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The start of a new year also signals further new beginnings at TDRNews. As part of our redesign and continuing improvements, we are launching a new column, ‘TDR Briefly,’ highlighting short updates on news of note and personalities of interest, for easy reading. Please send us any contributions on TDR-related personalities and TDR-supported innovations that you deem worthy of note – and we will consider them for publication.

This new “briefs” section also responds to reader preferences as expressed in the recent TDRNews readership survey. We were indeed enthused to see such a large response to the survey. Between February and August 2007, we received 535 replies from among our nearly 20,000 subscribers. It was always a pleasure to open our mail in that period and see that yet another scientist in Africa, Asia or Latin America had taken the time to respond, often adding original comments of their own. It was also gratifying to see the global span of responses – which came from some 76 different countries, including all 6 WHO-defined regions of the world. Nearly 40% of our respondents were from Africa, followed by 19% from Europe, 17.1% from the Americas, 16% from South-East Asia, 5.3% from the Western Pacific and 4.7% from the Eastern Mediterranean region. This regional breakdown is roughly parallel to that of our newsletter circulation.

What you told us was the following: In terms of general content preferences for the newsletter, 58% of respondents cited “News updates on scientific innovations” as their greatest interest, followed by “In-depth research articles” (30%) and “Information on grants” (25%). Malaria was the most-often cited as the disease of greatest interest among our readers (66%) of respondents, followed by tuberculosis (26%), leishmaniasis (21%), schistosomiasis (20%), and filariasis (17%).

In terms of research themes, some 45% of readers said that “strategic and discovery research” was their greatest area of interest, followed by “implementation research and methods” (32%) and “research capability strengthening” (22%). African region respondents, however, expressed an even greater interest than the average in research capacity strengthening, which is indeed one of TDR’s top priorities.

About one-quarter of respondents said they were already on the TDR scientific email listserv. However, another 52% asked to be added to this valuable email network. In addition, nearly half of the respondents (45%) said they also would be interested in joining other TDR-managed listservs for specialized audiences. Those cited of greatest interest were networks for health care agencies, donors/development agencies, and government/policy-makers.

The survey also confirmed that even in our age of email and internet, the print version of TDRNews is highly popular. Some 42% of the respondents prefer it, while 13% preferred the e-version, and 43% ask for both versions. In the coming year, we will indeed be launching an improved e-version of the newsletter, in a new and more accessible format – and that may indeed enhance its appeal. In addition, we will continue to monitor your views and opinions, both through follow-up questionnaires and through the launch of a readers’ column, planned for the spring issue.

Finally, we would like to mention those survey respondents who competed in the prize drawing and won an edition of Advances in Parasitology (Vol. 61) covering latest advances in control methods for many TDR-related diseases. We would like to thank all of those who participated and congratulate the winners: Dr Maryada Venkata Rami Reddy, Mahatma Gandhi Institute of Medical Sciences, India; Mr Edward Zakayo Samba, National Institute for Medical Research, Tanzania; Dr Virgil O.N. Onama, Makerere University, Uganda; Professor Santhath Sermrsri, Mahidol University, Thailand; Dr Silvano Wendel, Hospital Sirio Libanes – Blood Bank, Brazil; Mr Gabriel Parra-Henao, Instituto Colombiano de Medicina Tropical -CES, Colombia; Dr Nicholas J. Kavana, Institute of Development Management, Mzumbe University, Tanzania.

Wishing our readers a productive and healthy New Year-2008.

Elaine Ruth Fletcher
Editor, TDRNews
An intergovernmental working group is currently meeting under WHO auspices with a bold and ambitious goal. The group aims to define a global strategy and plan of action on public health, innovation and intellectual property with the potential to stimulate research into diseases disproportionately afflicting developing countries.

The title, Intergovernmental Working Group on Public Health, Innovation and Intellectual Property, is a tongue twister. The acronym, IGWG, (pronounced IgWig) is not much easier going. However, the implications of the debate are anything but abstract. The IGWG could indeed yield far-reaching and practical results, bringing more resources to developing countries, both for laboratory and field research.

A global meeting of the IGWG took place in Geneva in November 2007, and another major session will take place in late April in preparation for the planned May presentation of a draft global strategy at the 61st World Health Assembly (www.who.int/gb/phi).

The fact that over 100 country representatives have come together to talk about a global strategy to promote health-related research and development is an unprecedented event – worthy of notice by everyone serious about combating diseases of poverty.

The IGWG debate provides an opportunity for many issues relevant to TDR to rise to the top of the policy agenda – and stimulate discussion not only in health forums but in the corridors of commerce, trade, and development.

Three key goals of the IGWG dovetail with important elements of TDR’s new Ten Year Strategy. Those include: the fostering of innovative research on neglected diseases of poverty; stimulating research in developing countries under the leadership of developing country institutions; and ensuring greater coherence of national, regional and global efforts.

The IGWG was created by the World Health Assembly in 2006 in response to a report by the WHO Commission on Intellectual Property Rights, Innovation and Public Health (CIPIH). New WHO Director-General Margaret Chan has taken an active leadership role in moving the process forward.

Previous WHO-sponsored intergovernmental initiatives have had major impacts on public health policy. A WHO Intergovernmental Working Group successfully led the 2005 revisions of the International Health Regulations, measures that aim to reduce spread of disease due to travel and migration and to enhance reporting and control of disease outbreaks. The 2003 World Health Assembly adoption of the WHO Framework Convention on Tobacco Control resulted from another intergovernmental process.

This IGWG has potential to pave the way for more coordinated global research partnerships for neglected diseases and higher levels of research financing, particularly for developing countries.

Dialogue is set against the broader debate about intellectual property rights in developed and developing countries. Players – private and public, grassroots and commercial, national and regional – often have very different interests and agendas.

The IGWG forum, however, offers a unique opportunity to bring together diverse parties in dialogue, and articulate common goals for delivery of improved health care for those in need. This was indeed the aspiration of the November discussions, described as “historic” by Director-General Chan.

In TDR’s own experience, when issues are carefully sifted and examined, a shared aim to promote public health, disease control and scientific advance can usually outweigh more partisan agendas. This is the aim towards which we at TDR are working as part of the WHO-sponsored IGWG secretariat. Meanwhile we encourage the broader health and scientific community to take notice of this important process and make your views heard. Then, come April and May... watch this space!

Dr Robert Ridley, TDR Director
Closing the gap in health access

Community-directed interventions featured at JAF-13

For years the health community has struggled with the question of how to get simple, primary health care interventions to poor, rural African communities. Now, the results of an unprecedented study are final. A model of “community-directed interventions” (CDI) developed by TDR has been incredibly effective in getting basic treatments, such as home-administered anti-malarials, to those who need them in remote rural areas. The same “community-directed” approach developed by TDR a decade ago to deliver the drug ivermectin to more than 55 million Africans at risk of river blindness (onchocerciasis), was tested in 40 health districts of Nigeria, Cameroon, Uganda and Tanzania for wider applications. The study found that use of home administered anti-malarials through CDI networks doubled, even exceeding Roll Back Malaria targets of 65% coverage. Bednet use was twice as high as in control districts, and Vitamin A and ivermectin coverage were also significantly higher. The total cost to the health system of delivery was nonetheless similar in the CDI and control districts, making CDI more cost-effective.

Findings on the groundbreaking study were presented at the 13th session of the Joint Action Forum (JAF), the governing board for the African Programme for Onchocerciasis Control (APOC), 3-6 December 2007, in Brussels. The JAF endorsed the key recommendations emerging from the study – namely that CDI systems used for distribution of ivermectin should now be used more broadly for other health treatments. The JAF also called on TDR to spearhead new research on practical guidance and tools for the use of CDI. “The findings indicated that the community-directed approach has potential for far broader applications,” said TDR’s Dr Hans Remme who oversaw the research. The essence of CDI is exactly what the term implies, communities decide for themselves how to deliver drugs and who will be in charge. Inherent to the success of the TDR-tested model is the systematic nature of its stakeholder consultations and consensus-building process – “unlike any other model,” says Remme.

Look for details of how CDI really works on the ground and the new advances it is making in health care in the next issue of TDRNews.

MIM Secretariat Coordinator

Dr Francine Ntoumi

In 1992, as a young lecturer at the University of Marien Ngouabi, Brazzaville, Dr Francine Ntoumi received her first TDR Research Training Grant to do post-doctoral training in the molecular epidemiology of malaria parasites at the Pasteur Institute in Paris. It was the beginning of a long association with TDR and the world of global research, which reached a new milestone recently with Ntoumi’s appointment as coordinator of the Secretariat of the Multilateral Initiative on Malaria (MIM). MIM was launched in 1997 as part of a global initiative to strengthen the capacity of malaria endemic countries in Africa to effectively research and develop tools for malaria control. It is hosted by the AMANET Trust in Dar es Salaam. TDR administers the research capacity strengthening grant programme (MIM/TDR) of the initiative.

Before joining MIM, Dr Ntoumi was a Senior Scientific Officer for the European and Developing Countries, Clinical Trials Partnership (EDCTP). She holds a Masters’ degree and a PhD in Molecular Biology from the University of Paris, as well as an undergraduate degree from the University of Marien Ngouabi, Republic of Congo. She serves on several international committees, and is a reviewer for several scientific journals. Since 1992, she has been the recipient of over a dozen TDR research grants.
A native of the Republic of Congo, Dr Ntoumi has said one of her largest concerns as a malaria researcher is promoting African involvement in and commitment to malaria initiatives: “I believe that Africans have to participate actively in tropical disease research. This can only be done if networks of competencies are built up in Africa.” As Secretariat Coordinator of MIM, she will have the opportunity of doing just that.

**Health, Innovation and Intellectual Property**

**WHO advances Global Strategy in IGWG**

In a round of talks described by WHO Director-General Margaret Chan as “historic,” a WHO-sponsored Intergovernmental Working Group (IGWG) on Public Health, Innovation and Intellectual Property inched towards agreement on a draft global strategy designed to stimulate health research vital to the needs of developing countries.

The principal basis for negotiations has been a draft strategy issued by the WHO IGWG Secretariat on 31 July 2007. The strategy aims to: prioritize research and development needs; build and improve innovative capacity in developing countries; and assure transfer of technology while guarding intellectual property rights.

The IGWG deliberations represent “one of the most significant discussions ever by WHO member states on ways to improve R&D capacities for much-needed health products in developing countries,” says TDR Director Dr Robert Ridley, a member of the Secretariat steering the process. Speaking to the delegates in their closing session on 10 November, Chan reiterated her commitment to “moving the Organization forward in the areas” of intellectual property rights, innovation, and public health to provide greater incentives for medical innovations and technology transfers that help developing countries. “We are gearing ourselves up to do more,” she stated. “I will need your specific guidance from the strategies and plan of action.”

The IGWG process continues in early 2008, with the November meeting resuming 28 April to 3 May.

**Bill & Melinda Gates Foundation**

**TDR diagnostics research boosted**

TDR’s Sexually Transmitted Diseases Diagnostics Initiative (SDI), has been awarded a US$ 9.2 million grant from The Bill & Melinda Gates Foundation to expand an innovative programme to improve access to quality-assured diagnostics for STIs (sexually transmitted infections). The Bill & Melinda Gates Foundation had provided SDI with an initial grant of US$ 952,452 in 2005. That project demonstrated a broader need for test evaluation and field research to halt the spread of curable STIs in developing countries.

Under the new 3-year grant, a TDR team led by Dr Rosanna Peeling will work with researchers and health officers in 8 countries in Africa, Asia and Latin America to demonstrate the concrete health benefits derived from increased access to STI diagnostics and to develop and test approaches for the introduction and sustainable adoption of quality-assured rapid tests for sexually transmitted infections in resource-limited settings.

“Lack of access to diagnostics can kill just as easily as bad drugs or lack of access to drugs,” said Peeling, adding, “The few tests that are available in developing countries are often sold and used with little evidence of their effectiveness, due to lack of regulatory standards. Research is urgently needed to determine which tests are effective and then demonstrate cost-effectiveness in real-life settings. This grant thus represents a major commitment to continue diagnostics research at TDR to fill a significant public health need.”

An estimated 1 million new cases of curable bacterial STIs occur each day worldwide. While STIs are often asymptomatic in adult carriers, in sub-Saharan Africa alone, an estimated half a million babies die each year from congenital syphilis. Effective diagnostic testing is the best way to ensure treatment and cure. However, with a plethora of tests on the market, countries and clinics need hard evidence on which ones are most effective, and for what settings. Such operational research projects serve the twin goal of exposing health care practitioners to new diagnostics, as well as sensitizing them to their use in effective treatment of STIs.

Global Forum for Health Research

**Dr Gill Samuels is Chair**

Dr Gill Samuels, a member of TDR’s Scientific and Technical Advisory Committee (STAC), was appointed as the Chair of the Global Forum for Health Research’s key governing body, the Foundation Council, at
WHO reorganization

TDR joins new WHO cluster

As part of WHO Director-General Margaret Chan’s strategic reorganization plan, the TDR Special Programme has been attached to the WHO Information, Evidence and Research (IER) cluster. This change, announced in late 2007, is designed to improve coordination between TDR’s research functions and WHO’s system-wide research efforts. Under the new structure, TDR welcomes the engagement with Dr Tim Evans, Assistant Director-General of the IER cluster, who will serve as the TDR Special Programme Coordinator on behalf of WHO. TDR also bids farewell and thanks former Special Programme Coordinator Dr David Heymann, Director-General of the Health, Security and Environment cluster (formerly ADG of the Communicable Disease cluster) for his support of the Programme over recent years.

Meanwhile, within TDR, several staff have been named coordinators of key functions that are part of TDR’s new Ten Year Strategy implementation and Business Plan. Those include: Dr Ayoade Oduola, Stewardship; Dr Juntra Karbwang-Laohavorn, Empowerment (acting); Dr Hans Remme, Research on Neglected Disease Priorities; Dr Fabio Zicker, Portfolio Policy and Development, and Dr Jane Kengeya-Kayondo, Strategic Alliances. Further details on the TDR business plan as well as a complete listing of all TDR research business lines and their managers, are noted on the TDR website at: http://www.who.int/tdr/about/strategy/business_lines.htm.

Helminth Drug Initiative

Expedite tests of potential anti-helminthic agents

The past year of TDR-industry collaborations have led to the identification of multiple new compounds, including animal health products, that show significant activity in vitro and in vivo screens relevant to human helminthic infections, such as schistosomiasis, river blindness and lymphatic filariasis. Further progression of these compounds into the discovery process should be expedited.

This was one of the recommendations emerging from the first meeting of the recently launched TDR Helminth Drug Initiative (HDI) Task Force, which met 3-4 December 2007 in Geneva. The Task Force is led by Dr Graham Kayondo, Strategic Alliances; Dr Ayoade Oduola, Stewardship; Dr Juntra Karbwang-Laohavorn, Empowerment (acting); Dr Hans Remme, Research on Neglected Disease Priorities; Dr Fabio Zicker, Portfolio Policy and Development, and Dr Jane Kengeya-Kayondo, Strategic Alliances. Further details on the TDR business plan as well as a complete listing of all TDR research business lines and their managers, are noted on the TDR website at: http://www.who.int/tdr/about/strategy/business_lines.htm.

