research are achieved through investigator-initiated research projects, and through creating project-dedicated networks of investigators and institutions aiming to address research and public health needs. As in other areas of TDR, these activities are managed with the assistance of steering committees of international experts; for strategic research, the activities covered are: pathogenesis and applied genomics, genomics and discovery research, molecular entomology, and social, economic and behavioural research. Much of the work overseen by these committees is documented within the different disease sections of the report. In this section we describe some of the cross-cutting activities and achievements.

Pathogenesis and applied genomics

Studies in this area focus on efforts to understand pathogenesis of tropical diseases using tools based on genomics data and technology. Innovative approaches looking at cell signalling pathways and immunopathological markers of infection are among the topics under investigation. In addition, studies to identify novel targets for drugs against malaria, TB, and African sleeping sickness, and develop a test for infection in leprosy, are supported as a line of work that exploits available genome data in efforts to meet the needs of control programmes.

To support the discovery of new tools, one emphasis has been on establishing

model assays based on novel standard and new DNA technology systems (in vivo and in vitro models, artificial and genetically modified chromosomes, pathogens with markers for quantitative and qualitative analysis in infections), and on using these models to identify new targets for drugs, diagnostics, and immunological reagents. For example, a severely compromised immune deficient (SCID) mouse model has been prepared for malaria studies, and artificial chromosomes for studies on Chagas' disease. A network for transfection and use of reporter genes for drug screening for malaria and leishmaniasis has been set up.⁷⁶

Work to establish, acquire, and evaluate novel standards, new DNA technology, model assay systems, and renewable reagents for appraisal of potential drug, vaccine and diagnostic targets and products was initiated in 2004. The aim is to develop and enhance access of disease-endemic country (DEC) investigators to reagents that facilitate research in tropical diseases. The establishment of satellite reagent resources and validation techniques in three laboratories in Africa, Asia, and Latin America is being explored, and support is being provided for producing parasites with reporter genes for drug studies through applications of transfection.

Through its Research Capability Strengthening(RCS)-Plus bioinformatics initiative, TDR is helping to develop expertise in DEC in bioinformatics, applied genomics, and related molecular biology. There is increased involvement of DEC scientists and institutions in postgenomic R&D, and TDR is establishing bioinformatics training centres and career programmes in Africa, Asia and Latin America. A call for three career development grants in functional genomics for tropical diseases was posted in 2003, and one award was made in Latin America. So far, TDR has

trained over 100 DEC scientists in bioinformatics, and continues to support regional bioinformatics training courses in Sao Paulo, Brazil; Cape town, South Africa; Bangkok, Thailand; and New Delhi, India.

Two centres for functional genomics applied to insect vectors of human diseases, one in Thailand and one in Mali, were established in 2004; capacity strengthening is ongoing through the Biology of Disease Vectors course and the Functional Genomics Applied to Insect Vectors course. The aim is to train young scientists to use genome sequence data for disease vectors. Regional research networks are being established; they focus on applications of bioinformatics and functional genomic approaches to study vectors and pathogens, and are expected to be sustainable.

Drug discovery

At the end of 2004, TDR's drug discovery activities were integrated into the Strategic Research area. This move should enable the results of recent work on parasite genome sequences, particularly descriptions of new potential drug targets and biochemical pathways, to feed more easily into focused drug discovery programmes.

The backbone of these programmes consists of a network of laboratories that evaluate the activity of compounds against parasites in different laboratory models. The compounds are supplied by academic researchers or come from industry. Testing is normally carried out under a confidentiality agreement at no cost to the supplier, who retains compound ownership and any associated intellectual property rights, with the proviso that rights to use or develop the compound for named tropical diseases will be made available on reasonable terms. Tests are performed for activity



Plasmodium falciparum parasites expressing green fluorescent protein. The ability to derive transgenic parasites expressing proteins such as green fluorescent protein (GFP) and luciferase has opened up new possibilities for high throughput drug screening.

Credit: BIOTEC/Chairat Uthairatibull

76 <http://www.who.int/tdr/grants/workplans/transfection.htm>

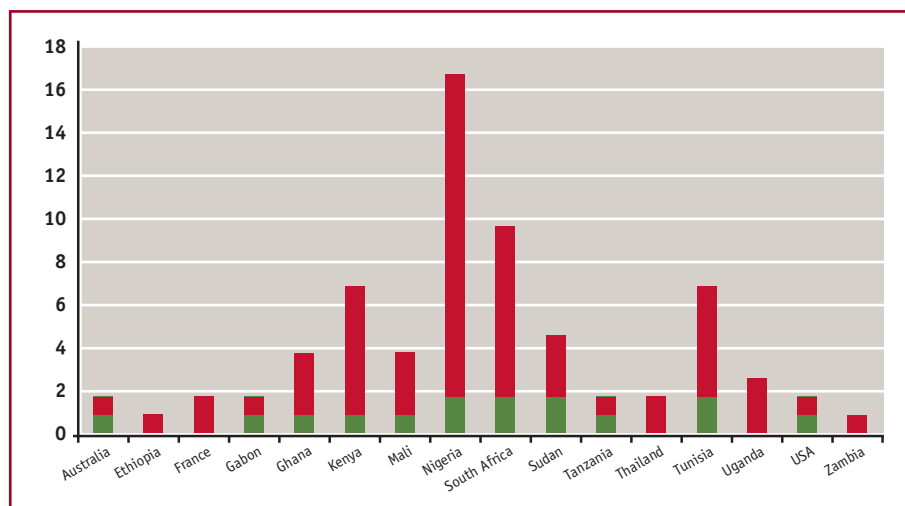


Figure 8
Africa regional training
course on bioinformatics:
number of applications
received and accepted in
2003.

against the parasites responsible for malaria, leishmaniasis, African trypanosomiasis, Chagas disease, onchocerciasis, lymphatic filariasis, and schistosomiasis. The capacity to test against schistosomiasis, in laboratories in Cairo and London, was added in 2003. In addition, as part of an RCS-supported programme to systematically investigate the antiparasite potential of natural products, a planning workshop on this subject was held in 2003, and two antimalarial testing centres in Kenya and Nigeria have now been funded and will be ready to test new natural products for activity in 2005.

