Phase III

TDR’s third decade was one of expansion — new diseases, a new sponsor (UNICEF), and expanded outreach and collaborations. Dengue and TB were added to the portfolio, as well as diagnostics for TB and sexually transmitted diseases. TDR helped incubate and launch several new public–private partnerships for drug and diagnostics development, and led a major initiative in global drug discovery research networks. The programme also stimulated global collaborations in genomics, including sequencing of the *A. gambiæ* genome. Field research was extended to help scale up interventions, and social, economic and behavioural research played an enhanced role. TDR moved into broader spheres of capacity-strengthening, including good research practices, ethical review, South–South collaborations, and international research networks linked by new technologies.
In the world

Globalization became the driving force of politics and economies worldwide, and a powerful factor shaping patterns of development. The privatization of many formerly state-controlled economies reflected the growing recognition that the public sector cannot do it all. A similar trend evolved in health care and health research and led to the growth of new public–private partnerships (PPPs), including several nurtured by TDR.

The turn of the millennium was marked by hopes for a new era of peace, but brutal conflicts continued in many regions of the world. The Millennium Development Goals (MDGs), set by the UN General Assembly in 2000, articulated concrete targets to address key barriers of poverty and inequity, gender inequality, environmental degradation and diseases such as TB/HIV and malaria. But strategies to meet those targets often fell short of the mark. The 2002 World Summit on Sustainable Development in Johannesburg set out a roadmap for greater environmental responsibility, and yet runaway greenhouse gas emissions today make climate change a major global concern. On a more positive note, decentralization and democratization in many parts of the world gave more people a direct say in their lives and destinies. The internet has made the currency of knowledge more widely available and increased mobility has stimulated knowledge exchange and cultural sensitivity. In developing countries, the ranks of trained professionals, including health professionals and scientists, are swelling. Asia has continued to prove itself as an economic and technological powerhouse, and there is strong interest and investment in science and technology not only in Asia, but also in Latin America (such as in Brazil and Mexico), Africa (such as in Kenya, Nigeria and South Africa); and the eastern Mediterranean (for instance, in Tunisia, Egypt and the Islamic Republic of Iran).

In public health

Old diseases like TB were re-emerging, particularly among the poor and in HIV-positive populations. Malaria resurged on the back of resistance to old drugs. An epidemic of dengue caused public health concern in Latin America and Asia, and at the same time, previously unheard of diseases such as severe acute respiratory syndrome (SARS) and avian flu appeared, often stimulated by social, environmental and climatic changes. WHO was called upon increasingly to respond to humanitarian health crises from disease outbreaks as well as to crises generated by extreme weather, wars and natural disasters.

Dr Gro Harlem Brundtland, Director-General of WHO from 1998 to 2003, set four strategic directions for WHO: reducing the burden of disease; reducing risks to health; creating sustainable health systems; and developing enabling policies in the health sector. The 2002 World Health Report focused on the global effort to better define the burden of disease for key risk factors and also define cost-effective strategies to reduce risks, many of them associated with unhealthy lifestyles, such as tobacco use and degraded environments.
Dr Brundtland’s successor, the late Dr LEE Jong Wook, launched the ‘3 × 5’ initiative to bring new anti-retroviral drugs to developing countries. The year 2000 also saw the establishment of the WHO-led Commission on Macroeconomics and Health, which placed a focus on cost-effective health systems as well as promoting the need for more research.