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Diagnostics Evaluation Expert Panel

Meeting on quantitative diagnostics

Evaluation of quantitative diagnostic tests was the focus of the 4th annual meeting of the Diagnostics Evaluation Expert Panel (DEEP) held 28-29 November 2007 in Geneva. DEEP was established in 2004 by WHO/TDR and the Foundation for Innovative New Diagnostics (FIN Diagnostics) to advise on the best practice in the design and conduct of diagnostic trials. Under the DEEP’s supervision, three guides have so far been published on the design and conduct of diagnostic evaluations in collaboration with Nature Reviews-Microbiology, including diagnostics for malaria, sexually transmitted infections and visceral leishmaniasis. This year’s DEEP meeting addressed issues relevant to the evaluation of quantitative assays, using comparative assessment of CD4 assays as an example. Quantitative diagnostic assays are important insofar as they provide a numerical value of measurement, as compared to a simple positive/negative result. In patients infected with HIV, the CD4 count is used to predict the risk of infections and to guide initiation of antiretroviral therapy.

Mosquito mouthpart with emerging third stage infective larvae of Brugia malayi, one of the two main parasitic strains responsible for lymphatic filariasis, now focus of a global elimination campaign fostered by TDR research. (see p. 25.)
On location in Nigeria

BBC Survivors’ Guide series profiles TDR-research

From the muddy roads of Nigeria to field clinics in Haiti, TDR has been tracking and recording its research and collaborations that have yielded concrete health benefits in a rich and ongoing series of video productions.

The most recent is a 22-minute video, Nigeria: Community Empowered, aired on BBC World’s highly rated Survivors’ Guide series November 30 2007. It follows one of TDR’s recent achievements, the groundbreaking research done in Africa into methods of “community-directed interventions” for prevention and treatment of ailments ranging from river blindness to malaria.

In addition, a five-part television news series of 3 minute videos showcasing TDR-sponsored projects across Africa and the Caribbean was released in October. The series shows how research is helping to: combat congenital syphilis in rural Haiti; refine methods for “home management” of malaria in Africa; build systems for community-based treatment for malaria, river blindness and other ailments in Nigeria and elsewhere; and define innovative ways to sell malaria drugs through small, entrepreneurial community-based “Child and Family Wellness Shops” (CFWs) in Kenya and other countries of Africa. A fifth part in the series looks at TDR research being done on traditional natural medicinal remedies in Kenya that might have potential to become modern drug treatments (see TDRNews cover story).

All videos are available free for non-commercial purposes of broadcast and viewing to educational institutions, TV stations, NGOs and the general public.

The lastest film Nigeria: Community Empowered follows Cleophas Bakari, a Community Drug Distributor (CDD) in a rural area in Nigeria. Bakari distributes ivermectin, as well as essential anti-malarial drugs and preventives (insecticide-treated bednets) and Vitamin A tablets, to his community with pride and care. Community Drug Distributors cannot replace doctors and nurses, but the video shows how the CDI approach is proving that communities can manage simple but life-saving health interventions themselves.

Jamie Guth, communications manager at TDR, travelled with the news crew through Nigeria to reach the most remote study sites to film Bakari and others. She describes the experience saying, “We flew into Abuja, then drove 12 hours to Jalingo over deeply rutted roads during the rainy season. Using Jalingo as a base, we travelled each day to smaller villages, such as Garbacede, a market community for the semi-nomadic cattle farmers of the region. Farmers walk miles and miles in their bare feet to sell their cattle in this town. And so this is also a place where they can get medicine from a Community Drug Distributor such as Bakari.”

If research continues to demonstrate that such community directed intervention systems are effective in delivering a wide range of interventions, these could provide a “very important model” for responding to a broader range of health needs in far-flung communities beyond the reach of traditional health care systems, says Dr Hans Remme, TDR coordinator of this study.

For More information:
The BBC Survivors’ Guide documentary Nigeria: Community Empowered, as well as the five-part news series, are available free of charge upon request, and also can be viewed on the TDR website at www.who.int/tdr/about/press_center/default.htm. Scripts of the shorter news series are available in Arabic, Chinese, French, Portuguese and Russian.

For the complete story on the development of community directed treatment of onchocerciasis (river blindness) see: Eliminating River Blindness; Highlights from TDR’s Making a Difference, at www.who.int/tdr/topics/ir/cdi.htm

Contact: Jamie Guth guthj@who.int
NAIROBI, KENYA – Call it a new age of exploration. The quest is not for copper, gold, diamonds or oil… 
but medications for malaria, which kills approximately 1.2 million people a year, most of them African and most of them children. Using the tools of modern science, experts from Madagascar to Sudan, from Zanzibar to Nigeria, are taking a closer look at an oft-overlooked resource — plants. In a TDR-sponsored initiative, a new research hub in Kenya is now systematically screening traditional African herbal remedies to generate much-needed empirical data on their properties, and to see if active ingredients from even a few might have potential for development as modern anti-malarial drugs.

In recent decades, constant evolution of the malaria parasite has rendered the cheapest and most widely available anti-malarial treatments ineffective. Fortunately, artemisinin-based compounds developed first in China arrived on the market just at the time when resistance to drugs like chloroquine and sulfadoxine-pyrimethamine was becoming an issue.

Now, however, scientists are fearful that the parasite responsible for malaria, Plasmodium falciparum, might also soon develop resistance to artemisinin-based compounds.

So the search for still newer more effective malaria cures is a major concern. Taking a cue from the story of artemisinin, TDR is leading a unique five-year initiative to build capacity for African institutions to screen and test indigenous herbal remedies, which previously had to be shipped abroad for sophisticated screening and medicinal chemistry evaluations. The US$ 400 000 effort, now in its fourth year, involves a TDR partnership with a network of Kenyan institutions, including the Kenya Medical Research Institute (KEMRI), the University of Nairobi, Department of Chemistry and Faculty of Pharmacy, and the Kenyatta University.

Through the effort, scientists hope to come up with at least one lead compound from an African herbal remedy that could display sufficient efficacy against the parasite to make it worthy of investment in a second phase of development.

Drugs derived from the ancient Chinese herb Artemisia annua may today be the most powerful weapon in the global war against malaria, but scientists are searching urgently for new drugs, given the possibility that, sooner or later, resistance to artemisinin may develop. A TDR-led effort to support drug discovery in Africa based around traditional herbal remedies is now in its fourth year. It involves an ambitious effort to foster pan-African hubs and laboratories for in vitro and in vivo natural product screening, which can serve scientists across the continent. Hopes are that over the next few years, at least one viable lead compound might be identified.
Why traditional medicine?

Traditional medicine is still the first point of healthcare for many people in sub-Saharan Africa, where there has been a long and rich tradition of sourcing treatments from herbs and trees.

And in the case of malaria, Africa’s traditional healers use hundreds of indigenous plants for remedies. Among the better known, a tree called *Warburgia ugandensis* is prescribed regularly by Kenyan healers as a malaria treatment. As a prophylaxis, a drink made from the Neem tree is often prescribed.

Professor Jacob Midiwo, an expert in natural product research at Kenya’s University of Nairobi, who is one of the principle investigators in the TDR-backed initiative, is optimistic that the TDR-supported research will confirm that certain plants used by healers contain anti-plasmodial active ingredients.

“Medicinal plants have been part of African culture for centuries,” he says. “We believe traditional plants that have been used to cure malaria are bound to give us effective lead compounds.”

The Kenyan network led by Dr Geoffrey M. Rukunga, Director of the Centre for Traditional Medicine & Drug Research at KEMRI in Nairobi, has so far isolated about 50 compounds that display anti-malarial properties. The project has generated four peer-reviewed articles on the research, and has been published in international journals as well as a number of PhD and MSc theses (see resources list).

Researchers who are part of the hub are resolved that African scientists should take a lead role in research addressing what is, essentially, an African problem.

Dr Rukunga adds, “The burden of malaria is here in Africa. If you can do everything here, that is better.”

“If we stopped looking for new anti-malarials, we would run out of drugs that can kill malaria parasites,” adds Midiwo. “So we must pursue every avenue.”

The history of research on natural products for malaria

Until the 1950s, when synthetic chemistry began to dominate drug research and development (R&d) efforts, most drugs developed and registered in the pharmacopoeia were in fact based on natural products. Plant alkaloids, quinine among them, were among the first components of natural herbal remedies to be extracted and refined for more effective use in the early 19th century (see box).

Some 150 years later, quinine is still used in treatment. However, the drug has toxic side-effects, hence its use is limited to that of a second-line drug for severe or complicated malaria cases.

Although some natural product discoveries – whether quinine for malaria or ivermectin for onchocerciasis – were discovered largely by chance or serendipity, others have resulted from extensive systematic searches. The discovery of penicillin by Alexander Fleming in 1929 prompted a search for other similar compounds, which led to the discovery of streptomycin and other antibiotics. In the 1960s, the United States National Cancer Institute started a programme for the systematic screening of chemical compounds extracted from a wide range of natural plant sources. The screening programme led to the 1962 discovery that the bark of the Pacific Yew tree...
Drug discovery – early beginnings

It was in 1806 that a German apothecary first succeeded in purifying morphine from opium. Quinine, another plant alkaloid extracted from the bark of the Latin American cinchona (Quechua in Inca) tree, was one of the next. The cinchona bark had long been used by the indigenous Quechua communities of Peru in dried and powdered forms to halt both cold and fever-induced shivering. A Jesuit brother living in Lima in the early 1600’s noticed its properties and shipped it back to Rome for testing, where its efficacy against malaria was confirmed. The bark was used widely in Rome to combat malaria, then endemic to the swamps and marshes surrounding the city. In 1817, the bark’s active ingredient, quinine, was isolated by the French researchers Pierre Joseph Pelletier and Joseph Bienaimé Caventou. Quinine thus became, and remained, the anti-malarial drug of choice for travellers, merchants and colonialists in Africa, Asia and Latin America until the 1940s, and is described by some historians as having paved the way for colonialist expansion in countries where malaria was endemic. Even today, natural products remain a significant source of new drugs, particularly for infections and tumours treatments. In addition, some experts believe that part of the success of malaria drugs, such as artemisinin, may be linked to mechanisms whereby parasite resistance develops more slowly to these drugs.

contained certain anti-cancer compounds. Five years later, Wall and Wani of North Carolina’s Research Triangle Institute isolated the bark’s active ingredient, Paclitaxel, and published its structure in 1971.

The hunt in Africa for a new anti-malarial drug is thus part of a long research continuum, with scientists observing the work of traditional healers as a research starting point, and then systematically trawling through traditional medicines to find promising drug candidates.

Panning for gold

Plants and other natural products can contain hundreds of different chemical compounds. In the artemisia annua plant, for instance, scientists have identified at least 126 different compounds.

In the TDR-sponsored initiative, phytochemists from KEMRI, and the Universities of Nairobi and Jomo Kenyatta, are tasked with finding and extracting at least one compound amongst several hundred in a single plant that perhaps is responsible for anti-plasmodial activity.

To that end, they remove the fibrous parts of the plant by creating a plant extract using a range of solvents that are eventually removed by rotary evaporator. The remaining extract is often a dark, richly-coloured oily paste. Water is then routinely lyophilized (removed) leaving a concentrated extract.

Scientists then conduct an in vitro screen, exposing the malaria parasite to the raw plant extract in the laboratory, to test whether the extract is suitably ‘active’ against the parasite. The screen is carried out as a specialist service by the TDR-supported team at KEMRI headed by Dr Geoffrey Rukungu, Principle Investigator, as well as Professor Anastasie Guantai and Dr Sabah Omar.

Two different screening processes may be involved. One screen, the Plasmodium Lactate Dehydrogenase (pLDH) assay, adds an enzyme to parasites that have already been exposed to plant extract. Detecting how much enzyme is depleted by the parasite determines how many parasites are still alive and how effective – or ineffective – the plant extract may have been.

An alternative in vitro screening method uses tritiated hypoxanthine, a radioisotope labelled assay that replaces the enzyme assay and is considered to be the best confirmation of parasite activity. Particularly in Africa, it is a more expensive technique and is used only on the most promising purified compounds rather than extracts.

After the initial in vitro screening, the process to find the precise ingredients in the extract responsible for anti-plasmodial activity begins in earnest.

By using fractionating methods, such as column chromatography, scientists separate the extract into smaller groups of compounds, again screening each one to determine which subset may contain the active ingredient. The subset, or fraction of plant extract showing anti-malarial activity, is itself fractionated and individual fractions are screened once again.

A natural healer grips the bark of Warburgia ugandensis, one of the plants from which traditional medicinal remedies are drawn.
Traditional healers, health and biodiversity

While the medicinal qualities of many traditional medicinal plants are now being scrutinized by researchers in modern laboratory conditions, the survival of the same plants in the wild is threatened both by deforestation and over-exploitation. *Prunus Africana*, a hardwood tree used for prostate treatments, is now an endangered species. So is the herb, *Swertia Chirata*, which grows in the Himalayas and is being investigated for its anti-malarial properties in an Indian government-backed initiative.

Globally, development and deforestation are threatening ecosystems where medicinal plants thrive. In Kenya’s Nyeri region, for instance, where wild plants such as *Lippia Javanica, Euclea divinorum*, and *Maytenus Heterophylla* are routinely harvested for uses ranging from medicines to anti-pest treatments (e.g. lippia), land is increasingly being cleared for farming cash crops such as coffee. The gradual disappearance of these ecosystems containing plants with potential medicinal value, both known or as yet undiscovered, has become an issue to health experts, as well as those concerned with biodiversity, development and climate change, as evidenced by a 2005 WHO report addressing the issue as part of the *Millennium Ecosystem Assessment Series.*

In Kenya, the ‘Green Belt’ movement led by Nobel Prize winner Professor Wangari Maathai, Assistant Minister of Environment, Natural Resources & Wildlife, has sought to preserve large swathes of state-owned forests for public access, protecting them from sale and clearance.

Maathai, a professor of veterinary anatomy, also has defended the right of traditional healers to access Kenya’s protected areas in order to harvest medicinal plants – while also engaging them in the struggle to protect such wild plants from over-harvesting.

In the area around Nyeri, for instance, over 170,000 acres of virgin forest were scheduled to be parcelled and sold at one point, including areas rich in source materials for traditional remedies, but plans were later modified, due in part to Maathai’s movement. “They were going to cut [into the forests] for houses. She [Prof Wangari] raised her voice,” said one Nyeri-based traditional healer, Jack Githae, who also has a veterinary degree from a US institution. Healers such as Githae now are formulating strategies to cultivate the most popular plants commercially, so that they are no longer over-picked and farmers on whose land they grow are provided with an alternative source of income.

“Coffee has helped us, but medicinal plants will help us more,” Githae observes.

The process continues until scientists have isolated the single compound responsible for killing malaria parasites.

This progressive fractionation of samples and subsequent testing for activity in the malaria culture lab can take two to three months. However, it has already led to the successful isolation of a number compounds that display in vitro anti-malarial activity, says Dr Rukungaa.

False positives

Many compounds are discarded because, even after the long process to isolate them, they do not then exhibit anti-plasmodial activity at high enough levels, killing less than half the parasites in a given sample.