TDR's efforts to proactively search out and test potentially interesting compounds increased during the biennium, during which about 20 000 compounds from over 120 suppliers were tested against one or more parasites. Collaborations with industry have allowed access to compounds pre-selected to have potential antiparasitic activity, as well as access to large compound collections, either chemically diverse or with a selected focus (e.g. on kinase or protease activity). New compounds that were active against parasites in relevant animal models included some with antimalarial activity and some that were active against *Onchocerca*.

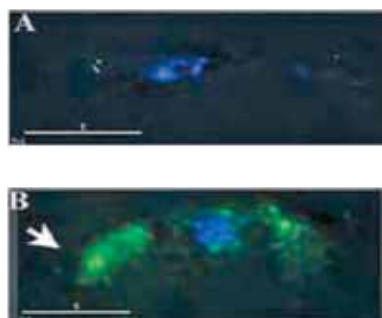
TDR support for high-throughput screening (HTS) on molecular targets also increased during the biennium. HTS campaigns are currently being supported at two centres, the Walter & Eliza Hall Institute (WEHI) in Melbourne and the pharmaceutical company Ares Serono in Geneva. Good progress on several screens was reported at WEHI. The collaboration with Ares Serono is a good example of in-kind contribution from industry to antiparasite drug discovery and research capacity strengthening. HTS campaigns on two targets, a protease and a kinase from *P. falciparum*, are being carried out as part of an RCS-supported project, which has allowed two investigators from disease-endemic countries (Brazil and Cameroon) to use the expertise and facilities available in a large pharmaceutical company.

Regional training course on
bioinformatics.



MalariaSphere used to examine gene introgression and allele frequency dynamics of *Anopheles gambiae*.

Credit: G. Yan, TDR project no. A10429



Indirect immunofluorescence microscopy analysis of anti-PgCMT2-binding 1C3 ScFv to *P. gallinaceum* ookinete.

Credit: J.M. Vinetz, TDR project no. A00407

Molecular entomology

Research in this area is aimed at interrupting malaria and dengue pathogen transmission through the exploitation of advances in molecular biology and genomics. Research and capacity building activities mainly focus on:

- identifying genes responsible for disruption of parasite/virus growth
- developing methods to spread selected genes in wild mosquito vector populations
- developing molecular tools to genetically transform mosquito vectors
- requirements to be considered before deploying refractory transgenic insect vectors
- support and coordination for international activities in insect genome sequencing and mapping and post-genomics research

- capacity building in the use of insect vector genome data.

Identifying genes responsible for disrupting parasite/virus growth will lead to understanding of the molecular basis of vectorial resistance. Activities include studies on vector-parasite/virus interactions, and on targets that can be inhibited in the midgut, haemolymph and salivary glands to prevent growth of a parasite. Achievements in this area include the identification of several effector genes that could be targeted to inhibit the growth of malaria parasites in the mosquito. RNAi-induced inhibition of malaria parasite development⁷⁷ and dengue virus replication was also accomplished.

To develop methods for spreading selected genes in wild mosquito vector populations and apply them effectively in the field, we need to understand the biology, genetics and dynamics of mosquito populations. Research is ongoing on gene flow, mating barriers between wild mosquito populations, adaptive

⁷⁷ Nirmala X, Marinotti O, James AA. The accumulation of specific mRNAs following multiple blood meals in *Anopheles gambiae*. *Insect Molecular Biology*, 2005, 14(1):95-103.

mechanisms to environmental conditions, and evaluation (in the field and laboratory, and by computer modelling) of factors (e.g. mating, host-seeking behaviour, oviposition, and gene driver systems and genomic stability) affecting the competitive fitness and vectorial capacity of *Anopheles* and *Aedes*.

The genetics and insecticide resistance of *Anopheles* and *Aedes* species have been characterized in some African, Latin American and South-East Asian vector populations. Results include establishing the distribution of M and S molecular forms of *Anopheles gambiae* in Africa,⁷⁸ and the frequency distribution of insecticide resistance genes (Kdr, Ace1, Cyt P450) among vector populations. Population structure of *Ae. aegypti*, *An. funestus* and *An. culicifacies*⁷⁹ was studied using molecular markers. Odorant-binding proteins from *An. gambiae* and *Ae. Aegypti*⁸⁰ were cloned and characterized, and the genes encoding candidate odorant receptors that are selectively expressed in olfaction organs were identified in *An. gambiae*.

Molecular tools for genetic transformation of mosquito vectors are being developed in order to engineer insect vectors resistant to pathogen transmission and to improve germline transformation methods. Improved transposable elements constructs were developed and used for mosquito transformation, resulting in stable, reproducible germline transformation of *Ae. Aegypti*, *An. stephensi* and *An. gambiae* in the laboratory. Transposable elements and endosymbiotic *Wolbachia* bacteria are being explored as means of increasing the frequencies of genes (gene driver mechanism) introduced into mosquito populations. Tissue-specific (midgut, salivary glands, hemocytes, fat body) promoters and fluorescent dominant protein markers were shown to function in transgenic mosquitoes. Before deploying refractory transgenic

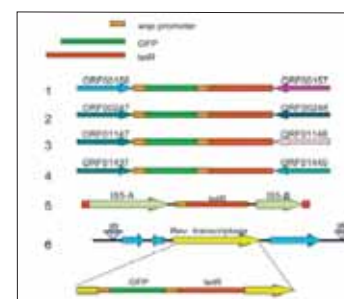
insect vectors, research into a variety of issues is needed in order to develop an evidence base for policy and minimize the risk to humans and the environment from use of this biotechnology. Activities include research into: biosafety; evaluation of risk/benefit; development of guidelines and principles; site preparation; collection of baseline data on vector biology, ecology and genetics; and studies into the ethical, legal and social implications (ELSI) issues surrounding use of transgenic insects. Achievements include the establishment of a forum to bridge laboratory and field research; the designation of a research agenda on genetic control of disease vectors; and the setting of criteria for identifying and preparing potential sites. These were defined during a meeting in Nairobi, July 2004, co-organized by TDR, the US National Institutes of Health (NIH), the International Atomic Energy Agency (IAEA), and Wageningen University.⁸¹

Insect genome sequencing and mapping and postgenomics analysis are ongoing in the international arena. One aim is to identify novel insecticide resistance mechanisms, as well as tools to monitor these in field populations. The main achievements during the biennium were exploitation of the RNAi technique for gene function analysis, and the convening of a consortium by TDR, in January 2004, which created the International *Glossina* Genomics Initiative (IGGI) to support and coordinate sequencing activities on the tsetse fly genome (see pages 27-28).