As in the broader economy, the accelerated development of technologies and innovations in the health sector demanded increased levels of specialization and investment that broad multi-functional public sector institutions could not provide alone. At the same time, private sector investment in diseases that were global public health priorities had been stagnant or declining. Yet, out of a seeming impasse and perhaps from a shared sense of need and obligation, new forms of PPP would emerge at the turn of the millennium. PPPs welded private sector resources to public health priorities — and public sector accountability. Major partnerships created around key health care priorities included: The Global Fund for AIDS, TB and Malaria; the GAVI Alliance; Roll Back Malaria; and the Stop TB Partnership. TDR, meanwhile, participated in the incubation of several major research-oriented PPPs. A key force behind this new trend was the Bill and Melinda Gates Foundation, which was founded in 2000. Almost overnight, the Gates Foundation became the single most significant non-governmental sponsor of health care initiatives, investing nearly US$ 8 billion in global health, including US$ 2 billion in infectious disease control and nearly US$ 800 million in health research. This new era of PPPs required both WHO and TDR to carefully define their roles, in order to complement and not collide with these new global health partnerships and entities. Yet, despite the plethora of new global initiatives, the delivery of good primary health care remained a major challenge in many developing countries. As the decade progressed, the weakness of ‘vertical’ programmes driven by donors became more apparent. Community-directed and home-based health care approaches, including models fostered by TDR for onchocerciasis and malaria, gained wider interest and attention.

In TDR — catalyzing partnerships and collaborations

A third external review in 1997/98, as well as the departure of Dr Tore Godal and the arrival of Dr Carlos Morel, a former president of FIOCRUZ with a background in molecular biology, biotechnology and national policy making, heralded yet another shift in the tenor and tone of TDR. Indeed, if the foundation decade was focused on disease portfolios, and the second decade increased emphasis on field research, the third decade of the programme would re-focus on product development and partnerships for new research efforts. Although TDR had always operated as a network-based organization, the programme would assume a greater role as a catalyst and leader of initiatives in drug development, diagnostics, genomics and research capacity strengthening that would,
in many cases, go on to be formally developed by other entities. In recognition of TDR’s impact on health and its vital contribution to attaining the MDGs, a new UN co-sponsor the United Nations Children’s Fund (UNICEF) committed its support in 2003.

A ‘trans-disease’ approach was introduced, with activities organized in business-like managerial structures, with reference to both a matrix of diseases and functional areas of research (Morel, 2000). Priority setting was driven both by identifiable research opportunities and the needs posed by the burden of disease. One immediate issue was the global re-emergence of both TB and dengue in epidemic proportions. Morel, who had observed the worrisome resurgence of both diseases in Brazil while a member of the Brazilian Ministry of Health’s internal cabinet, came to TDR determined to address these issues. Shortly after arriving, he would win Joint Coordinating Board (JCB) approval to add both dengue and TB to TDR’s portfolio of diseases. In 2000, a pilot project on diagnostics for sexually transmitted infections was also conditionally approved by JCB as part of the TDR portfolio.

The development of new drugs and other product tools remained major goals. At the same time, social science research and field research became even more firmly embedded into the overall TDR strategy. Applied field research was evolving into what is commonly known today as implementation research. Implementation research tests not only the efficacy of a new drug or strategies (what works and what does not) through large-scale community studies, but also asks a question critical to improving disease control efforts: how can proven health interventions be scaled up more effectively? Social and economic research, meanwhile, was also re-emphasized and redefined as social, economic and behavioural research, reflecting the complex interactions between these factors. It would focus more attention on issues related to gender, and to social, economic and environmental factors related to infectious disease prevalence and transmission.

Simultaneously, the emerging knowledge in genomics, proteomics, bioinformatics and combinatorial chemistry would help drive discovery research for new drug leads. The focus of TDR’s basic research efforts shifted to genomics, including a global consortium to sequence the genome of Anopheles gambiae, the main malaria vector, as well as the final publication of the genome sequences of the Tritryps parasites responsible for Chagas disease, leishmaniasis and sleeping sickness. Lastly, there was a greater emphasis on communication and knowledge management (Juma & Yee-Cheong, 2005). This included the recognition that TDR needed to share its experiences and communicate its institutional strengths more effectively to donors, the scientific community, the media and the general public through more strategic use of communication tools.