Interestingly, other highly active compounds end up being thrown away because they are indeterminately cytotoxic – killing in vitro cultured human cell lines as well as malaria parasites. One active ingredient in the traditional herbal remedy, *Warburgia ugandensis*, for example, is extremely toxic to the host cells. That rules it out as a potential drug lead, says Beatrice Njeri Irungu, research officer at KEMRI, who runs cytotoxicity tests – exposing pure compounds and extracts to mammalian cell lines. Traditional healers typically do not administer *Warburgia ugandensis* on its own, but rather in combination with several other medicinal plants, she adds. It is thus possible that the other medicinal plants help mask or even ameliorate the toxicity of *Warburgia ugandensis*’ active ingredient, says Irungu, who was sponsored by Medicines for Malaria Venture (MMV) to train in methodologies of drug screening at the Swiss Tropical Medicine Institute.

Once a single ingredient has been isolated, its molecular and chemical structure must be determined using a combination of infrared (IR), ultraviolet (UV) and nuclear magnetic resonance (NMR) spectroscopy.

Understanding a compound’s structure can offer further insights into exactly how the compound functions against the parasite, as well as enhancing knowledge about the parasite’s genome targets, according to Profess-
sor Abiy Yenesew, a chemist at the University of Nairobi. Determining exactly which part of the molecule is responsible for anti-parasitic activity is yet another new research frontier in this field. That may mean cleaving the most promising molecules into pieces and screening those parts separately for activity.

Spectroscopists, who elucidate structures of active compounds, are progressively identifying similar groups of molecules as they plough through the purified compounds isolated by phytochemists. Following in vitro screening and elucidation of chemical structures, the next step is in vivo screening. Mice are infected with a rodent malaria parasite and the effectiveness of compounds at suppressing the parasite within the animal is tested.

This procedure is not trivial. Phytochemists must constantly return to the beginning of the process to increase the amounts of the single compound required for testing on animals. That is what presently occupies Dr Rukunga’s team at KEMRI. It has already tested five potential candidates in mice but many more promising candidates are in the pipeline.

The precious substance for which Dr Rukunga searches is a product that has the ability to kill with high efficacy the malaria parasite in vivo. He remains confident that within 18 months he’ll have successfully isolated a lead compound from an indigenous African plant which also fits such criteria for drug development.

BUILDING COLLABORATIVE NETWORKS

The challenges

With so many scientists on the job, it is perhaps surprising that no African lead compound has already emerged. One scientist ventured that this failure is due to a lack of coordinated planning. “Maybe we are not working in a very coordinated way, making a concerted effort,” he says.

Scientists often tend to be concentrated in specific silos of research, such as botany or phytochemistry, and do not borrow each other’s expertise to work towards the common goal of a lead compound.

This individualistic approach is, in part, a result of poorly developed management of intellectual property on the continent. While, on the one hand, an active compound with a specific identified anti-parasite activity can indeed be patented by law, individual scientists remain reluctant to hand over a molecule with potential to another institute for further development because there is a lack of well-established institutional and legal processes to ensure equitable benefit-sharing. Scientists fear that they will lose control over their innovations even if a patent is eventually filed.

African scientists also continue to suffer from a paucity of resources. As a result, plant samples still may be sent elsewhere, e.g. to in vitro screening centres in the USA and Europe.

Looking forward, the step beyond the isolation of a lead compound – using medicinal chemistry to synthesize the active ingredient, modifying its structure to work more effectively, and scaling up for manufacture – requires resources that do not exist in many African countries.

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2 J Am Chem Soc. 1971 May 5;93(9):2357-7

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**Selected drugs derived from natural products**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>Anticoagulant, synthetic compound derived from dicoumarol, found in spoiled sweet clover.</td>
</tr>
<tr>
<td>Heparin</td>
<td>Anticoagulant, occurring naturally in mammalian tissues.</td>
</tr>
<tr>
<td>Hirudin</td>
<td>Anticoagulant, from leech, now produced by genetic engineering.</td>
</tr>
<tr>
<td>Opiates</td>
<td>Analgesic compounds from poppies.</td>
</tr>
<tr>
<td>Statins</td>
<td>Used to reduce plasma cholesterol. Lovastatin is a fungal metabolite. Other compounds such as mevastatin and pravastatin are synthesized from lovastatin.</td>
</tr>
<tr>
<td>Cromoglycate</td>
<td>Asthma prophylaxis. Synthetic compound based on khellin, a plant used as a herbal medicine.</td>
</tr>
<tr>
<td>Vinca alkaloids</td>
<td>(vincristine, vinblastine) Anti-cancer drugs from plants of the periwinkle family.</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>Anti-cancer drug from the yew tree.</td>
</tr>
<tr>
<td>Etoposide</td>
<td>Anti-cancer drug synthesized from podophyllotoxin, produced by the mandrake plant and used in folk medicine.</td>
</tr>
<tr>
<td>Artemether</td>
<td>Anti-malarial drug, semi-synthetic derivative of artemisinin, produced by the Chinese herb Quinghao or sweet wormwood.</td>
</tr>
<tr>
<td>Ivermectin</td>
<td>Anti-helminthic drug, semisynthetic derivative of avermectin, a fungal metabolite.</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Too numerous to list. The majority of current antibiotics are derived from fungal metabolites.</td>
</tr>
</tbody>
</table>

The TDR response

In an effort to stimulate and build capacity within a pan-African network of natural product discovery, TDR first set out in 2003 to create hubs, or central laboratories, which can carry out in vitro screening on samples sent by scientists from all over the continent.

TDR’s initial call to African institutes interested in housing the hub was met with applications from 42 countries – testimony to the enormous interest in natural product discovery and networking.

Shortly thereafter, KEMRI in Kenya and the Malaria Research Centre at the University of Ibadan and the National Institute for Pharmaceutical Research and Development (NIPRID), Abuja in Nigeria, were selected to provide twin screening hubs, one serving eastern and southern Africa, the other the west side of the continent.

“We selected the institutes based on their expertise and their potential to develop as centres of excellence,” says Dr Hashim Warsama Ghalib (on left), manager of R&D driven research capability strengthening initiatives within TDR. “But our other requirement was that we wanted to start them working as a network to expand in Kenya, Nigeria and then around Africa.”

Kenya has proven to be a worthy partner. Phytochemists at Jomo Kenyatta University and the University of Nairobi are sending samples across to KEMRI for screening. They already collaborate extensively on the use of equipment such as spectroscopy machines. KEMRI has also struck up a working relationship with the East African Herbarium of Kenya’s National Museum to identify plants for screening. It also collaborates with traditional healers during ethnomedical/ethnobotanical surveys.

As a result, KEMRI is expected to receive TDR certification as a member of the TDR/WHO global in vitro screening network within the next six months. It will then be able to accept samples from all across Africa.

TDR also aims to sponsor five African phytochemists from around the continent to bring samples to the centre in 2008. “KEMRI is capable of screening thousands of compounds per year,” says Ghalib.

However, even with screening hubs in place, natural product drug discovery will remain a complex and uncertain process. Despite their important place in the history of drug treatments, natural products are notoriously difficult to synthesize, and the use of fast and effective methods of screening – such as high throughput screening – are relatively more complicated.

“Our primary goal was to build capacity in Africa to conduct screening for natural products, and in collaboration with KEMRI, we have accomplished that objective,” emphasizes Ghalib. “The KEMRI centre is undergoing the final stages of validation to function as a TDR reference center for in vitro and in vivo screening of compounds coming from scientists around Africa. It can function as an African model centre.

“We also now have screened compounds that appear promising for further development.” However, he cautions by saying, “A lead compound is very difficult to come up with. If we come up with one [lead] compound out of thousands tested, that would be considered a success.”

– With reporting by Tatum Anderson in Nairobi, Nyeri and Kilifi, Kenya

RESOURCES ON NATURAL DRUG DISCOVERY:

TV news video

A 3 minute television news report on the TDR-sponsored effort in natural plant products research in Africa is now available as one of a five-part DVD series on TDR research, produced by Rockhopper TV Productions. Transcripts of the film dialogue are available in multiple languages. To view the film or order DVD copies, see: http://www.who.int/tdr/about/press_center/default.htm

Published papers from the TDR-supported African initiative


MSc Theses


Contact: Dr Hashim Ghalib ghalibh@who.int

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A new drug

The public health case for a joint research initiative of TDR, the African Programme for Onchocerciasis Control (APOC) and Wyeth Pharmaceuticals
The search is heating up for a new drug to prevent and treat river blindness (onchocerciasis) – one that could kill or sterilize the parasite outright, and thus avoid the need for repeated annual treatments that are now required with ivermectin. A team of TDR and APOC-sponsored researchers in Ghana are currently conducting a Phase II clinical trial of a new drug candidate, moxidectin, owned by Wyeth Pharmaceuticals. Can this drug eradicate the disease that is the world’s second leading infectious cause of blindness?

From the manufacturing facility in France to remote African communities, getting annual ivermectin treatment to the tens of millions of people living with, or at risk of onchocerciasis infection, is a task that must be repeated year after year to sustain impact – along distribution routes that can be arduous and demanding for resource-strapped health services.

Dr Tony Ukety, the Geneva-based WHO officer responsible for coordinating nongovernmental development organizations in the fight against onchocerciasis, has personal experience with the difficulties and hazards. As an ophthalmologist working in the Democratic Republic of Congo in the late 1980s, he was one of the first doctors to introduce ivermectin to rural communities in the country’s north-eastern region.

“When you see a young man, 24 years old, who has gone blind due to onchocerciasis, and he can no longer earn a living, and then he tells you he is going to commit suicide – that motivates you to do something,” says Ukety, describing how he got involved. The route he travelled then personally to deliver the drug remains essentially the same today.

“When from Entebbe, Uganda, you have to hire a small Cessna 206 plane and fly to Bunia (DRC), right on the border with Uganda, and from there fly to Buta in the northeastern region, which takes you four to five hours in all,” relates Ukety, drawing a rough map of the relevant airports, towns and borders.

“From Buta, you hire motorcycles to cover the villages of Bas-Uele and Haut-Uele districts, where the disease is endemic,” he continues. “But sometimes, if you don’t have enough money to hire a private plane all of the way to Buta, then you might take a regular flight from Bunia to the airport at Kisangani, DRC, which is quite a bit further to the south-east than Buta, and hire motorcycles to cover the rest of the distance.”

Ivermectin: achievements and limitations

In 2006, annual ivermectin treatment was reaching more than 55 million Africans through innovative systems of community-directed treatment (see Box 1). By 2015, when some 80 million people are targeted to receive treatment, coverage of target areas will be virtually complete. That is a remarkable public health success considering that the drug only became available in 1987 (see Box 2) and the parasite, transmitted by black flies breeding in fast-flowing rivers, is endemic in some 30 different countries of Africa.

“Thanks to community-directed distribution of ivermectin, onchocerciasis has been eliminated as a public health problem in large areas of West Africa, and will also be eliminated in the remain-
Since TDR’s creation in 1975, research to support onchocerciasis control programmes has been a major focus of TDR and one of its crowning achievements. TDR provided critical research findings that helped drive the initial vector control operations of the Onchocerciasis Control Programme (OCP) that operated in 11 West African States in the 1970s and 1980s.

TDR discovery research networks and screening systems were important in identifying ivermectin as a drug potentially effective against onchocerca parasites in the 1970s, paving the way for Merck’s development of the drug for use in affected human populations. Following Merck’s unprecedented decision to donate the drug for onchocerciasis control (see Box 2), TDR and OCP jointly sponsored the large scale community studies required to determine the safety and effectiveness of ivermectin for mass drug administration.

In the mid-1990s, TDR-supported research documented that not only onchocercal blindness and low vision, but also itching and skin lesions (the major manifestations of the disease in the APOC regions), have an enormous socio-psycho-economic impact. This provided the policy justification for the formation of APOC and thus extension of control efforts from West Africa to central and east African countries where the disease is endemic.

The drawback of ivermectin is that it is mainly a ‘microfilaricide’, meaning it kills the parasite offspring (microfilaria), which cause disease symptoms and facilitate disease transmission, but not the macrofilaria (adult worms). These continue to live inside their human hosts for around 12 years and regularly produce more microfilaria. Therefore, except in locales with favourable entomological and epidemiological conditions (e.g. foci in Africa currently under TDR-sponsored investigation), disease transmission cannot be permanently interrupted with ivermectin. As a result, annual ivermectin treatment must continue for an indeterminate length of time. That is a formidable task for resource-strapped Africa.

The progress that has been made in combating river blindness represents one of the most triumphant public health campaigns ever waged in the developing world.”

(UNESCO World Science Report 2005)
meetings of APOC’s governing board, the Joint Action Forum (JAF), including the most recent meetings in Tanzania (2006) and in Brussels in December, 2007.

Moxidectin: a new weapon in the battle?

One new potential treatment, that has been gradually moving through the drug development pipeline under TDR/APOC stewardship, and in collaboration with Wyeth Pharmaceuticals, is an anti-parasitic agent called moxidectin.

Moxidectin is currently being evaluated in a TDR-sponsored Phase II clinical trial involving some 192 people infected with the parasite. The trial is being conducted in Ghana under the leadership of Dr Kwablah Awadzi, founder and director of the APOC-supported Onchocerciasis Chemotherapy Research Center (OCRC). Wyeth, the owner of moxidectin, is providing the drug and operational support. The trial has been designed to show whether moxidectin can inhibit the production of microfilaria more effectively than ivermectin, either by killing the macrofilaria or by permanently sterilizing them.

If this should be the case – and preliminary results will not be available for at least another year – moxidectin might turn out to be a drug with the capacity to interrupt the onchocerciasis transmission cycle. If further clinical tests over a number of years show it to be sufficiently safe and efficacious, it could potentially be evaluated in community studies as a tool for eradication of onchocerciasis in all endemic countries.

While the Phase II trial is continuing, TDR and Wyeth are therefore preparing a Phase III clinical trial of mox-
idectin in a larger population, involving other endemic areas in the sub-Saharan region, says Dr Janis Lazdins, who coordinates TDR’s programmes for development of new drugs. The Phase III trial would take around 2.5 years to complete and could, if successful, also provide the basis for a study to determine a safe and effective dose for children.

At the 2006 meeting of APOC’s JAF in Tanzania, Wyeth Pharmaceuticals expressed its “commitment to the development of moxidectin as a macrofilaricidal agent,” and its commitment to contribute significantly to the financing of the Phase III clinical trials of the drug.

One of ivermectin’s key advantages is its low toxicity, permitting mass drug administration to nearly everyone over five years of age in the at-risk communities, notes TDR scientist Dr Annette Kuesel, who is managing TDR’s moxidectin development effort. “Moxidectin would need to demonstrate a similar safety profile to be suitable for mass drug administration under community direction – if it is to be effective as a tool for disease eradication.”

In drug development that “if” is always a big one. Pending positive outcomes of the clinical trials, registration of moxidectin in real community settings. Such ‘community effectiveness studies’ would determine the safety as well as the effect of two, and possibly three, successive annual moxidectin treatments on disease transmission. Only when these studies are completed, sometime in 2014, will it be possible to answer the crucial question: could moxidectin interrupt onchocerciasis transmission and thus eradicate onchocerciasis across all endemic areas?

**New drug development – a lengthy process**

The pathway for new drug development is littered with delays and unforeseen obstacles. Moxidectin has seen its share.

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**Box 2. 20 years of ivermectin**

“Merck is undertaking to make appropriate arrangements, if necessary, with other interested parties, to make needed quantities of the drug available to these governments and patients at no cost to them for the treatment of onchocerciasis.”

(Excerpt of telex from Robert D. Fluss, Merck, to TOR Director, Adetokunbo Lucas, 20 June, 1986).