Capacity to use insect vector genome data is being built in disease endemic countries (DECs) through training and participation in molecular biology, genomics, and postgenomics activities (e.g. bioinformatics, gene discovery, functional analysis), and support is being provided to DEC investigators for the exploitation of insect vector genome

Figure 9
Schematic representation of different constructs created for *Wolbachia* genetic transformation.

Credit: S. O'Neill, TDR project no. A10708



78 Della Torre A., Tu Z, Petrarca V. On the distribution and genetic differentiation of *Anopheles gambiae* s.s. molecular forms. *Insect Biochemistry and Molecular Biology*, 2005 (in press).

79 Sujatha Sunil et al. Isolation and characterization of microsatellite markers from malaria vector, *Anopheles culicifacies*. *Molecular Ecology Notes*, 2004, 4:440-442.

80 Ana Claudia et al. Identification of a chemosensory receptor from the yellow fever mosquito, *Aedes aegypti*, that is highly conserved and expressed in olfactory and gustatory organs. *Chemical Senses*, 2004, 101:5058-5063.

81 A report of this meeting is to be published by Wageningen University (Frontis) in 2005.

data. Two training centres in functional genomics and bioinformatics for insect vectors were established (in Thailand and Mali) in 2004; the first courses have already been held.

Social, economic and behavioural research

Over the past 25 years, TDR has sponsored research related to social, economic, behavioural and policy issues in the control of tropical diseases.⁸² According to its 2000-2005 strategy, TDR addresses these issues through both strategic and implementation research.

Social research is important as control tools frequently do not reach affected populations, most often the poor and marginalized, as health systems fall short of potential for effective delivery. Social factors, to a large extent, shape the epidemiology of infectious diseases and the challenges for control. Social research can identify bottlenecks in health service delivery systems and suggest pathways for better and more efficient diffusion of control technologies; it can lead to policy for reducing barriers to access, imposed for example by treatment costs inflicted on the most vulnerable groups (women, infants, children, the very poor). Research can elucidate social and economic forces as they affect biological events, e.g. inadequate health services and sub-optimal drug supply mechanisms together with non-adherence to treatment schedules and falsification of pharmaceutical products can lead to drug resistance. Social research can illuminate the inequalities between men and women that lead to increased vulnerability of women to poverty and infectious diseases such as AIDS and tuberculosis, and can suggest gender-specific approaches to disease control.

The range of activities includes research on health policy and systems, access issues,

policy processes, gender and gender-sensitive interventions, the linkages between conflict and tropical diseases, health economics, and the ethical, legal and social implications of developments in biotechnology and their transfer to resource-poor settings.

Over the past eight years, TDR has supported more than 70 studies on health systems, and a number of these studies were published in 2004 as a special journal issue⁸³ following data analysis and scientific writing workshops. This complements two previous special issues.⁸⁴ The 2004 publication presents TDR-sponsored research carried out in ten countries (Colombia, China, Ghana, the Lao People's Democratic Republic, Mexico, Nigeria, the Philippines, Sudan, Tanzania, Uganda) on the impact of health sector reforms on tropical disease control programmes. The case studies presented show that health sector reforms stopped at a sub-optimal level. Despite very different epidemiological and socioeconomic settings, the approaches were remarkably similar and, in several situations, turned out to be inappropriate. This knowledge indicates that devising suitable information and monitoring structures and improving the governance of health systems are critical for successful implementation of health sector reforms.

TDR aims to ensure that its health systems and policy research projects are relevant and lead to improved policy-making. In this context, in May 2004, a research dissemination seminar for high-level policy-makers was convened in China and a publication on *Health policy and systems research in China*⁸⁵ was launched during the Ministerial Summit on Health Research in Mexico, November 2004.



82 *Social science research on tropical diseases, 1979-2004: 25 years of TDR-sponsored research*. CD-ROM. Geneva, WHO/TDR, 2004.

83 Health sector reform and tropical diseases: opportunities and threats. *The International Journal of Health Planning and Management*, 2004, 19.

84 *Health Policy and Planning*, 2001, 16(suppl 2); 2002, 17(suppl).

85 Meng Q et al. *Health policy and systems research in China*. WHO/TDR, 2004 (TDR/GEN/SEB/04.1). A co-publication of TDR, the Ministry of Health of China, the China Network for Training and Research in Health Economics and Financing, and the Alliance for Health Systems and Policy Research.



School children visit houses in their community to talk to inhabitants about dengue. The school is taking part in a project to create health awareness.

Social factors, to a large extent, shape the epidemiology of infectious diseases and the challenges for control.

SEB supports research on the impact of health-system change and globalization on infectious disease. What are the implications of the changing social, political and civil structures for health systems serving vulnerable populations? How do the linkages between global, national and local-level policies affect their ability to respond to key health issues? What exactly is the role of evidence in policy-making, and can it lead to innovative approaches to defining and responding to emerging problems? There is much to be understood about how wide-ranging global changes are impacting on infectious dis-

eases. A review of the evidence about links between globalization and infectious diseases in terms of changes in disease distribution, transmission rate, and in some cases management of disease, was published;⁸⁶ several TDR-supported studies, some of which are ongoing, highlight the impact of various health-system changes on infectious disease control.

TDR prioritizes research that brings about effective tools for public health and disease control. Concerned with improving access of poor populations to

86 Saker L. et al. Globalization and infectious diseases: a review of the linkages. *Social, Economic and Behavioural Research, Special Topics No.3*, 2004 (TDR/STR/SEB/ST/04.2).



A health education flip chart (no. 6 in a series of 13, in Spanish) used by teachers to inform schoolchildren about dengue

both prevention and treatment, such research aims to clarify the health impact of various forms of social inequality, including socioeconomic status, gender, ethnicity, and geographic factors, that influence the occurrence of infectious diseases and their control. A number of studies are ongoing in this area.