Merck this year celebrates the 20th anniversary of its commitment to donate ivermectin for as long as needed in the amounts needed and the creation of an unprecedented programme to support distribution for ivermectin (Mectizan®) to disease-endemic countries. To date, Merck has donated 1.8 billion tablets.

Ivermectin, donated under a special agreement negotiated by TDR and WHO, was first distributed for free through the Onchocerciasis Control Programme (OCP) of 11 West African countries in 1987. National control programmes in those countries eventually took over the annual distribution task in West Africa. In the 19 other central and east African countries where the disease is prevalent, the African Programme for Onchocerciasis Control (APOC) continues to oversee the systems of annual community-directed treatment with ivermectin. In the Americas, the efforts to ensure distribution of ivermectin to communities in the 6 countries with endemic foci are coordinated by the Onchocerciasis Elimination Programme of the Americas (OEPA).

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**Resources:**

www.mectizan.org
www.merck.com/cr/enabling_access/developing_world/mectizan/

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**Monitoring development and reproduction of the parasite**

**Macrofilaria (adult parasite):**

1. Identification of a subcutaneous nodule (onchocercoma).
2. Excised nodule under a dissecting microscope.
3. Macrofilariae isolated from a nodule.

**Microfilaria (offspring):**

4-5. A piece of skin is excised, the resulting wound covered with a small strip of plaster.
6. The skin snip is weighed on a sensitive balance and then incubated for 8-24 hours and the number of microfilariae are counted under the microscope at 100x magnification.
Preparations for TDR’s Phase II clinical trial involved coordination with policy makers as well as the painstaking recruitment of suitable volunteers at field level, and expansion of clinical trial capacity in the designated site.

The planned 2004 commencement of the trial was then delayed for nearly two years after a public controversy erupted in the USA over an animal drug containing moxidectin, and used to prevent heartworm in dogs. Wyeth subsequently withdrew the drug from the US market, pending a United States Food and Drug Administration Center for Veterinary Medicine review still ongoing – although the drug continues to be sold in Europe and Australia.

In response, TDR convened an informal consultation of independent experts in Ghana in 2005, to exhaustively review the safety evidence prior to commencement of the Phase II clinical trial.

The panel included three scientists from France, Nigeria and Sudan and representatives of the Ghana regulatory authorities and the national ethics review committee. It reviewed around 500 pages of summaries of safety data on moxidectin. The panel concluded that the first study in subjects with onchocerciasis should be initiated as soon as possible. In September of 2006, the Phase II trial of moxidectin in Ghana finally got underway.

Onchocerciasis: a history of high impacts, often hidden

It has only been over the last 30 years that the true impact of onchocerciasis has become more apparent to policy makers, and control efforts thus more strenuous.

Growing recognition of the economic impacts of the disease in West Africa, where it drove communities away from fertile riverbeds where vectors bred, was one factor that prompted the World Bank and WHO to first take action. Together with national leaders, the Onchocerciasis Control Programme (OCP) was launched in 1974, and over two decades succeeded in eliminating onchocerciasis as a public health problem in 11 West African countries. Control focused initially on large scale control of the vector, Simulium blackflies. Then, ivermectin was introduced into OCP regions following Merck’s 1987 decision to donate the drug free of charge and studies showing ivermectin to be safe for mass treatment.

In 1995, the formation of the African Programme for Onchocerciasis Control (APOC) and the development and validation of an innovative system of ‘community-directed treatment’ with ivermectin provided the basis for expanding ivermectin mass treatment into the onchocerciasis endemic areas of the remaining 19 African countries.

But given the epidemiology of the disease, it is not sufficient to rely upon past successes, observes Dr Boakye Boatin, Director of the Onchocerciasis Control Programme (OCP) in West Africa from 2000 to 2002 and now working in TDR. “We need to be continually improving upon our research and control efforts in order to sustain and expand the public health impacts,” he says.

Clearly, if we can find a drug that will eradicate onchocerciasis after several treatment rounds, that would be preferable,” says Dr Hans Remme, who has led the research efforts on community-directed treatment with ivermectin at TDR headquarters for over a decade.

“Meanwhile, the community-directed systems of treatment that have been developed for ivermectin can be harnessed for other important primary health care interventions, and ultimately moxidectin.”

Resources:
www.who.int/tdr/topics/ir/cdi.htm
www.apoc.bf

Contacts: Dr Annette Kuesel
kuesela@who.int
Dr Janis Lazdins
lazdinsj@who.int
Making a differ
As TDR celebrates the 30th anniversary of its Joint Coordinating Board (JCB), we share excerpts from TDR’s new history of the ‘people, products and partnerships’ that made a difference to public health.

**Phase II**

TDR’s second decade focused on field research and genomics. Simple tools, such as bednets for prevention of malaria, were shown to dramatically reduce deaths. In onchocerciasis, malaria and other diseases, field research identified ways to expand use of new drugs, diagnostics and vector-control tools by empowering community members to take simple health and disease-control measures. High-level meetings on genomics launched a new era in basic research, including work on a genetically-engineered *A. gambiae* mosquito incapable of transmitting malaria and efforts to sequence the genomes of the parasites responsible for leishmaniasis, sleeping sickness and Chagas disease.

**WHO Director-General**
Dr Hiroshi Nakajima (1988–1998)

**TDR Director**
Dr Tore Godal (1986–1998)

**Highlights**
- Insecticide-treated bednets for malaria prevention
- Unit-dose packaging for home and community administration of anti-malarials
- Rapid epidemiological mapping of onchocerciasis (REMO)
- DNA probes for lymphatic filariasis and onchocerciasis detection
- Improved blood-bank screening and diagnostics for Chagas disease
- Community-directed treatment for onchocerciasis
- Development of liposomal amphotericin B for visceral leishmaniasis and artemether for malaria
- Tsetse fly traps and screens in sleeping sickness control
- Initiatives for Tritryps genome-sequencing and genetic modification of the malaria vector *Anopheles gambiae*.

Photo – Korania village: A woman sleeping under a bednet in the compound surrounding her house. The nets are erected outdoors or on the roofs of houses so that people can sleep in the open, safe from mosquito bites.
New emphases: applied field research

By the beginning of TDR’s second decade, dozens of new products and innovations were in various phases of development, and 20 TDR-supported products were being used in disease-control programmes. Yet the fact that product development alone was not enough was underlined in the second external review in 1987 (Otero, 1988). This review reflected the growing concern in the health community that many drugs and other health tools imported by developing countries were being used inefficiently in the field, if at all. There was a pressing need for more field and socio-economic research to analyse how new and existing drugs, diagnostics and other tools could be used more effectively (TDR, 1992; Singer, 1989). Although TDR had conducted some field research, the Second TDR External Review determined it should become a top priority.

Dr Tore Godal, a prominent Norwegian immunologist who had served as the chair of TDR’s flagship Steering Committee on leprosy, became the new Director of TDR in 1986. Godal would tackle the challenges of applied field research with characteristic fascination, energy and vigour. By 1994, the budget for field research activities had approximately doubled (TDR, 1995) as TDR shifted away from its disease focus of previous years, creating interdisciplinary task forces for field research, which over time would examine not only safety and efficacy of new drugs, diagnostics, and tools in real-life settings, but also barriers to access or use of particular interventions, and opportunities for improved service delivery. The JCB also called for social and economic research to receive greater emphasis, examining broad issues such as gender discrimination, violence and poverty.

Applied field research was a complex endeavour, involving multiple actors and close cooperation with WHO control departments. Still, many of TDR’s most significant breakthroughs in its second decade emerged from field research. These included community-directed treatment for onchocerciasis; insecticide-treated bednets for malaria prevention; the development of unit-dose packaging (blister packs) for the easy use of anti-malarials at home; and field testing of new artemisinin-based combination therapies (ACTs). All were effective, simplified treatments that empowered people in homes and communities.

Insecticide-treated bednets

In early 1992, striking results from a modest TDR-supported study showing a 63% reduction in child mortality in The Gambia among households using insecticide-treated bednets spurred TDR to embark on one of its most ambitious studies ever – to establish unequivocal evidence of how this new tool could help malaria control. Large scale trials of insecticide-treated bednet use involving 400 000 children were launched in sites in Ghana, Burkina Faso, Kenya and The Gambia. The four-country study was, at that time, quite unique – a classic cluster-randomized controlled trial carried out in a field setting. The participation of international experts in the design not only ensured rigour, but ensured findings would be taken seriously by the scientific community and policy makers. Bednets were distributed free of charge to children in trial villages, and compared with control villages. The multi-country studies demonstrated that insecticide-treated bednets could reduce overall childhood mortality by an average of around 20% (Cattani et al., 1998).

From one small study… to multi-country trials

Jacqueline Cattani recalls how TDR’s readiness to build upon the surprising results of just one small study on bednets from The Gambia helped trigger a revolution in public health in Africa. She was head of FIELDMAL in the early 1990s, when the study attracted the steering committee’s interest:

“FIELDMAL had funded a couple of very small village to village comparisons of different vector- and malaria-control strategies. One small study from The Gambia had shown a 63% reduction in childhood deaths after bednets were used. It was a very small trial and highly controlled – people had been visited every night in the villages to ensure they were sleeping under their nets. Still, it caught our attention.”

“At the time, bednets cost US$ 25 a piece and were available mostly in major cities for the wealthy. But in The Gambia they had some tradition of use, which was why they carried out such a study. I recall a discussion with TDR Director Dr Tore Godal during one of our staff meetings. We both agreed that for this to make a difference, we would have to show an impact in a large population and in a rigorously designed trial. I would never have dreamed that TDR would be willing to fund such large-scale trials. But Godal’s response, effectively was, ‘Let’s go for it. If these things work, if you can even show a fraction of this 63% reduction in a more real-life setting, then this is a really big impact.’”

“I think it was one of the most expensive investments TDR had ever made. Godal, to his credit, was willing to make it.”

DR JACQUELINE CATTANI, Professor of Global Health, University of South Florida, Manager FIELDMAL Steering Committee, TDR, 1990–1997.
Hunkuyi village. Healthy Women Counselling Guide research team members sit with the village radio listening group and make written notes. The group listens to radio dramas depicting health messages. They hear the story, suggest refinements and help develop stories to best reflect how the message should be presented, as part of a social research initiative fostered by TDR.

New drugs for malaria

The chemotherapy equivalent of FIELDMAL was CHEMAL, funding research on malaria drugs. Chaired by Nobel prize winner Professor Gertrude Elion, and subsequently by Professor Dyann Wirth, it was at this committee’s 1989 special meeting in Beijing that Chinese researchers first presented their results on artemisinin derivatives, and the dossier for registration of artesunate and artemether in China, therein describing what some regarded as the most significant advance in treatment since the entry of quinine into the British Pharmacopoeia in 1677. The next 10 years were dominated by research on these artemisinin derivatives, principally in South East Asia.

The artemisinin derivatives were unprotected by patent and therefore not of wide interest to industry. Consequently, CHEMAL funded the necessary research and development to improve the understanding of the efficacy and safety of various artemisinin derivatives, their mechanism of action and toxicity. In addition, CHEMAL also supported drug development and partnerships with Chinese, European and US institutions and firms to register artemisinin derivatives in developed countries.

In South-East Asia, TDR’s Anti-Malaria Task Force (ANTIMALS) supported field research on how to improve the use and distribution of anti-malarials in rural areas. Some of the first anti-malarial drugs in easy-to-administer unit-dose ‘blister packs’ came out of this initiative. This set the stage for community- and home-based malaria treatment, lifesaving measures that are now key components of WHO strategies.

The introduction of artemisinin-based drugs was so rapid and widespread that it soon triggered concerns about the emergence of parasite resistance. In the mid and late 1990s, TDR thus would lead large-scale, multi-centre clinical trials with various international partners to demonstrate the efficacy of artemisinin-based combination therapies (ACTs). Trials in South-East Asia, funded by the Resistance and Policies (RAP) Task Force, documented how ACTs could improve cure rates while reducing the resistance of malaria parasites to any one drug. Ultimately, this research provided an evidence base upon which WHO was able to promote use of ACTs as a core component of malaria treatment policy.
Community-directed treatment of onchocerciasis

The beginning of TDR’s second decade of operations also marked the start of the full-scale mass administration of ivermectin for the treatment of onchocerciasis (river blindness). The disease, transmitted by Simulium blackflies living near streams, is endemic in more than 30 countries in Africa and in the late 1980s, an estimated 37 million people were infected. Different parasite strains are prevalent in the west African savannah region, where gradual progression to blindness often occurs in infected individuals, and in the more forested central and eastern African regions, where debilitating itching and disfiguring skin lesions are the primary symptoms.

Following Merck’s announcement of ivermectin’s donation, questions still remained as to how to use this new drug most effectively. Many believed that the drug should be distributed through a system of mass administration, and not only for treatment of individual cases. Yet safety and efficacy of the drug in programmes of mass drug administration had to be tested.

New TDR Director Dr Tore Godal would meet the challenge. Together with the Onchocerciasis Control Programme in West Africa (OCP), covering 11 countries in the region, TDR collaborated in 13 large-scale Phase IV community trials confirming safety and determining efficacy of ivermectin in mass treatment (TDR, 1995). Results also indicated, however, that annual ivermectin treatment would have to be sustained over a period of years to interrupt transmission, and almost indefinitely in hyper-endemic areas (Remme, 2004). This posed a significant challenge to disease control.

Meanwhile, there was also mounting pressure to extend ivermectin distribution to areas outside of the OCP regions, where some 80% of the population at risk for onchocerciasis actually lives. In these forested regions of central, southern and eastern Africa, vector control tools used in West Africa’s broad savannah were not an option, making drug treatment all the more imperative.

Yet in order to expand ivermectin distribution to non-OCP areas, and to optimize its distribution in remote OCP regions, critical policy questions still needed to be answered by research, including: how to justify massive control in forest areas where the main disease symptom was skin disease, rather than blindness; where to target control; and how to sustain an annual system of drug treatment. In December 1995, a new umbrella organization, known as the African Programme for Onchocerciasis Control (APOC) was created involving 19 endemic countries of central, southern and eastern Africa. Concurrent with this, the World Bank offered US$ 1.2 million to accelerate research, and TDR launched a special initiative for Onchocerciasis Operational Research.

The TDR research effort would thus support APOC, providing both the evidence to justify control to policymakers, as well as guidance on where and how to carry out operations. TDR-supported research would document the health, economic and psycho-social impacts of oncho-related skin disease, making the policy case in areas where the disease pathology that had not been well appreciated (AFR Reports/TDR, 1995). TDR-supported scientists also provided timely new tools for the rapid epidemiological mapping of onchocerciasis (REMO) based upon examination for palpable onchocerciasis nodules in sample communities, and thus targeting of areas for mass treatment with ivermectin.

In 1994, TDR-supported researchers also launched a multi-country, multi-disciplinary study to answer the key question – how to distribute the drug most effectively. The teams developed a new framework for ‘community-directed treatment’ (ComDT) with ivermectin. The rationale was simple. Communities empowered to organize their own drug distribution system would do so in a manner best suited to them, with health services providing necessary training. ComDT was adopted by OCP as its ivermectin delivery strategy and became the backbone of APOC operations in 1996.

By 2007, ComDT has succeeded in extending the annual ivermectin treatment to more than 55 million Africans out of a target population of approximately 80 million. In collaboration with APOC and local research institutions, TDR research over the past decade helped fine-tune ComDT methods. Continuous collaboration between research and control officers has proven to be the secret of success in onchocerciasis control. This and the ComDT strategy have helped make onchocerciasis control one of the biggest public health successes ever in Africa’s history.


Full text available at: www.who.int/tdr/about/history_book/anniversary_book.htm
From LF control to elimination

How research triggered the global campaign

In 1994, filariasis was still the second leading cause of permanent disability worldwide, with more than a billion people in 80 countries at risk. At the same time, major new innovations in diagnostics and drugs for the disease were just being put into use, many developed with TDR support and sponsorship. It was in that same year that Dr CP Ramachandran, Secretary of the TDR Steering Committee on Filariasis and also chief of filariasis control at WHO, perceived the opportunity to develop a coherent strategy for disease elimination. He convened a meeting at the Universiti Sains Malaysia (USM), in the presence of then-TDR Director Dr Tore Godal, to examine and synthesize the new research findings regarding diagnosis and drug treatment. A year later, Ramachandran was lobbying top WHO officials for a resolution in the World Health Assembly on a global programme for the elimination of lymphatic filariasis. In May 1997, the World Health Assembly passed the resolution and in the year 2000, the Global Programme for the Elimination of Lymphatic Filariasis (GPELF) was born. Since then, burden of LF has declined dramatically. And while many challenges remain to be overcome, the elimination of LF as a public health problem is a realistic goal in many endemic countries.

* Second of two parts on the history of lymphatic filariasis: from control to elimination

**INTERVIEW: PROFESSOR DATO DR CP RAMACHANDRAN**

*How did you initially become involved in LF at TDR and WHO?*

I came in as a consultant at the invitation of Dr Adetokunbo Lucas, TDR’s Director, to help the new TDR programme in various facets. I spent the first few months with Dr Jose Barzelatto, who had been put in charge of the Research Capacity Strengthening unit. Together we put together a strategic plan for institution strengthening along with Dr Gordon Smith from the London School of Tropical Medicine and Hygiene, and then I made a number of visits to India and other places along with Professor W.W. Macdonald from the Liverpool School, propagating what TDR is all about. Effectively, I became a salesman for TDR and all over South-East Asia; my name went from “CP Ramachandran” to “TDR Ramachandran.” Since my background was in filariasis, I also worked together with Brian Duke, then chief of the WHO filariasis unit. After having identified a wide range of institutions in South-East Asia, the Western Pacific and African regions that would work on tropical diseases, and specifically on filarial infections, we supported them with long term grants and research training grants, helping build a core of researchers and or research expertise.

*What was the key research breakthrough that paved the way for global elimination?*

You cannot talk about only one breakthrough, but there were a series of events. In 1985, TDR developed a strategy for LF issues that needed immediate attention. I had taken over as the Secretary of the TDR Steering Committee for Filariasis. Dr Eric Ottesen, then-chief of parasitological research at the National Institutes of Health, USA, was committee chairperson, and together we developed a strategy for intensified research in LF. For the following
decade, we pursued a range of therapeutic approaches – from basic immunology, to diagnostics, chemotherapy, epidemiology, pathogenesis, and management of clinical disease symptoms. The whole spectrum was covered through TDR research grants.

Another important moment was the discovery that a single treatment of DEC, then the only drug available for LF, was just as effective as the accepted 14-day regime. The story behind this is a classic example of how TDR stimulates innovation: ivermectin had just been registered for use against onchocerciasis (river blindness). In the context of the ongoing oncho research, Dr Ottesen and Dr V Kumaraswami in Madras examined the impact of ivermectin against LF and found that even a dosage as low as 10mcg/kg would kill LF microfilaria. We got excited over that, and that led to larger TDR-sponsored studies of ivermectin against LF in various sites in India, South-East Asia, Papua New Guinea, French Polynesia, Africa and Brazil, in collaboration with prominent national and international researchers. Naturally, we then wanted to compare the effectiveness of ivermectin and DEC. However, we agreed that meant comparing a single dose of each. To everyone’s surprise, we found that a single dose of DEC was as good as the accepted multiple dosage. The discovery that a single annual dose of either DEC or ivermectin could be effective was a breakthrough that opened the possibility for a much more ambitious control effort based upon mass drug administration.

**But the WHO recommendation for LF treatment is DEC + albendazole or DEC + ivermectin. So how do you get to those combinations?**

After we tested a single dose of DEC against a single dose of ivermectin, we tried a combination and found that the combination, DEC + ivermectin, worked better than one or the other drug on its own. However, in Asia, studies led by Professor Mahroof Ismail also were showing us that albendazole would kill the adult worm and not just the offspring (microfilaria) over a period of about 5-8 years. So ultimately, we began to recommend that DEC be combined with albendazole in the Asian and Pacific regions, where that combination had a slightly better result. In Africa, we continued to recommend a single dose of ivermectin along with albendazole, since one cannot use DEC in onchocerciasis co-endemic regions.

**But as we all know, drugs alone are not enough. What about diagnosis?**

In terms of diagnosis, since the parasite is only active at night, traditionally we would have to go to the villages and wake people up to take blood samples for diagnosis. This was a big obstacle not only to treatment but to epidemiological tracking. Through TDR, we sponsored the development of rapid diagnostics at James Cook University based on antigen assays (ICT cards), using monoclonal antibodies to identify the presence of the major disease parasite strain, *Wuchereria bancrofti*. So within two minutes, day or night, you could get a result. For the second parasite strain, *Brugia malayi*, a rapid antibody dip stick test was developed by Professor Rahmah Noordin at USM in Malaysia.

**What other research advances paved the way for an integrated global strategy?**

The discovery that many people who appear, on the surface, to be asymptomatic carriers of LF also suffer from damage, helped make the case for a major global programme. This came as we advanced knowledge about the disease and its progression. Looking at asymptomatic cases, we found that dilation of the lymphatic vessels occurs very early, and through lymphoscintigraphy and ultrasound techniques developed in Brazil by Dr Gerusa
Dreyer, we could see that even very young people with the infection had lymphatic damage. The new antigen assays show very clearly that LF also is a disease of children. Finally, studies by Professor R.K. Shenoy in Kerala, clearly showed the benefits of early treatment in children (over two years of age you can treat with combination drugs).

**And what about treatment of existing chronic disease cases?**

The fact that secondary bacterial infections played a major role in lymphatic infections and swelling was another important discovery. These studies also were carried out by Dr Dreyer in Brazil, as well as by others in Haiti and India. Once that was finally confirmed, we were able to advocate that infected people could greatly improve their condition by keeping their legs clean with soap and water, using the occasional antibiotic when really necessary. Chronic severe attacks were significantly reduced as was the progression of gland enlargement (lymphoedema). That was a second major breakthrough.

**So how did the 1994 meeting in Malaysia lead to a global strategy?**

During the August 1994 meeting at USM, Penang, we synthesized research findings into a set of clear control strategies offering guidance to managers and policymakers. These were published in an official WHO/TDR document. We also realized that we had most of the basic disease diagnosis, control and treatment elements in place needed to launch a global elimination campaign.

So in 1996 and 1997, I began to lobby for a World Health Assembly resolution, together with Dr Ottesen, who would take over my WHO post as Chief of Filariasis Control when I retired. The resolution was passed by the World Health Assembly in May 1997. That paved the way for the launching of the Global Programme for Elimination of Lymphatic Filariasis in 2000.

Where is the campaign now, and how far do you have to go?

It is remarkable what we have achieved. Of the nearly 80 endemic countries, 40 are using mass drug administration (MDA). Countries that have not yet started are largely in the African region – although African countries such as Ghana and Burkina Faso, are already into the fourth and fifth rounds of MDA. Sri Lanka, Malaysia and Thailand now have very low levels of LF transmission, thanks to MDA. Bangladesh is doing very well. Egypt has almost eradicated the infection. India and Indonesia are major challenges in terms of number of people infected but steady progress is being made to provide MDA to millions in endemic states. So if you look at it globally, the progress has been tremendous in terms of bringing down infection and transmission rates in communities. The precise length of time it will take to bring down infection rates to below 1% depends on the initial microfilarial load in a particular community. If it is not that high, it make take 5 or less rounds, if higher, then more rounds. So monitoring and evaluation at all levels is integral to the Global Programme. At the same time, the suffering of those already infected has been greatly reduced through better self-care and where necessary, medical treatment. People no longer regularly have to take time off from work due to an attack.

What are the GPELF campaign goals?

The WHA resolution talks about eliminating LF as a public health problem – bringing down community infection to such a low level that it is not a major clinical disease. To achieve that, our main tool is chemotherapy, secondly, helping chronic cases through better self-treatment, and thirdly, vector control – although in the case of LF that can be expensive. If we can bring the infection rate below 1%, then we may disrupt transmission. That happened in China, where they have declared themselves LF free. There are locales, such as islands in the Pacific, where we may have to bring the rate down even lower. Still, so far it looks very promising for elimination using the drug combinations.

What else does the future hold?

Now the new buzzword is “integrated approaches” to disease control at the primary health care level. So we are looking at how the LF control programme and strategies can also be used to address soil-transmitted helminths, schistosomiasis, and other neglected tropical diseases that pose problems in the same communities. At the same time, we need to expand the programme to African areas where no systematic control programme exists. The resources are available, knowledge and strategies exist, and WHO, through TDR and the Department of Neglected Tropical Diseases, have made firm commitments. So now, it is a matter of political will to carry out the commitments.

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ramacp@hotmail.com
10-year review of consortium-sponsored research

TDR’s Molecular Entomology Committee helped unlock mosquito genome’s secrets

A recent ten-year, independent review of research funded by the Molecular Entomology Committee, Biology and Control of Vectors (BCV), a partnership of research institutions and experts, underlines the high impact scientific findings fostered by the work of this TDR committee – most notably the complete sequencing of the genome of *Anopheles gambiae*, the main malaria vector.

Since 1994, the TDR Molecular Entomology Committee (BCV) has been supporting disease vectors research aimed at applying new knowledge of molecular biology and genomics to malaria, dengue, and human African trypanosomiasis (HAT) prevention and control. The BCV, a global partnership of research institutes and experts, was founded as a follow-up to the 1991 TDR-sponsored landmark meeting held in Tucson, Arizona, to explore prospects for malaria control by genetic manipulation of vector populations (Figure 1).

A new 10-year, independent review of BCV-funded research underlines the high impact scientific findings fostered by the Committee's work – most notably the complete sequencing of the genome of *Anopheles gambiae*, the main malaria vector, research published by *Science* in 2002 (Morel et al, 2002). In addition, the BCV has also sponsored groundbreaking research into the genetic modification of the mosquito *Anopheles gambiae*; new understandings of *Anopheles gambiae* vector population genetics and resistance to insecticides in Africa; description of gametocyte development at the molecular level; and the construction of laboratory strains of malaria-refractory mosquitoes – that is, insects unable to transmit the parasite.

The BCV review was undertaken by Professor Christos Louis of the Institute for Molecular Biology and Biotechnology (IMBB), University of Crete, Heraklion, Crete (Greece).

"BCV-sponsored research has yielded significant new research findings relevant to disease control, and boosted research especially in disease endemic countries through the funding of capacity-strengthening activities and specialized courses," said Louis, summarizing the report’s conclusions. “Through fostering research into modern technologies, such as genomics, TDR was decisive in transforming a neglected scientific area into a thriving research field.”

Figure 1. Timeline, projected in 1991, for the development of malaria vectors unable to transmit parasites through genetic modifications of the embryos (eggs).

The basic goal of the programme was to use mosquitoes, engineered so that they could no longer transmit malaria, to replace existing populations in the wild. The three milestones identified by the green line are i) the genetic transformation of mosquitoes, ii) the achievement of laboratory-based proof-of-principle, and iii) the initiation of field tests, once it is known how the novel “refractoriness genes” can be safely spread in the wild. The deadlines set for those objectives have, so far, been met.
Between 1994 and 2005, BCV funded a total of 117 research projects relating to vector population biology and ethology in the wider sense of the terms, to genomics and molecular genetics, as well as providing support to wards a range of scientific meetings and international ad hoc coordinating committees involved in the sequenc ing of the *Anopheles gambiae* genome and other research ventures.

Training of an estimated 200 young scientists, almost all from disease endemic countries, was another important feature of the projects. BCV supported trainees participating in individual research, or courses in molecular entomology, bioinformatics and functional genomics, as well as a ‘Methods book’ in the field of the biology of disease vectors.

**Modest investment of US$ 6 million**

An evaluation of the research projects’ final reports indicated that more than half (see Table 1) were of high scientific quality, while about 17% would be regarded as having lower scientific value. TDR-supported research yielded a total of 341 publications, including several published in high impact journals, such as *Nature* and *Science*.

While the impact of the projects funded was high, the overall TDR investment was modest. US$ 6 million was spent during the entire period on research projects and training, with each project averaging US$ 54 500 and taking between 1-3 years to complete (see Table 2). The majority of funds (80.6%) were allocated to projects carried out in the United States and the European Union, while about 16% (see Table 3 on next page) involved projects whose principal investigators were located in Disease Endemic Countries (DECs).

**Research and training activities funded**

Between 1994 and 2005, BCV funded a total of 117 research projects relating to vector population biology and ethology in the wider sense of the terms, to genomics and molecular genetics, as well as providing support to-
Recent activities of BCV have focused on:
• identifying the genes responsible for disruption of parasite/virus growth;
• determining methods for spreading selected genes in wild mosquito vector populations;
• considering requirements before deploying refractory transgenic insect vectors;
• supporting and coordinating international insect genome sequencing, and mapping and post genomics research activities;
• activities in the areas of molecular entomology and genomics applications for human African trypanosomiasis vectors;
• building capacity for molecular entomology research activities.

Activities remain focused on three single insects: *Anopheles* mosquitoes (mostly, but not uniquely, *Anopheles gambiae*); *Aedes* mosquitoes; and more recently, the tsetse fly (*Glossina*).

**BCV role in TDR's 10 Year Strategy**

The review recommended a number of measures to improve the already high standard of BCV-sponsored activities. These included administrative streamlining and a greater focus on fewer selected topics and, in the case of restricted budgets, awarding more funds to fewer projects, rather than a series of smaller awards. Training should be maintained as a key component of BCV and perhaps even expanded in collaboration with TDR's other empowerment and research capacity strengthening activities. Finally, the review recommended that BCV be proactive in fostering development of a strategy for disease control based on the use of refractory transgenic insects, by organizing relevant scientific meetings and publishing their findings and recommendations.

“The impact of past BCV committee activities on the advancement of vector biology has been outstanding, especially if one considers the modest expenditures that supported these efforts,” said Dr Marcelo Jacobs-Lorena, chair of the BCV committee and professor of molecular microbiology and immunology at Johns Hopkins School of Public Health. “Under the new TDR Ten Year Strategy, a new committee will have an expanded remit beyond molecular entomology, overseeing activities that are part of a business line in Innovative Vector Control Interventions. This streamlined modus operandi should make major contributions toward the goal of reducing disease burden.”