Gender is a matter of particular interest to the issue of access, inasmuch as both biological sex differences and socially-constructed gender differences affect exposure, risk factors, and vulnerability to tropical diseases. Gender also influences disease effects and illness-related experience, behaviour, and treatment outcomes. Social science studies are helping to address specific needs for improving infectious disease control among both women and men. In tuberculosis, for example, a TDR-funded multisite study carried out in Bangladesh, India, Malawi and Colombia between 2000 and 2004⁸⁷ illustrates how questions about gender-specific needs and gender-related barriers to utilization of health services can be resolved to improve the effectiveness of timely case detection, diagnosis, treatment and case-holding.

Gender-sensitive interventions are especially crucial and difficult to design for tropical diseases with a chronic course and long-term consequences. Such a disease is lymphatic filariasis, and a report of the value of support groups for women with lymphatic filariasis was published (see page 43). Community involvement is the subject of two other reports, one on the history of the idea of community participation and its implementation in resource-poor settings,⁸⁸ and the other related to dengue control.

Armed conflicts and other complex emergencies most often disrupt health systems and increase the burden of infectious diseases. Exploring the interface of

the TDR diseases with conflict and other crises in today's uncertain world is another area taken up by the TDR SEB Steering Committee. While there is attention to technical aspects of humanitarian responses in complex emergencies, there is lack of knowledge regarding options for health services delivery and policy implementation in societies suffering from protracted armed conflict. Particularly, there has been limited research, at least from within the public health field, on how individuals, communities and health systems cope with adversity. As an initial step, TDR funded a multicountry study on the *Resilience of community and health systems under conflict for responding to infectious diseases*, carried out in the Democratic Republic of Congo, South Sudan, Uganda, the Philippines and Sri Lanka. An international workshop/symposium on *Resilience and infectious disease in the context of war* was held in collaboration with the University of Peradeniya and the Center for Intersectoral Community Health Studies in Kandy, Sri Lanka, August 2004, to compile and discuss preliminary findings and develop guiding principles and specific action points for facilitating coping and resilience in vulnerable populations and health systems as they respond to malaria and TB in war situations. Research results are expected to be published in 2005-2006. It is anticipated that the multicountry study will generate insights and hypotheses for research in other settings that may have similar experiences of collective violence. Literature reviews of conflict and infectious disease, and of research ethics in conflict settings, are also currently under production.

Economic factors, including issues related to human resources and costs, clearly affect infectious disease control programmes. During 2004, health economics research was re-emphasized by the SEB Steering Committee, focusing initially on two

87 Weiss MG et al. *Gender and tuberculosis: cross-site analysis and implications of a multi-country study in Bangladesh, India, Malawi, and Colombia*. Unpublished report, September 2004 (in press).

88 Espino F, Koops V, Manderson L. Community participation and tropical disease control in resource-poor settings. *Special Topics in Social, Economic and Behavioural Research Series*, No 2, 2004 (TDR/STR/SEB/ST/04.1).

topics: human resources for infectious disease and transaction costs analysis.

Non-availability of human resources at the periphery is an important reason why health systems fail to reach their potential. In rural health systems where there are poor and marginalized populations, human resources are often lacking or emigrate to more lucrative places. An analysis of international data on health labour migration, and on levels of pay of different cadres of health worker in absolute and relative terms, is ongoing; it is planned to fund specific research projects starting in 2005. The aim is to elucidate the impact that the international labour market is having on the availability of human resources for infectious disease control programmes, and to compare the effectiveness of interventions (e.g. rural practice allowances, non-recruitment agreements with northern countries) in securing availability of skills at the periphery.

Transaction cost analysis (TCE), which allows the costs of business transactions to be evaluated (e.g. the costs incurred in searching for information on the price, quality and availability of goods and services), might help health systems target their activities more to the poor. A review of the TCE issue is under preparation, and research projects are planned to begin in 2005. The aim is to elucidate the usefulness of TCE in the design of disease control programmes in specific settings, and see if TCE can predict the performance of programmes in targeting activities to the poor.

Health biotechnologies to fight infectious diseases, such as molecular diagnostics, new-generation vaccines, natural products, and genetically-modified insect vectors, have great potential for improving health in developing countries. In order to better harness these biotechnologies in a re-



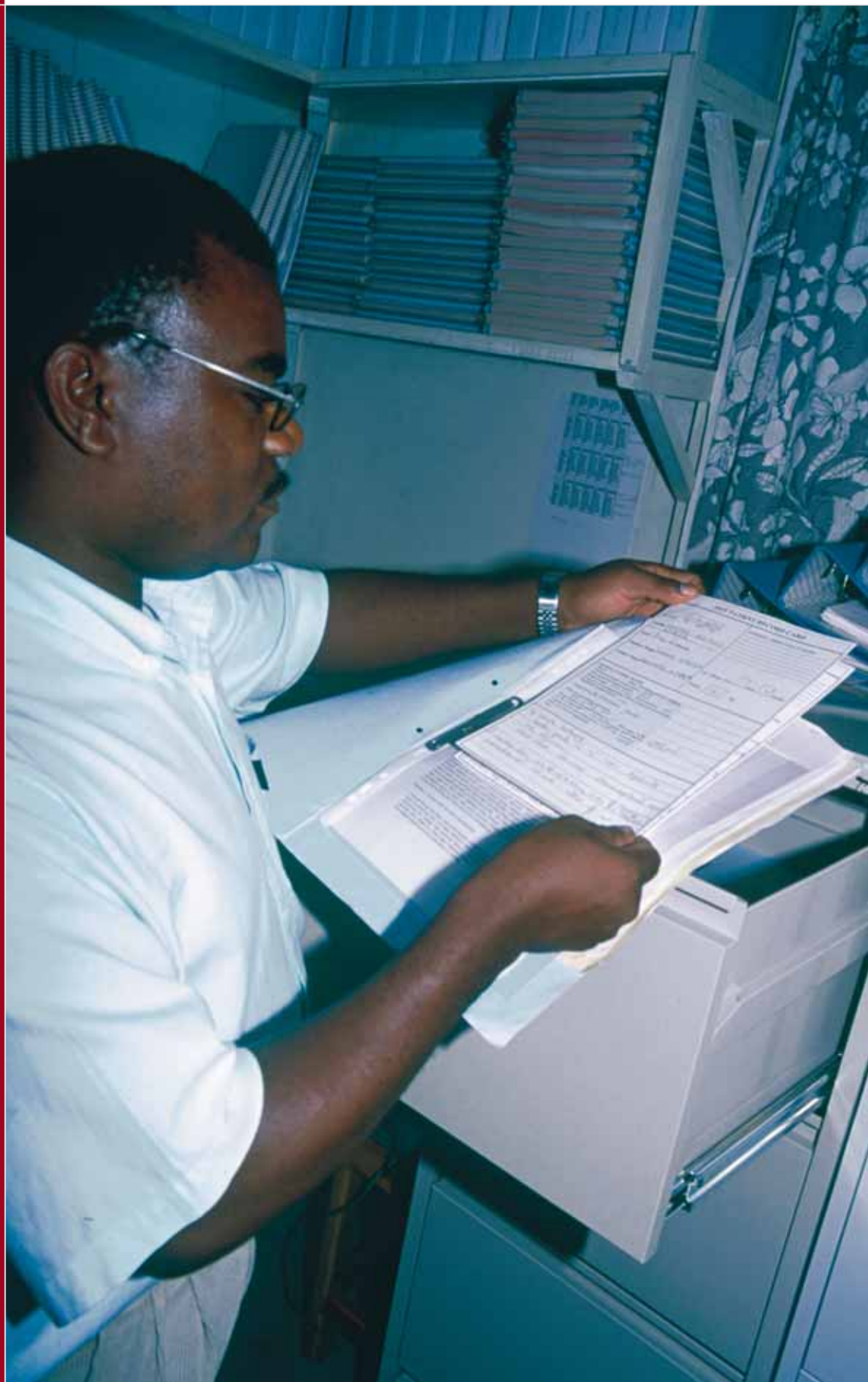
sponsible manner, the SEB Steering Committee created a programme focus on the ethical, legal and social implications (ELSI) of health biotechnology development and transfer into resource-poor settings. A major review on ELSI pertaining to genetically modified disease vectors⁸⁹ was published in 2003, and a review of consent in resource-poor settings, including case studies, is in peer review.

Capacity strengthening efforts in social research include technical support to individual studies, and workshops on methods, analysis and scientific writing. TDR also undertakes focused research capability strengthening, e.g. the project to conduct social science research relevant for DOTS (directly observed treatment, short-course, for TB) expansion in support of national tuberculosis control programmes in Kazakhstan and Haiti.

Social research is important as control tools frequently do not reach affected populations, most often the poor and marginalized.

Credit: WHO/TDR

⁸⁹ Macer D Ethical, legal and social issues of genetically modified disease vectors in public health. *Social, Economic and Behavioural Research Special Topics No.1*, 2003 (TDR/STR/SEB/ST/03.1).



A principal investigator consults a patient's file: all records are kept under lock and key as part of good clinical practice (GCP).

Credit: WHO/TDR/Crump

Building capacity for research

In making research work to address the health needs of the poorest populations, a vital ingredient is to have local research capacity available. While it is not requisite that every country develops cutting-edge innovative research programmes, it is necessary that every country has the research capacity to identify, innovate, and adapt technology to its own needs and constraints in order to better address its burden of neglected tropical diseases.

Research capacity building is an approach that starts with people, and what they need; TDR has a pipeline of RCS activities according to the needs of each country. For the least developed countries (LDCs), there is a focus on training of individuals and strengthening of institutions, and on provision of information. For more developed countries, the focus changes to partnerships. Finally, for advanced developing countries (ADCs), there is an emphasis on utilization of the capacity already developed in these countries, especially on good practices. TDR works on the principle that, to achieve long-term outcomes, what is needed are comprehensive capacity building programmes that provide continuing professional development, support, and an enabling environment, rather than scientific training alone.

Capacity building cuts across all TDR activities. While disease-specific research capability strengthening (RCS) activities are mentioned throughout this document, TDR's overarching capacity building measures are described below. During 2003-2004, TDR Research Capability Strengthening (RCS) activities became more fully integrated into the pro-

gramme's R&D activities through its RCS-Plus initiative. So the programme's activities are increasingly being driven by its R&D agenda, and in this way are becoming more pertinent to the research needs of each country's population. To date, TDR has supported over 1400 post-graduate students, 400 research groups and institutions in about 80 disease-endemic countries.

Support to individuals

For the least developed countries (LDCs), TDR supports individual-driven capacity strengthening for tropical diseases research. This includes investment in infrastructure and the research environment, with improved access to scientific information and to training opportunities for young scientists. Collaborative research with scientists and institutions from more advanced countries is encouraged, and a range of opportunities allows individuals to develop a research career. The aim is to develop a critical mass of trained scientists in disease-endemic countries (DECs) for identifying needs and developing solutions to public health problems caused by infectious diseases, and to increase the number of experts and centres engaged in research, product development, and capacity building.

Training opportunities

■ Research training grants

During 2003-2004, 51 TDR-funded students completed their graduate training. This included 10 MSc students and 41 PhD students. Twenty-eight new training grants were awarded in 2004; it should be noted that no new

It is necessary that every country has the research capacity to identify, innovate, and adapt technology to its own needs and constraints in order to better address its burden of neglected tropical diseases.

awards were made in 2003. Partnerships with WHO Regional Offices⁹⁰ supported relevant control-related research and training, and partnerships with academic centres⁹¹ and global initiatives⁹² supported development of training capacity to address relevant research and training gaps. (See box 2 for details of current portfolio.)

■ Grants for postgraduate degrees and specialized training

These grants are for supporting scientists in disciplines and skills relevant to national needs and to TDR R&D priorities.

■ Career development fellowships

To better target training funds to priority areas and to develop local resources that TDR can draw upon in the future,

the Career Development Fellowship was initiated in 2000. The goal is to train individuals in situ with relevant partners to develop specialized skills not readily taught in academic centres. During 2003-2004, fellowships were undertaken in priority areas in partnership with various organizations.⁹³ On completion of the fellowship, individuals return to their home institutes to add to the local capacity and become a valuable resource for TDR and their region.

■ Re-entry grants

The objective of these grants is to enable young scientists to establish independent research agendas in their home institutes after completing a graduate degree or postdoctoral training. An annual call is put out for applications.