![More information: Details of workplan, committee members and various activities at www.who.int/tdr/topics/mol_entomology/default.htm](https://www.who.int/tdr/topics/mol_entomology/default.htm)

**Table 3. Geographic breakdown of BCV spending on research projects**

<table>
<thead>
<tr>
<th>Research projects</th>
<th>Number</th>
<th>Total funds US$</th>
<th>%</th>
<th>US$/Project</th>
<th>%/DEC funds</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>43</td>
<td>2,731,377</td>
<td>48.2%</td>
<td>63,520</td>
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<tr>
<td>EU</td>
<td>32</td>
<td>1,831,271</td>
<td>32.3%</td>
<td>57,227</td>
<td>--</td>
</tr>
<tr>
<td>Other, non DEC countries</td>
<td>4</td>
<td>214,013</td>
<td>3.8%</td>
<td>53,503</td>
<td>--</td>
</tr>
<tr>
<td>DEC countries</td>
<td>25</td>
<td>895,241</td>
<td>15.7%</td>
<td>35,809</td>
<td>100.0%</td>
</tr>
<tr>
<td>Latin America</td>
<td>9</td>
<td>272,259</td>
<td>4.8%</td>
<td>30,251</td>
<td>30.4%</td>
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<tr>
<td>Brazil</td>
<td>5</td>
<td>112,963</td>
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<td>22,593</td>
<td>12.6%</td>
</tr>
<tr>
<td>Guatemala</td>
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<td>67,496</td>
<td>13.5%</td>
<td>67,496</td>
<td>75.0%</td>
</tr>
<tr>
<td>Mexico</td>
<td>2</td>
<td>65,800</td>
<td>12.9%</td>
<td>32,900</td>
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<tr>
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<td>26,000</td>
<td>5.2%</td>
<td>26,000</td>
<td>2.0%</td>
</tr>
<tr>
<td>Asia</td>
<td>6</td>
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<td>41,946</td>
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<tr>
<td>Vietnam</td>
<td>1</td>
<td>24,500</td>
<td>4.4%</td>
<td>24,500</td>
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<tr>
<td>India</td>
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<tr>
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<tr>
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<td>1.8%</td>
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<td>1.1%</td>
</tr>
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</table>

Contact: Dr Yeya T. Touré tourey@who.int
A global, web-based knowledge management portal (www.TropIKA.net) was launched by a consortium of partners on 30 October 2007 in Beijing at the Global Forum for Health Research (Forum 11). TropIKA.net was developed to enhance access to and sharing of information on diseases of poverty, addressing important issues that affect public health practitioners, research professionals and policy makers working in the field of infectious diseases of poverty. Anyone interested in tropical disease research and policy setting is encouraged to visit the site, provide commentary, ask questions, and participate. TropIKA provides a uniquely flexible, dynamic and peer reviewed platform that facilitates: knowledge exchange; identification and proactive dissemination of information on priority research needs and gaps for these diseases; and enhanced and equitable access to research information, especially in disease endemic countries.

TropIKA.net is part of a broad-based, new strategy by TDR to help build on existing knowledge management capacity in infectious diseases of poverty and expand research capacity in developing countries.

“The initiative is about making the connection between the world of research and the world of control. It is about bringing all the partners around the table to set an agenda for research that makes sense for countries in which these diseases are so prevalent,” said Dr Robert Ridley, Director of TDR.

TropIKA.net is sponsored by TDR in collaboration with a range of partners. The editorial team and technical platform is hosted by BIREME, the Latin American and Caribbean Centre on Health Sciences Information of the Pan American Health Organization in São Paulo, Brazil. The service runs under the guidance of an international advisory board.

At the Global Forum for Health Research–Forum 11 meeting in Beijing in October-November 2007, the meeting support module was piloted, and included daily summaries of sessions, as well as pre- and post- meeting coverage. The goal was to provide additional materials for such events that can help all stakeholders discuss and equally contribute to agenda setting and common commitments in fostering better health for the communities.

TropIKA’s objectives and activities

In partnership with established information sharing institutions and initiatives, TropIKA.net will provide broad access to literature. In addition, the TropIKA.net team will be commissioning authoritative reviews, calling on experts to write commentaries and editorials on published research results, and promoting peer to peer post-publication reviews through original interactive features (blogs, communities of practice, comments). The site offers a virtual platform for the acquisition, review and sharing of the most current and up-to-date information and relevant knowledge on:

- Public health research needs and scientific opportunities;
- Research-based evidence in support of infectious disease control and related public health policies;
- High profile research activities and control projects;
- International research funding and support opportunities;
- Potential innovations for disease control interventions.
**TropIKA.net Features**

- Commissioned reviews on key issues in the field of infectious diseases of poverty.
- Summaries and highlights of research and news on infectious diseases useful for both research and policy-oriented audiences.
- Virtual journals consisting of carefully crafted search strategies run on PubMed against a selection of around 200 selected biomedical journals.
- Research articles and expert meeting reports introduced and commented by scientific experts with possibility of peer to peer post-publication review.
- Daily reporting on major health forums, conferences and events.
- Interactive features such as blog postings, discussion forums and communities of practice.
- Networking functionalities.
- Resources (training packages, factual databases, multimedia).
- Research funding opportunities in the field of infectious diseases of poverty.

**TropIKA.net Team Partners**

- BIREME/Pan American Health Organization/World Health Organization
- PubMed at the US National Library of Medicine (NLM)
- Health InterNetwork Access to Research Initiative (HINARI)
- Global Health Library (GHL) and Virtual Health Library (VHL)
- Public Library of Science (PLoS)
- Scientific Electronic Library Online (SciELO).

"**TropIKA provides a window on the world of research relating to infectious diseases of poverty.**"

ROBERT G. RIDLEY, Director of TDR, at the Beijing launch of the new web portal, 30 October 2007.

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**"Equitable access" is the theme of Forum-11**

BEIJING – Research is key to providing equitable access to health services, said WHO Director-General Dr Margaret Chan, speaking at the 11th annual conference of the Global Forum for Health Research.

Chan called on research institutions and agencies “to do more” to answer basic questions about how to generally improve public health systems in developing countries and improve the health of the poor.

“If we want health to work as a poverty-reduction strategy, we must reach the poor. This has implications for research on equitable service delivery. If we want health to reduce poverty, we cannot allow the costs of care to drive impoverished households even deeper into poverty. This has implications for research on fair financing and social protection,”

WHO Director General Margaret Chan speaking at the Global Forum for Health Research.
said Chan in a keynote address at the 29 October-2 November 2007 conference focusing on the theme of equitable access to health services.

Chan highlighted several key examples of TDR-sponsored research that have improved access, notably recent TDR field research on innovative systems for community-directed interventions to get basic healthcare treatments to rural African populations. “Community-directed interventions have been used for more than 10 years to sustain high treatment coverage with ivermectin to treat river blindness in Africa,” Chan noted.

“Now, findings are demonstrating that this approach works for other health care treatments,” she added. “In communities using the approach, the number of children sleeping under a net tripled. The number of children receiving appropriate treatment for malaria within 24 hours after fever onset more than doubled. The number of pregnant women sleeping under a net increased fourfold.”

TDR-sponsored research of new rapid diagnostics for sexually transmitted infections such as congenital syphilis, also received kudos.

“Each year, half a million children are still-born because of congenital syphilis and another half a million are born with this disease,” Chan observed. “This occurs despite the fact that low-cost tools to prevent congenital syphilis have been available for more than 50 years. Again, we see a classic problem of service delivery. With TDR support, research evaluated numerous rapid diagnostic tests. Those found to work well were placed on the WHO procurement list so that governments could purchase them at low cost.”

The conference, which drew over 800 delegates to 8 plenaries and 46 parallel and special sessions, devoted each day of sessions to various aspects of the inequities theme. Life expectancy can differ by as much as 40 years between people in developed and developing countries, noted Pramilla Senanayake, the outgoing Chair of the Forum’s Foundation Council, speaking in the first plenary session devoted to a global review of equity issues.

Inequities in access to knowledge about research carried out elsewhere is the result of numerous factors, including language barriers, it was noted. For example, over 90% of papers dealing with the problems of the most vulnerable groups in Mexico are published in English.

At the same time, the failure of the traditional R&D system to come up with solutions for health problems in the developing world, underlines the importance of getting lower and middle income countries access to research resources. “We need to build our capacity and R&D to solve our own particular problems,” said Sri Lanka’s Minister of Science and Technology, Tissa Vitarana.

Senior policy-makers present at the conference – including representatives from countries as farflung as Tunisia and Costa Rica – also discussed ways of structuring national health research systems. In the final plenary session, Adel Mahmoud, Professor of Molecular Biology at Woodrow Wilson School, Princeton University, called for more support for basic research on diseases of the poor, but also stressed that money is not a silver bullet. “Dangling money in front of a scientist does not lead to discoveries,” he said.

Tim Evans, Assistant Director-General of WHO’s Information, Evidence and Research cluster and TDR Special Programme Coordinator, cited some positive trends, nonetheless. Research is becoming more ‘open-source’, he said, and health-related research is broadening to include disciplines beyond the traditional bio-medical fields (e.g. social or environmental determinants). Nonetheless, there is still much more to do, he said. “We must remain as, or even more, committed to ensuring that we move more quickly towards the more equitable distribution of research resources related to public health problems of the world’s disadvantaged populations.”

More TDR-related events at Forum-11

Special session on TB access

Dr Johannes Sommerfeld, TDR Scientist-Research Manager, co-organized and moderated a special session on Access to tuberculosis care in China on 30 October. Several researchers presented projects supported by the TDR Steering Committee on Social, Economic and Behavioural Research on public health challenges and access issues related to treatment and control of tuberculosis (TB), which has emerged as a major public health problem in the People’s Republic of China.

Operationalizing research for neglected diseases

While many high quality diagnostic tests for infectious diseases are available to patients in the developed world, many of the same tests are neither affordable nor accessible to patients in developing countries. Dr Rosanna Peeling, Manager of TDR’s diagnostics research and development, spoke 1 November at this parallel session, Promises and challenges of translating research on use of rapid syphilis tests into policy and practice. Based on TDR experiences testing and evaluating rapid syphilis tests in rural Haiti, she discussed the challenges and opportunities for reaching rural populations elsewhere with syphilis screening.

Contact: Jamie Guth

guthj@who.int
Integrated vector management in Africa: contributions of molecular entomology, biochemistry and social science to malaria control

PHILADELPHIA – The heavy toll of malaria in Africa requires intensified research on vector management and control. This was the theme of a TDR/MIM sponsored symposium at the 56th Annual Meeting of the American Society of Tropical Medicine and Hygiene (ASTMH), 4-8 November 2007. The symposium highlighted the value of integrated vector management (IVM). The symposium presented several of the issues related to key tools in the vector control arsenal, including: insecticide-treated bednets; chemical vector management which recommends the reintroduction of DDT (as per the national control programme in Nigeria); research on new drugs and chemicals to combat pesticide resistance; and increased knowledge of vector genetics and ecology, particularly of the West African Anopheles funestus.

The symposium was chaired by Dr Hilary Ranson, Liverpool School of Tropical Medicine, and Dr Olumide Ogundahunsi, WHO/TDR.

Socio-cultural practices and longevity duration of efficacy of insecticide treated bednets in Benin, Burkina Faso and Côte d’Ivoire – presented by Dr Julien M. Doannio of the National Institute for Public Health, Abidjan, Côte d’Ivoire.

Washing practices can have a significant impact on the efficacy of bednets, and those practices vary not only from country to country, but also from village to village. These were among the findings of a study on the longevity and efficacy of long-lasting insecticidal nets (LLINs). The study was conducted in defined areas of Benin, Burkina Faso and the Côte d’Ivoire, where household bednet utilization was more than 70% and frequent washings of the nets is the norm. The study also found that washing processes – soaking, type of soap used, quality and quantity of water, and drying processes – all impacted the efficacy and longevity of the LLINs. Efficacy declined in areas where a hard surface was used to scrub the nets in comparison to where washing was done by hand. Modern soaps also decreased efficacy more than traditionally prepared soaps. All nets showed a significant drop in insecticidal concentration after 6 months. The findings underlined the importance of sensitizing communities that use bednets to practices that will enhance the quality and durability of their LLINs.

Status of insecticide resistance in Kenya – presented by Dr Luna Kamau of the Kenya Medical Research Institute (KEMRI), Nairobi, Kenya.

Insecticide-treated bednets and indoor residual spraying have contributed to the recent dramatic reduction of malaria transmission in Kenya. However, there is concern about increased resistance to the insecticides as a result of this increased insecticide use. A proper understanding of the status of resistance and of resistance mechanisms is therefore important to making informed choices on insecticides use. This study, in which resistance was determined to four classes of insecticides approved by WHO for indoor residual spraying, provided an update on the status of insecticide resistance in Anopheles gambiae s.l. (s.l includes both strains of An. gambiae s.s. and An. arabiensis) and Anopheles funestus mosquitoes from western and central Kenya. The prevalence of the so-called ‘knock-down-resistance’ (kdr) mutation, which has been associated with resistance to pyrethroids and DDT in An. gambiae s.s., was also investigated. Over 98% mortality was observed for tests using all insecticides on both An. gambiae s.l. and An. funestus. Kdr rates were not significantly different between An. gambiae s.l. and the Kisumu strain control. Based on conventional criteria (susceptibility = mortality rates > 98 % 24 hours after exposure), no evidence for resistance was found, implying that vector control measures employing any of the insecticides tested would be unhampered by resistance. Observed frequencies of the kdr mutation (≈ 24 % in the an. gambiae s.s. strain) do not appear to compromise insecticide effectiveness. The use of pesticides in rice agricul-
Insecticide resistance also does not appear to encourage resistance in the mosquito populations. Findings from the study will provide a baseline to monitor the development of insecticide resistance.

**Insecticide susceptibility data in the rational use of DDT for malaria vector control in Nigeria** – presented by Dr Taiwo Samson Avalolola from the Nigerian Institute for Medical Research in Lagos.

This study on insecticide susceptibility and resistance to various kinds of chemical vector control tools led to a recent policy recommendation to reintroduce DDT into a rational, indoor-residual spraying (IRS) programme for malaria vector control in Nigeria. The three year study, conducted between 2003 and 2006, examined insecticide susceptibility/resistance of *Anopheles gambiae* s.s. in 36 sites and 5 ecological zones to a range of chemical vector control tools including: organophosphates, organochlorines and pyrethroids. The study found a high level of mosquito resistance to organophosphates and to the organochlorine, dieldrin, but low levels of resistance to DDT and pyrethroids in field populations of *A. gambiae* s.s.

Presently there are 12 insecticides recommended by the WHO Pesticide Evaluation Scheme for indoor residual spraying against malaria vectors, one of which is DDT. Of these, only DDT, which has the longest residual effect (>6 months), is not yet used in Nigeria. The reintroduction of DDT into the Nigerian malaria vector control programme is expected to provide a mosaic defence against the development of resistance.

**The ecological genetics of the West African Anopheles funestus** – presented by Dr Sagnon NFale, Centre National de Recherche et de Formation sur le Paludisme (CNRFP), Ouagadougou, Burkina Faso.

*Anopheles funestus* is increasingly recognized as an important malaria vector across Africa. Previous studies in Burkina Faso have suggested the existence of two sympatric but reproductively isolated taxonomic units (Folonzo and Kiribina chromosomal forms).

This study of the ecological genetics of *An. funestus* in West Africa, focused on resting behaviour and host preference of the different chromosomal forms. While in Burkina Faso, molecular data are congruent with cytogenetic data, in Senegal, molecular analysis did not find any difference between these forms. It is therefore crucial to elucidate the taxonomic status of these chromosomal forms towards a better understanding of their role in malaria transmission. The study involved the colonization of *An. funestus* at the CNRFP, which is considered a great success, as it is only the second known colonization of this mosquito in the world.