90 Pan American Health Organization (PAHO), WHO Eastern Mediterranean Regional Office (EMRO), WHO South-East Asia Regional Office (SEARO), WHO Regional Office for Africa (AFRO)

91 e.g. Makerere University, the University of Witwatersrand, l'Université d'Abomey-Calavi, Institutum Tropologicum Helveticum

92 e.g. the International Network of field sites with continuous Demographic Evaluations of Populations and Their Health in developing countries (INDEPTH), the International Clinical Epidemiology Network (INCLEN) Trust, and the European and Developing Countries Clinical Trials Partnership (ED-CTP)

93 GlaxoSmithKline; the Wellcome Trust; Serono; the Strategic Initiative for Developing Capacity in Ethical Review (SID-CER); the Infectious Disease Research Institute (IDRI); three WHO Regional Offices: AFRO, EMRO, SEARO.

Box 2

Research Training Grant portfolio: current breakdown

- 20 MSc students; 72 PhD students (33 at northern universities; 59 at regional/local universities)
- 27 female students; 65 male students
- 58 students from the WHO African Region (AFRO); 6 from the WHO Americas Region (AMR); 8 from the WHO Eastern Mediterranean Region (EMR); 14 from the WHO South-East Asia Region (SEAR); 6 from the WHO Western Pacific Region (WPR)
- 57 students from least developed disease-endemic countries; 35 from more developed disease-endemic countries
- 5 studies in health economics; 18 in entomology; 49 in epidemiology; 3 in immunology; 9 in molecular biology; 8 in social science
- 1 study on Chagas' disease; 2 on dengue; 4 on lymphatic filariasis; 6 on leishmaniasis; 1 on leprosy; 58 on malaria; 2 on onchocerciasis; 3 on schistosomiasis; 9 on TB; 6 on human African trypanosomiasis.

In 2003 and 2004, 42 new proposals were reviewed and 21 recommended for funding (see box 3 for details of current portfolio). Re-entry grants are the bridge between professional training and an established research career.

Research environment

To enable the research environment in LDCs, TDR/RCS promotes access to information. For example, it supports the Health InterNetwork Access to Research Initiative (HINARI⁹⁴), and produced a HINARI CD-ROM in 2004. The Initiative⁹⁵ provides free or low-cost online access to major journals in the biomedical and related social sciences for local, non-profit institutions in developing countries, and is proving invaluable to many institutions in countries which cannot afford to subscribe to essential journals. HINARI runs on the principle of ensuring equitable access to health information.

Support to institutions

A number of institutes in selected LDCs with high disease burdens are under long-term institutional strengthening support from TDR. The strategy is to build a critical mass of stable and active

research institutions, with adequate human resources working in a conducive research environment, to address country-specific research agenda.

Institution-support projects are ongoing in Africa, Asia, Latin America and the Middle East. In Africa, two projects focus on malaria natural products (in Burkina Faso and Tanzania) and one on natural products for human African trypanosomiasis (in Congo), and four projects are under development on: African trypanosomiasis (in Angola), TB (in Burkina Faso), malaria (in Eritrea), and schistosomiasis (in the Democratic Republic of the Congo).

TDR provides long-term institutional strengthening for selected institutions from countries with low research capacity. In 2003-2004, funds for this were designated to support institutions to build capacity for research in human African trypanosomiasis (HAT). Because none of the incoming proposals could be recommended for funding however, stakeholders formed a consortium for HAT, and the Trypanosomiasis Research Centre, Kenya, was selected to be the lead institution in proposal development.



In 2003-2004, funds were designated to support institutions to build capacity for research in human African trypanosomiasis (HAT).

Box 3

Re-entry grant portfolio: current breakdown

Of the 45 projects in the current portfolio, there are:

- 1 study(ies) on Chagas' disease, 2 on dengue, 1 on lymphatic filariasis, 2 on leishmaniasis, 25 on malaria, 5 on schistosomiasis, 6 on TB, 3 on human African trypanosomiasis.
- 9 studies in epidemiology, 22 in molecular biology/immunology, 11 in molecular entomology, 2 in natural products, 1 in social science.

94 www.healthinternetwork.org

95 Spearheaded by the World Health Organization (WHO) and launched as a public-private initiative in September 2000 by the United Nations Secretary General.

Meeting of MIM Principal Investigator's in 2004, Addis Ababa. Credit: WHO/TDR/Ogundahunsi



Research environment

TDR, in partnership with the WHO Regional Offices, operates a Small Grants Scheme, which allows researchers from academia and control programmes to jointly develop projects to address local research questions. This scheme is very successful. The aim is to strengthen the research capacity of disease control programmes to address local research questions pertaining to topics of regional relevance. The partnerships with EMRO, AMRO, SEARO, and AFRO are jointly funded, and there is an annual call for applications. Within EMR, 38 of the papers resulting from small grant supported research were published in the *Eastern Mediterranean Health Journal*⁹⁶ in 2003.

Research collaboration partnerships

For more developed countries, TDR has an emphasis on partnerships. For example, the Multilateral Initiative on Malaria in Africa (MIM - see page 73) 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, which promotes capacity strengthening in Africa through R&D for new tools for malaria control. The partnerships and collaborations set up in support of this R&D promote technology transfer and provide training opportunities. Currently 21 projects are being supported, and there is leverage for additional funding. Since 1998, 42 African scientists have received training (at PhD and master's degree levels) in specialized techniques through these MIM grants.

The annual meetings of MIM/TDR-funded principal investigators facilitate networking and collaboration between the scientists. In addition, focused group learning activities organized by TDR in collaboration with the MIM partners continue to enhance skills in obtaining grants, developing and using standard operating procedures, managing research, and collaborating on a regional basis to address common research questions.

96 Vol. 9, no. 4, July 2003

Research environment

TDR supports partnerships with academic centres and global initiatives to develop training capacity to address relevant research and training gaps.

Academic programmes in clinical epidemiology that have been developed with support from TDR are ongoing in Uganda, South Africa and Benin, and regular enrolment of students is in place. As well, learning materials from the HINARI programme on how best to access, manage and utilize the vast amount of electronic information were made available on CD and online. A training package on qualitative research methods is being developed with the Swiss Tropical Institute, and another package on project planning is under development, with a view to possible eventual development of distance learning degree programmes, for which discussions are under way with INCLEN, INDEPTH, and the Partnership for Social Sciences for Malaria Control in Africa (PSSMC).