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### Also at ASTMH:

#### Development and evaluation of diagnostics for tropical diseases

Another TDR-organized symposium brought together scientists from various regions of the developing world to review progress on TDR-related efforts to develop and evaluate diagnostics for selected tropical diseases. Presentations included the following:

- **Diagnosis of Visceral Leishmaniasis - Where are we?**
  >> Dr Shyam Sundar, Kala-azar Research Center, India.

- **Evolution of diagnostics on human African trypanosomiasis, with special emphasis on sleep-wake disturbances**
  >> Dr Alain Buguet, Université Claude-Bernard Lyon, France.

- **Utility of existing diagnostic tests for *S. mansoni* and *S. haematobium* in areas of low intensity transmission**
  >> Dr Pauline Mwinzi, Kenya Medical Research Institute, Kisumu, Kenya.

- **Multi centre evaluation of dengue IgM tests**
  >> Dr Sutee Yoksan, Mahidol University at Salaya, Thailand.

Organizer - Dr Rosanna Peeling, TDR

### Other TDR presentations at ASTMH scientific sessions

- **Clinical studies in Sudan, Leishmaniasis Vaccine**
  >> Dr Hashim Ghalib.

- **Combination liposomal amphotericin B (AmBisome®AmB) and miltefosine (MF) for the treatment of visceral leishmaniasis (VL) in Northern Bihar, India**

- **Monitoring the efficacy and safety of artesunate+ amodiaquine (AS+AQ) over six years using the WHO in vivo protocol and a simple pharmacovigilance study in the district of Oussouye, Casamance, Southern Senegal**

- **Relationship between treatment outcome and molecular markers of resistance in *Plasmodium falciparum*: a systematic review and meta-analysis of published data**

- **Efficacy of artesunate-amodiaquine (ASAQ) for the treatment of uncomplicated falciparum malaria in sub-Saharan Africa: an individual patient data meta-analysis (IPDM) in 3,455 patients**
  >> Dr Piero Olliaro.

- **Evaluation of commercially available dengue IgM tests by a WHO/PDV Laboratory Network**

- **Diagnostics for sexually transmitted infections**
  >> Dr Rosanna Peeling.
meetings

Innovation in Africa topic at Global Creative Leadership Summit

"African scientists should not only be testing health products developed elsewhere, they should be part of the innovative process," said TDR Director Dr Robert Ridley, speaking at the Global Creative Leadership Summit in New York City, 23-25 September 2007.

The cross-disciplinary event, developed by the Louise T Blouin Foundation in collaboration with the United Nations Office for Partnerships, focused on how the world community can harness the technological revolution underway in the developed world to address poverty and stimulate economies in Africa.

Standing Committee urges advance on TDR strategy

TDR’s Standing Committee has urged that the new TDR 10 Year Strategy advance rapidly into full implementation; in terms of administration and personnel, operational timelines, and other matters. As of 1 January 2008, the Strategy became the legal framework for all TDR activities.

The Standing Committee, meeting in Berlin, 10-11 October 2007, also asked that plans for strengthened collaboration with each of TDR’s four co-sponsoring agencies be developed as part of the new Strategy implementation. Committee members stressed that such plans, including delivery milestones, would strengthen the relationship between the Special Programme and its major co-sponsors: UNICEF, UNDP, the World Bank and WHO.

The 82nd session of the Standing Committee, TDR’s senior executive oversight board, was hosted by the Government of Germany, and was largely devoted to a review of the actions needed to implement the TDR strategy, approved in June 2007, by TDR’s overall governance body, the Joint Coordinating Board. The Standing Committee urged rapid action on issues such as: appointment and recruitment of required new staff and completion of indicators and milestones identified in the strategy’s business plan and 11 business lines.

The Committee also welcomed TDR’s engagement in the Intergovernmental Working Group on Public Health, Innovation and Intellectual Property, convened by WHO and its partners in Geneva in November 2007. Finally, financial issues and governance matters were reviewed as were plans for the 31st session of the TDR Joint Coordinating Board (JCB) in June 2008 in Rio de Janeiro, Brazil.

The Standing Committee reviews TDR’s activities twice during the year. Following the next session in Spring 2008, it will report to the 2008 meeting of the JCB. The Committee comprises representatives of TDR’s four co-sponsoring agencies. Other ex-officio participants in the meetings include: the Chair and Vice-Chair of the JCB; Chair of the TDR Scientific and Technical Advisory Committee (STAC), and three JCB representatives – one from a country belonging to the Organisation of Economic Co-operation and Development (OECD), and two from disease endemic countries, including sub-Saharan Africa.

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For more information: www.creativeleadershipsummit.org/
Print and multimedia publications now available from TDR

All TDR publications are available free of charge upon request by faxing or mailing the publication order form accompanying this issue, or by email to tdr@who.int.

Also available for download from the TDR website at: www.who.int/tdr/publications

Five part TV news series on DVD
Scripts also available on the TDR website in Arabic, Chinese, French, Portuguese and Russian
TDR/DVD/07.1

The new 5-part TV news series takes viewers to far-flung regions of the globe to see how TDR-sponsored research is helping to combat infections such as syphilis, malaria and river blindness, which are responsible for an enormous burden of disease in the developing world. Produced by TDR through Rockhopper TV productions, the news series is available free for non-commercial purposes of broadcast and viewing to educational institutions, TV stations, NGOs and the general public.

The five parts include:
HAITI: Congenital syphilis on the way out
NIGERIA: Malaria, the killer of children
NIGERIA: Empowering communities to fight disease
KENYA: Malaria franchise shops
KENYA: Natural plant products

Available to view and order:
www.who.int/tdr/about/press_center/default.htm

Assessment of the safety of artemisinin compounds in pregnancy

WHO currently recommends that artemisinin compounds should only be used in the 2nd and 3rd trimesters of pregnancy "when other treatments are considered unsuitable" – a recommendation based upon two informal consultations convened by WHO and TDR in 2002. This current report is the product of a subsequent 2006 consultation to review the findings of animal studies of artemisinin performed since 2002 and consider their impact on clinical use of the drug in pregnancy. The consultation also discussed the possibility of establishing antimalarial pregnancy registries.

Reporte sobre la enfermedad de Chagas
96 pp., 2005 (TDR/GTC/06)
In Spanish

A pesar de que la interrupción de la transmisión de la enfermedad de Chagas se ha logrado en buenas partes de América latina con una significativa reducción del número de individuos infectados, la Enfermedad de Chagas sigue siendo una amenaza para la salud de 28 millones de personas. El reporte es producto del grupo de trabajo científico que fue iniciado en Abril 2005 en Buenos Aires, Argentina. El proceso incluyó mas de 66 expertos representando 17 países. El reporte describe la situación actual y el conocimiento de la enfermedad, define las prioridades de investigación para mejorar el diagnóstico, tratamiento, prevención y control de la enfermedad.

Despite the interruption of transmission in sizeable areas of Latin America and a significant decline in the number of infected persons, Chagas disease continues to be a health threat for an estimated 28 million people on the continent. This report is the product of a Scientific Working Group that was initiated by TDR and PAHO in Buenos Aires in April 2005. The consultation included 66 experts from 17 countries. The report outlines the current status of the disease and defines research priorities needed to improve diagnosis, treatment, prevention and control.
Effective project planning and evaluation in biomedical research

TRAINERS VERSION:

185 pp., 2007 (TDR/RCS/PPE/T/07.1), 41 pp., 2007 (TDR/RCS/PPE/T/07.2) and 127 pp., (TDR/RCS/PPE/T/07.3)

A 3-volume training set is now available. The training manual provides the slides to be presented at the skill-building course, accompanying text, and practical tips to support the trainers during the presentations. The step-by-step guide has the same content as the guide for participants but it also includes practical tips for trainers. The train-the-trainers manual is based upon a course developed with the South African Medical Research Council. Available for download from the TDR site. Hard copies restricted to course participants.

Bien planifier et évaluer les projets en recherche biomédicale

VERSION PARTICIPANTS (English already published):
Manuel de formation et Guide pas à pas (2 livres)

119 pp., 2005 (TDR/RCS/PPE/05.1) and 23 pp., 2005 (TDR/RCS/PPE/05.2)

Maintenant disponibles en français et en anglais, ces deux volumes Manuel de formation et Guide pas à pas suivent toutes les présentations et conduisent les participants à travers chaque étape de la planification de projet et du processus d’évaluation. Téléchargement disponible depuis le site web de TDR et distribution des exemplaires réservée aux participants des cours.

Now available in French as well as English, this 2-volume Training manual and Step-by-step Guide, follows all presentations and leads participants through each step of the project planning and evaluation process. Available for download from the TDR site. Hard copies restricted to course participants.

• e-mail: tdr@who.int
• fax or mail the publication order form accompanying this issue.

Ten Year Vision and Strategy

32 pp., 2007 (TDR/GEN/06.5/EN/Rev.2)
In English, French, Chinese and Portuguese

TDR’s new strategy, endorsed by its Joint Coordinating Board in June 2007, is guided by a vision of fostering “an effective global research effort on infectious diseases of poverty in which disease endemic countries play a pivotal role.” This document explains how the new TDR vision and strategy responds to a changing global research environment. It also describes the three major strategic functions that will underpin activities for the coming ten years – stewardship, empowerment and research on neglected priority needs.

TDR Business Plan 2008-2013

61 pp., 2007 (TDR/GEN/EN/07.1/Rev.1)
In English, French, Chinese and Portuguese

In order to implement its Ten Year Vision and Strategy, TDR is introducing a limited number of business lines, each supported by a plan of deliverables, timelines, milestones and partnerships. Eleven business lines are planned for the 2008-2009 biennium; two correspond to the strategic functions of stewardship and empowerment, and the other nine will correspond to the strategic function of research on neglected priority needs, which may change over time.
In collaboration with others/available through TDR

- **Evaluating diagnostics: the VL guide**
  *Nature Reviews Supplement: Microbiology*  
  Vol. 5, No. 11, November 2007

  This supplement on evaluating diagnostics for visceral leishmaniasis (VL) is the third in a series of user-friendly operational guides produced in a collaboration between TDR and *Nature Reviews* explaining how to conduct evaluations of diagnostic tests for infectious diseases that are of public health importance in the developing world.

  To download: http://www.nature.com/nrmicro/journal/v5/n11_supp/index.html#fd

- **Health related biotechnology in Africa: ethical, legal, and social implications (ELSI) of transfer and development**
  *African Journal of Medicine and Medical Sciences*  
  Supplement (36) 2007

  As African institutes become involved in biotechnology research and applications, there is a need to consider the ethical, legal and social implications of both scientific and technological advances developed on the continent or elsewhere, as well as their use/application. This supplement, based upon an International Workshop-Symposium on Health-Related Biotechnology in Africa: Ethical, Legal and Social Implications (ELSI) of Transfer and Development, held 4-6 April 2007, in Ibadan, Nigeria, was produced with the support of TDR.

  Download from TDR: http://www.who.int/tdr/topics/social-research/articles07_afric_journal.htm

- **Helminth drug initiative**
  *Expert Opinion on Drug Discovery*  
  Vol. 2, No. s1, October 2007

  WHO is supporting a drive to scale up the treatment of helminth infections. However, the kinds of drugs available are extremely limited, and there is always the threat of resistance developing to drugs that are now being used. This special issue of *Expert Opinion on Drug Discovery* documents the rationale for the Helminth Drug Initiative (HDI), initiated by TDR to stimulate drug discovery in this area. It provides reports on technical consultations and recommendations.

  To download or order: http://www.expertopin.com/toc/edc/2/s1

- **Equitable access to healthcare and infectious disease control: concepts, measurement and interventions**
  *Conference News, United Nations Research Institute for Social Development (UNRISD)*  
  No. 19, September 2007

  The symposium, organized in collaboration with TDR, brought together 31 international experts. Sessions discussed the relationship between access to health care and social determinants of health; reviewed ways of measuring and improving inequities in access; and summarized existing approaches within the UN as well as needs and gaps. It also highlights the contribution research on access to health care can make to the attainment of the Millennium Development Goals.

  To download: http://www.unrisd.org/80256B3C005BCCF9/HTPublications?OpenForm&view=type&count=1000&expand=4#4

- **Recommendations of the informal consultation on issues for clinical product development for human African trypanosomiasis**
  [Geneva, Switzerland 9-10 September 2004]  
  70pp., 2007 (WHO/CDS/NTD/IDM/2007.1)

  Researchers involved in clinical trials for the evaluation or development of new treatment modalities for human African trypanosomiasis (HAT), also known as “sleeping sickness,” convened in an Informal Consultation to review and discuss available data, and to develop a consensus framework for planning, conducting and analysis of clinical trials. The recommendations are in most cases also applicable or adaptable to the evaluation of new diagnostics. The Consultation also discussed the need for improving comparability of published data on drug efficiency, and made recommendations for the analysis and reporting of drug efficacy of treatment regimes under evaluation.

  To order: bookorders@who.int
TOPICS IN INTERNATIONAL HEALTH

Topics in International Health (TIH) is a series of educational materials produced by The Wellcome Trust in collaboration with TDR for medical and life sciences students, their teachers and other professionals. The following eight CD-ROMs are now available to order through TDR:

- **Dengue**
  2005, The Trustee of the Wellcome Trust
  ISBN 0 85199 494 6
  Developed in collaboration with TDR, the CD-ROM introduces complicated concepts such as the immunopathogenesis of dengue haemorrhagic fever using interactive graphics and animations.

- **Human African Trypanosomiasis**
  2007, The Trustee of the Wellcome Trust
  ISBN 9781841290653
  Developed in collaboration with TDR, these illustrated tutorials help the user recognize clinical features of the disease, understand disease pathology, and learn about diagnostic tests.

- **Leishmaniasis**
  2000, The Trustee of the Wellcome Trust
  ISBN 0851993702
  This CD-ROM covers the range of cutaneous and visceral manifestations of the diseases, their clinical features, diagnosis, and treatment, epidemiology, transmission and control, through interactive tutorials.

- **Leprosy**
  1998, The Trustee of the Wellcome Trust
  ISBN 0851993702
  This CD-ROM, which includes interactive tutorials, features all epidemiological data on leprosy and a comprehensive guide to all aspects of ocular leprosy.

- **Malaria (3rd edition)**
  2007, The Trustee of the Wellcome Trust
  ISBN 9781841290645
  The third edition of this bestselling CD-ROM is substantially updated and expanded to reflect recent changes in the field along with introductory material. It contains interactive tutorials and over 900 images.

- **Schistosomiasis**
  1998, The Trustee of the Wellcome Trust
  ISBN 085199248X
  This illustrated introduction to schistosomiasis covers the relation between the schistosome life cycle and the maintenance of transmission, and the effect this has on prevention and control modes.

- **Sexually Transmitted Infections**
  2003, The Trustee of the Wellcome Trust
  ISBN 085199310
  This fully revised, new edition of the bestselling CD-ROM provides a general introduction to sexually transmitted infections (STIs) in tropical areas along with interactive tutorials.
**Latest grants**

### Implementation research

#### NEW GRANTS

These grants will be funded for 12 months in the first instance, and for an additional 1 year if sufficient progress has been made in the first 12 months toward reaching the scientific objectives, and if sufficient funds are available.

**A60485**
Oladele B. Akogun
Federal University of Technology, Yola, Nigeria.
Role of rapid diagnostic tests for malaria in community level management of under-five febrile illnesses in Northeastern Nigeria.
US$ 47 340

**A70195**
Ivo Castelo Branco Coelho
Faculdade de Medicina da Universidade Federal do Ceará, Fortaleza-Ceará, Brazil.
Implementation of guidelines for triage and care of dengue cases in Brazilian clinical study sites.
US$ 25 000

**A70179**
Pascalina Chanda
National Malaria Control and Research Centre, Lusaka, Zambia.
The effectiveness of using RDTs and ACTs for home management of malaria in children under five years old in Zambia.
US$ 45 345

**A70170**
Lucy Chai See Lum
Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia.
Validation of new dengue guidelines in Malaysia.
US$ 25 600

**A70175**
María Andrea Nuñez
Centro Nacional de Diagnóstico y Referencia, Ministry of Health, Managua, Nicaragua.
Assessment of existing dengue guidelines and evaluation of improved dengue clinical guidelines in Nicaragua.
US$ 25 000

**A70210**
Sidiomoun Bienvenu Sirima
Centre National de Recherche et de Formation sur le Paludisme, Ouagadougou, Burkina Faso.
Home and community management of malaria and pneumonia in children under five in Burkina Faso.
US$ 242 100

**A70283**
Halidou Tinto
Institut de Rechercher en Sciences de la Santé/Centre Muraz, Bobo Dioulasso, Burkina Faso.
Pharmacovigilance for artemisinin-based combination treatments in Africa.
US$ 98 300

**A70196**
Eli Villegas
Universidad de los Andes, Trujillo, Venezuela.
Assessment of existing dengue guidelines and evaluation of improved dengue clinical guidelines in Venezuela.
US$ 25 000

### RENEWED GRANTS

**A60461**
Shireen Akhter
National Institute of Preventive and Social Medicine (NIPSOM), Dhaka, Bangladesh.
Cost-effectiveness of residual spraying, treated bednets and environmental management for sandfly control in Bangladesh.
US$ 20 000

**A00638**
Daniel Adjei Boakye
Noguchi Memorial Institute for Medical Research, University of Ghana, Accra, Ghana.
Trends in levels of transmission-and infection with W. bancrofti during mass treatment with ivermectin and albendazole.
US$ 86 991

**A60483**
Murari Lal Das
B. P. Koirala Institute of Health Sciences, Dharan, Sunsari, Nepal.
Cost-effective integrated vector management as a contribution to the visceral leishmaniasis (VL) elimination initiative.
US$ 20 455

**A40666**
Pradeep Das
Rajendra Memorial Research Institute of Medical Sciences (ICMR), Patna, India.
Implementation Strategies for Visceral Leishmaniasis treatment in India.
US$ 25 000

**A60546**
Pradeep Das
Rajendra Memorial Research Institute of Medical Sciences (ICMR), Patna, India.
Cost-effective vector management as a contribution to the visceral leishmaniasis (VL) elimination initiative in the Indian sub-continent.
US$ 19 400

**A50518**
Mohan Digambar Gupte
Indian Council of Medical Research, National Institute of Epidemiology, Chennai, India.
PHI study on "uniform-MDT regimen for all leprosy patients."
US$ 50 000

**A20189**
John O. Gyapong
Ministry of Health, Accra, Ghana.
US$ 393 000

**A20133**
Margaret Gyapong
Ministry of Health, Accra, Ghana.
Impact of large scale rectal artesunate deployment in the initial management of non per OS ill under five children.
US$ 27 180

**A60435**
Anand B. Joshi
Institute of Medicine, Tribhuvan University, Kathmandu, Nepal.
Implementation Strategies for Visceral Leishmaniasis treatment in Nepal.
US$ 25 048

**A60547**
Anand B. Joshi
Institute of Medicine, Tribhuvan University, Kathmandu, Nepal.
Cost-effective integrated vector management as a contribution to the visceral leishmaniasis (VL) elimination initiative in the Indian sub-continent.
US$ 20 000

**A60443**
Dinesh Mondal
ICDDR, Centre for Health and Population Research, Parasitology Laboratory, Dhaka, Bangladesh.
Implementation strategies for visceral leishmaniasis treatment in Bangladesh.
US$ 25 000

**A60482**
Dinesh Mondal
ICDDR, Centre for Health and Population Research, Parasitology Laboratory, Dhaka, Bangladesh.
Management of pre-existing program, assessment need and community perception for vector control in Bangladesh.
US$ 20 000

**A50525**
Dickson Shy Nsagha
Groupe de Recherche en Santé Publique (GRSP) Yaoundé, Cameroon.
Correct home-based treatment of malaria in children less than five years with prepackaged drugs in an urban setting.
US$ 5 093

**A20141**
George William Pariyo
Makerere University Institute of Public Health, Kampala, Uganda.
Home and community management of malaria and pneumonia in children under five: a cluster randomized controlled trial in Uganda.
US$ 422 360
A61119
Pascal Tshindele Lutumba
Institut National de Recherche Bio-Médicale, République démocratique du Congo.
Epidemiology and control of schistosomiasis in the Democratic Republic of the Congo.
US$ 59 200

A61011
Delia Rebeca Rivera-Canales
National Autonomous University of Honduras.
Mycobacterium tuberculosis genotype, drug susceptibility and immune response of Pulmonary TB patients of Honduras.
US$ 42 700

RENEWED GRANTS
A50845
Stafford Nikolambila Kibona
National Institute for Medical Research, Tabora Research Centre, Tanzania.
Drug sensitivity of T. b. rhodesiense isolates and the role of domestic animals in epidemiology of HAT in Tanzania.
US$ 14 000

A30933
Nicolas Mbongo
Laboratoire National de Santé Publique, Congo.
Research capacity strengthening for anti-trypanosomal compounds from medicinal plants.
US$ 15 000

A30930
Issa Nebie
Centre National de Recherche et de Formation sur le Paludisme, Burkina Faso.
Etude de l'activité antipaludique des plantes utilisées en médecine traditionnelle dans une région humide du BFA.
US$ 47 385

A41490
Omran Fadi Osman
University of Khartoum Faculty of Science, Sudan.
Transmission of visceral leishmaniasis in eastern Sudan: studies on reservoir hosts and vectors.
US$ 27 000

A41430
Jean-Bosco Ouedraogo
Institut de Recherche en Sciences de la Santé, Burkina Faso.
Improvements of indirect haemagglutination assay as sustainable tools for schistosomiasis diagnosis and control.
US$ 46 790

Re-entry grants

A61005
Luís Gabriel Brieba De Castro
Center for Advance Studies of the National Polytechnic Institute (Cinvestav), Mexico.
Transcription in Trypanosoma cruzi's kinetoplast: a potential target for rational drug design against Chagas disease.
US$ 20 000

A60983
Carlos Andrés Buscaglia
Instituto de Investigaciones Biotecnologicas, Argentina.
Structural/functional analysis of the surface molecules from Trypanosoma cruzi intra-cellular forms.
US$ 14 000

Research capability strengthening

Programme grants

NEW GRANTS
A60982
Seni Kouanda
Institut de Recherche en Sciences de la Santé, Burkina Faso.
Etude prospective, ouverte, comparative entre les régimes antituberculeux et ARV contenant la nevirapine VS Efavirenz.
US$ 61 023

A60978
Carla Polycarpo
Universidade Federal do Rio de Janeiro, Brazil.
RNAi ligases and tRNA modification enzymes of trypanosomatids as possible drug targets.
US$ 27 000

A61003
Dorothy Kyerewah Yeboah-Manu
Noguchi Memorial Institute for Medical Research, Ghana.
Molecular epidemiology of tuberculosis in Ghana.
US$ 11 200

A60999
Dario S. Zamboni
Universidade de Sao Paulo, Brazil.
Detection and restriction of T. cruzi and L. amazonensis infection by intracellular Nod-like receptors.
US$ 15 500

RENEWED GRANTS
A50904
Stephen Collins Ahorlu
Noguchi Memorial Institute for Medical Research, Ghana.
Community intervention to reduce malaria-related morbidity and mortality in the Shime sub-district in Ghana.
US$ 11 000

A50839
Luciana de Oliveira Andrade
Universidade Federal de Minas Gerais, Instituto de Ciencias Biologicas, Brazil.
Study of the mechanism of T. cruzi entry and development in non-phagocytic cells.
US$ 8 500

A50993
Daniella Bartholomeu
Universidade Federal de Minas Gerais, Instituto de Ciencias Biologicas, Brazil.
MASP gene family of Trypanosoma cruzi: from in silico to wet-bench characterization.
US$ 14 000

A50967
Alia Benkahla
Institut Pasteur de Tunis, Tunisia.
Global analysis of leishmania genes expression using SAGE libraries.
US$ 15 000
Project development grant

NEW GRANTS

A60977
Olivier Basena
Institut National de Santé Publique.
Analyse des coûts de la prise en charge du Paludisme au Burundi et Renforcement des compétences de l’INSP.
US$ 10 000

A60979
Thembal Mzilahowa
Malawi-Liverpool-Wellcome Trust Clinical Research Programme.
Malaria vector breeding sites and assessing their impact on local malaria risk.
US$ 13 212

A61091
Lucy Wanjiru Kariuki
University of Nairobi, Kenya.
PhD: Effect of maesnin on glucose oxidation in bloodstream and procyclic Trypanosoma brucei.

A61093
Edwin Kibet
KEMRI - Kisumu, Kenya.
PhD: The role of accreditation and TQM as a catalyst for continuous improvement in Kenya’s research laboratories.

A61095
Sujan B. Marahatta
Dhulikhel Medical Institute, Nepal.
PhD: Prevalence of tuberculosis infection relation to socio-demographic, environmental & economic determinants central Nepal.

A61101
Osbert Namafente
National Malaria Control Centre, Zambia.
MSc: Systematic entomology.

A61102
Lucas E. Matemba
NIMR-Tabora Research Centre, Tanzania.
PhD: Investigating the epidemiology of human African trypanosomiasis in western Tanzania.

A61106
Bryson A. Ndenga
KEMRI - Kisumu, Kenya.
PhD: Ecological characterization of Anopheles larval habitats in western Kenya highlands.

A61112
Jared Maska Siso
Institute of African Studies, Kenya.
PhD: Pharmaceutics: socio-cultural interpretation and appropriation of anti-malarials in rural Kenyan community.

A61113
Tahere Taheri
Pasteur Institute, Iran.
PhD: Gene disruption of type1 signal peptidase/evaluation of its role in growth, survival, infectivity protection in L. major.

A61115
Sammy Wambua
KEMRI - Kisumu, Kenya.
PhD: Band 3 as a molecular target for treating malaria.

Research training grants

NEW GRANTS

A61086
Joel Bazira
Mbarara University, Uganda.
PhD: Characterisation and drug resistance pattern of mycobacteria isolated from TB patients in Mbarara.

A61067
Aboma Kidist Bobosha
Armauer Hansen Research Institute, Ethiopia.
PhD: Evaluation of M.leprae unique antigens for early detection of leprosy and cytokine profile of reactive patients.

A61088
Mahamadou Ibrahim
Université Abdou Moumouni de Niamey, Niger.
PhD: Gene expression of Plasmodium falciparum within anopheline mosquito (Niger, West Africa).

A61118
Fredrick George Kabbage
Kamuli District Local Government, Uganda.
PhD: The effect of prolonged use of insecticide-impregnated bednets on the biting behavior of malaria mosquitoes in Kamuli.

NEW GRANTS

A41392
Dongmei Zhang
Second Military Medical University Department of Etiologic Biology, China.
Evaluation of a pichia-expressed binding domain of Pf EBA-175 as a component of malaria vaccine combination.
US$ 15 000

A41418
Marcelo Távora Mira
Pontificia Universidad Catolica del Ecuador, Ecuador.
A study of host genetic risk factors for leprosy susceptibility.
US$ 16 500

A50987
Guillermo R. Labadie
Instituto de Química Orgánica de Síntesis, Argentina.
Ergosterol biosynthesis as target of antiparasitic agents.
US$ 3 000

A51005
Ana Acacia Pinheiro
Universidade Federal do Rio de Janeiro, Instituto de Biofísica Carlos Chagas Filho, Brazil.
Molecular mechanisms triggered by P. falciparum derived GPs in cells of innate immune system: involvement of TLRs.
US$ 19 000

A50880
Rodrigo Pedro P. Soares
Centro de Pesquisas René Rachow, Fundação Oswaldo Cruz - FIOCRUZ, Brazil.
Role of L. chagasi & L. braziliensis LPGs & GIPs in the innate immune response in murine neutrophils & macrophages.
US$ 20 000

A41349
Hlaing Myat Thu
Department of Medical Research, Virology Research Division, Myanmar.
Sentinel surveillance of dengue in endemic regions of Myanmar.
US$ 3 000

A41118
Fredrick George Kabbage
Kamuli District Local Government, Uganda.
PhD: The effect of prolonged use of insecticide-impregnated bednets on the biting behavior of malaria mosquitoes in Kamuli.

A61091
Lucy Wanjiru Kariuki
University of Nairobi, Kenya.
PhD: Effect of maesnin on glucose oxidation in bloodstream and procyclic Trypanosoma brucei.

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A61095
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A61097
Lucas E. Matemba
NIMR-Tabora Research Centre, Tanzania.
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A61101
Osbert Namafente
National Malaria Control Centre, Zambia.
MSc: Systematic entomology.

A61106
Bryson A. Ndenga
KEMRI - Kisumu, Kenya.
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A61112
Jared Maska Siso
Institute of African Studies, Kenya.
PhD: Pharmaceutics: socio-cultural interpretation and appropriation of anti-malarials in rural Kenyan community.

A61113
Tahere Taheri
Pasteur Institute, Iran.
PhD: Gene disruption of type1 signal peptidase/evaluation of its role in growth, survival, infectivity protection in L. major.

A61115
Sammy Wambua
KEMRI - Kisumu, Kenya.
PhD: Band 3 as a molecular target for treating malaria.
The Royal Society of Tropical Medicine and Hygiene celebrated its 100th anniversary in London 13-15 September 2007 in ceremonies that acknowledged the contributions of many TDR partners and grantees. TDR was honoured to be a part of the conference, where Her Royal Highness, Princess Anne, Princess Royal of the British Royal Family was guest speaker.

1. Guest speaker HRH, Princess Anne, The Princess Royal, meets with (from left) RSTMH President Prof David Molyneux; Dr Brian Greenwood, London School of Tropical Medicine and Hygiene; Dr Adrian Hopkins of Christoffel Blindenmission, Nairobi; TDR Director Dr Robert Ridley; and Dr Lorenzo Savioli, Director of the WHO Department of Neglected Tropical Diseases.

2. Sir Herbert Gillies (on left), longstanding member of TDR committees and JCB observer on behalf of the Government of Malta, receives the Manson Medal Award, the Society’s highest mark of distinction from Dr. Molyneux.

3. Dr Uche Amizago, Director of African Programme for Onchocerciasis Control (APOC), a close collaborator with TDR, speaks at a panel session.

4. Dr Adetokunbo Lucas (left), TDR Director from 1976-1986, receives the Society’s Centenary Medal for lifetime achievement in tropical medicine.

TDR’s new strategy is now in place! Complete details on plans, grants and timetables are on the web at www.who.int/tdr.