TDR/RCS also supports the Forum of African Medical Editors (FAME), which aims to strengthen local publication of health research conducted in or relevant to Africa, and to gain greater visibility for African medical research. FAME, which was launched in 2002, held its first general meeting in October 2003. In 2004, the FAME constitution⁹⁷ and editorial⁹⁸ guidelines were published, and the Association was registered in Kenya.⁹⁹

FAME activities supported by TDR during the biennium included:

- a training course for editors co-sponsored with the *British Medical Journal*
- a training-of-trainers course on medical writing for French-speaking African countries (in Mali), December 2004
- a training-of-trainers course on *Getting*

the most from reviewers (in Uganda) for English-speaking countries, March 2005.

FAME has already given rise to new initiatives involving new donors and partners, such as journal twinning with mainstream biomedical journals (*British Medical Journal*, *Journal of the American Medical Association*, *Lancet*) under the auspices of the US National Institutes of Health/National Library of Medicine and Fogarty International Center, and training with the International Network for the Availability of Scientific Publications (INASP).

Capacity utilization

For advanced DEC, the emphasis is on using the scientific and institutional capacity already developed by TDR and others, which by now represents a critical mass with a comparative advantage for undertaking cutting-edge research in tropical diseases.

Initiatives

■ RCS-plus

The research priorities for the RCS-plus initiatives are determined by the TDR steering committees, i.e. they are driven by the TDR R&D agenda. The initiatives take advantage of the strengths of DEC institutions to address major areas of research, and investigators from all DEC, including the LDCs, are eligible to participate. The current RCS-plus portfolio supports studies which use new knowledge and technologies, including in bioinformatics, applied genomics, and health social sciences, to address R&D priorities – such as the ongoing:

- drug discovery from natural products
- clinical trial for the evaluation of efficacy of four-drug fixed-dose combinations (4FDC) in tuberculosis (TB) control



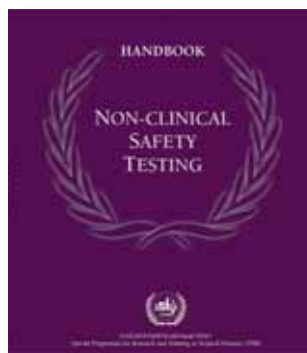
At the FAME workshop in Entebbe.

Credit: WHO/TDR/Wager

97 TDR/RCS/FAME/04.1

98 TDR/RCS/FAME/04.2

99 The FAME secretariat is located at Kenya Medical Research Institute (KEMRI), Nairobi



- clinical trials for the optimization of praziquantel for the control of schistosomiasis
- study of social, economic and behavioural factors hampering DOTS expansion in Kazakhstan and Haiti.

■ Technology transfer

The Thailand Tropical (T2) technology transfer programme was set up to build capacity in pharmaceutical product development for tropical diseases in Thailand. Under this programme, the first pharmaceutical product to be produced and developed by a Thai scientist (dihydroartemisinin for malaria) and registered by the Thai regulatory authority is under development; it is to be used in the control programme. Technology transfer has enabled: completion of studies resulting in the availability of Good Manufacturing Practice (GMP) grade product for clinical trials; training in Good Laboratory Practice (GLP) for pre-clinical studies (these studies are about to start); preparation of a Phase 1 protocol approved by the ethics committee; training in Good Clinical Practice (GCP); establishment of a data management centre; and making of arrangements for clinical monitoring.

need for general quality practices guidelines, a draft document on Quality practices in basic biomedical research is under preparation. A draft document was widely distributed in 2002-2003 and comments solicited from the scientific community.

■ Non-clinical safety practices

To catalyse development of expertise and build capacity to perform non-clinical safety testing activities in the DECAs, TDR published a handbook on Non-clinical safety testing¹⁰⁰ in 2004. A training workshop programme on general aspects of non-clinical safety testing has been developed, and one workshop held in Africa. Other training materials are being developed, including focused training on specific tests.

■ Laboratory practices

TDR has developed workshops to introduce scientists to the concepts of GLP and prepare them for performing pre-clinical studies under GLP conditions. Technical support is given to laboratories to help them upgrade to GLP standard, and networks of trainers are being established. A second trainer-of-trainers workshop was held in 2003; there are regular refresher courses.

Research environment

In advanced DECAs, there is an emphasis on training in and use of Good Practices, which aim to promote better conduct of research and production of reliable, credible and internationally acceptable data, particularly in resource-poor environments. Scientific capacity is already available in these countries, ready to be utilized after short-term training in one or more of the following good practices:

■ Quality practices

Based on the recognition that many biomedical science investigators have a

■ Clinical practices

Performing clinical trials under GCP conditions ensures that the rights and safety of participants in clinical trials are respected, and that the data are credible. Ongoing TDR activities in the area of GCP include: on-site investigator and monitor training; general GCP workshops for investigators, ethics committees, and monitors; annual refresher courses for monitors. In 2004, GCP training for investigators was completed at sites for specific projects – dihydroartemisinin-T2, TB-gatifloxacin, paromomycin, malaria vaccine –



Good laboratory practice (GLP) workshop. Credit: WHO/TDR/Kioy



in Shanghai and Japan, and a refresher course on GCP was held in Thailand.

■ Ethics practices

Wherever clinical research is carried out it is essential that there is a proper and competent ethics committee. TDR helped to set up a global Strategic Initiative for Developing Capacity in Ethical Review (SIDCER)¹⁰¹ to ensure protection of the rights, safety and wellbeing of human participants in health research through ensuring that appropriate and competent ethics committees are established in countries where research is carried out. Already under SIDCER, 6 regional forums and more than 15 national forums have been established; all have websites. Annual conferences are held for the regional forums.

Guidelines for ethics committees that review biomedical research were developed by TDR (in 2000) and widely distributed. Guidelines were later established on surveying and evaluating ethical review practices.¹⁰² Guidelines on data and safety monitoring boards are now being finalized through co-ordination with local government to

ensure political endorsement. TDR is facilitating discussion around ethics issues in each region, and helping to establish a bioethics course to be integrated into national curricula.

■ Data management practices

With respect to capacity for data management, TDR is helping to develop centres for data management in DECs. The objective is to establish a global network for clinical data management to ensure that data are credible. Already effective centres have been established in China, Thailand, India, Colombia, Ethiopia, and Japan, and a website for the network is established. Workshops on clinical data management for selected institutions with relevant infrastructure are already in place; regional centres, and an annual conference are to be established.

The efloornithine trials were conducted under GCP.

Credit: WHO/TDR/Karbwang



Data management workshop.

Credit: WHO/TDR/Karbwang

101 www.who.int/sidcer/en/

102 TDR. *Surveying and evaluating ethical review practices*. Geneva, WHO/TDR, 2002 (TDR/PRD/ETHICS/2002.1)



Programme management

Resources for research

TDR is co-sponsored by the United Nations Children's Fund (UNICEF), the United Nations Development Programme (UNDP), the World Bank, and the World Health Organization (WHO). The budget level is approved by the TDR Joint Coordinating Board (JCB), but actual funding received depends on the individual contributors. The impact on TDR is that its technical and scientific implementation has to be managed carefully as funds become available throughout the year.

From a financial point of view, this programme report spans the two budgetary biennia of 2002-2003 and 2004-2005. For 2002-2003, JCB approved a budget of US\$ 95.218 million while, for the current biennium (2004-2005), a budget of US\$ 99.753 million was approved.

The current working budget is US\$ 69.5 million, in line with forecasted contributions for 2004-2005 of US\$ 63.0 million, plus interest, other income, and carry-over.

While the biennia 2000-2001 and 2002-2003 showed significant increases in contribution levels, the current conservative forecast for 2004-2005 of US\$ 63.0 million is slightly lower than 2002-2003.

Designated and undesignated contributions

The income pattern has continued to show a shift, which started in the early 1990s, of a slow decrease in undesignated funds and an increase in designated funds for particular programmes (see figure 10).

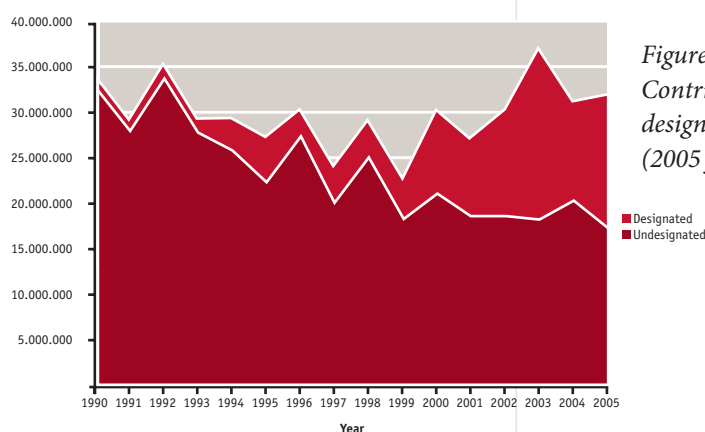


Figure 10
Contributions by
designation
(2005 forecast)

In 2004, new designated contributions were US\$ 10.7 million, compared to new undesignated contributions of US\$ 20.3 million.

Assuming all 2005 contributions are received before 31 December 2005, the total contributions are estimated at US\$ 31.9 million. This comprises US\$ 17.4 million of undesignated funds and US\$ 14.5 million of designated funds.



TDR Joint Coordinating Board
(JCB), 2004.

Biennium	1996-1997	1998-1999	2000-2001	2002-2003	2004-2005
TDR contributions US\$ million	54.4	51.6	57.0	67.1	63.0 (forecast)

Box 4
TDR income (1996-2005)

Use of funds: expenditures 2002-2004

In terms of funds used, expenditure for the various expected results ranged from 30% of total expenditure for New and Improved Tools, to 7% for each of Technical Information, New and Improved Methods, and New and Improved Policies and Strategies. Partnerships and Capacity Building absorbed 24%, while expenditure on New Knowledge was 11%. The Management function represented 14% of the total (see figure 11).

In terms of funds spent on the various diseases, these ranged from a high of 49% for malaria to a low of 1% for leprosy. With respect to other diseases, 19% of funds were spent on TB, 6% on leishmaniasis, and 4% on each of African trypanosomiasis and onchocerciasis. The remaining TDR diseases each absorbed between 2% and 4% of the total expenditure. Expenditure on other diseases totalled 6% (figure 12).

Figure 11
Expenditure 2002-2004
by expected result.

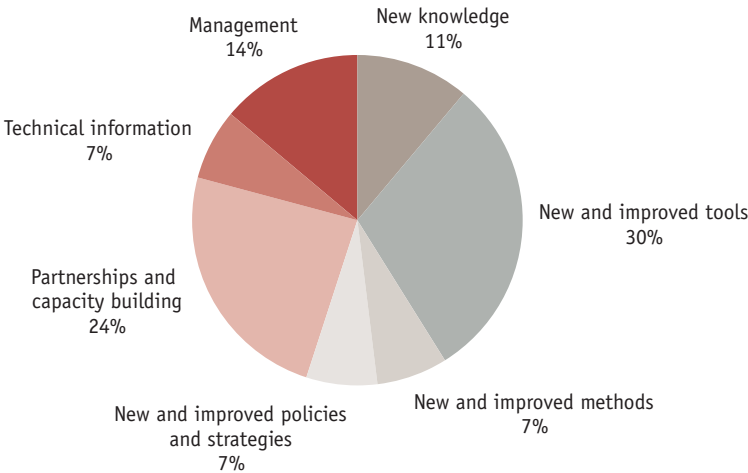
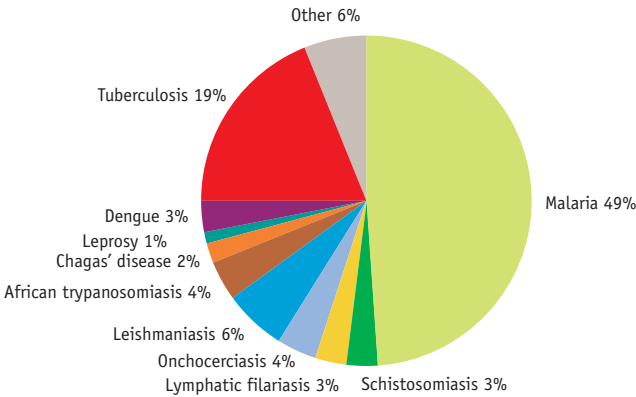


Figure 12
Expenditure 2002-2004
by disease.





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