The final years of TDR’s third decade, meanwhile, saw the departure of Morel, and the arrival of the present-day TDR Director Dr Robert Ridley. A fourth external review led to a new vision statement for TDR for the decade to come — ‘to foster an effective research effort on infectious diseases of poverty in which disease-endemic countries play a pivotal role.’ TDR’s third decade has been one, therefore, of great institutional dynamism with two directors and two periods of internal reorganization: the first period setting the stage and the second period building on that foundation to define the path for the future.

Promoting new partnerships for drugs, diagnostics and innovation

One of the remarkable aspects of TDR since its early days has been the pioneering collaborations the programme fostered between the public and private sectors. In the mid 1980s, many scientists from the private sector were participating in TDR scientific advisory committees, something that was perhaps unparalleled in other global public health institutions (TDR, 1986). However, as the volume of research activity increased, along with cost and complexity, more formal partnerships became necessary. TDR began to shift successful, but relatively expensive, product R&D projects into new or existing PPPs.

In 1999, TDR finalized the launch of the Medicines for Malaria Venture (MMV). A year later, TDR played a significant role in creating the Global Alliance for TB drug development (TB Alliance), which had the director of TDR as its first chairman of its board. And in 2003, TDR helped create yet two more PPPs, the Drugs for Neglected Diseases initiative (DNDi) and the Foundation for Innovative New
Diagnostics (FIND). As Morel was presiding over this new fostering of PPPs, he was also defending to donors and sponsors the need for TDR’s continued institutional, governance and budgetary independence. In a landscape of diverse research efforts and entities, TDR’s global leadership was all the more vital. At the same time, if I had the opportunity to say something about TDR, I would say more money should be invested in the programme. TDR is one of the best organizations I know. From the governance, where you have both developing countries and donors, to the teams, which get participation and recognition from developing countries, you have all the right ingredients. The health sector, donors and politicians want impact on the short term, while research aims to develop tools that can have an effect 10 to 20 years from now. That is why an independent governing board, the JCB, is critical to guiding TDR’s long-term strategic vision and objectives.”


Some people asked: ‘Why are you creating these PPPs? It is going to create more competition for TDR.’ Our response was we wanted new products, as quickly as possible, and in some cases it was more efficient. At the same time, through different routes. Miltefosine was developed as a direct collaboration between TDR, the pharmaceutical firm Zentaris and the Government of India. Paromomycin, on the other hand, was ultimately registered by a PPP, the Institute for OneWorld Health.

TDR has played similarly varied roles in the development of new artemisinin combinations for malaria treatment, initiating and then transferring two projects to MMV for final development, while carrying a third (rectal artesunate) through with a pharmaceutical partner to final registration, now pending. TDR also continued to lead the development of gatifloxacin for TB, a drug that potentially shortens treatment from six to four months, and thus improves the ability of patients to complete the course. Moxidectin, which is being investigated as a possible macrofilaricide for onchocerciasis, is now in Phase II trials. Meanwhile, the Multilateral Initiative for Malaria (MIM) has extended the partnership model to strategic research, policy research and capacity-building.
Genomics — towards a malaria-free mosquito

Genomics was another area where TDR would stimulate partnerships and collaborations, leading to major basic research advances. Already in 1991, TDR had convened a ground breaking meeting in Tucson, Arizona, together with the MacArthur Foundation, to propose the genetic engineering of *A. gambiae*, rendering it incapable of harbouring or transmitting the *Plasmodium* parasite (Morel et al., 2002). However, at the time of that meeting, recalls Morel, who was then a member of TDR’s Scientific and Technical Advisory Committee (STAC), the idea of actually sequencing the entire genome of a mosquito was out of reach. Not so a few years later, when genome sequencing became possible not just for microorganisms, such as the Tritrys, but for more complex species.

In 1998, TDR organized a consortium to sequence the *A. gambiae* genome. The initial meeting was small and high-level, including institutions such as TIGR, now the J. Craig Venter Institute (USA), National Institutes of Health (USA), the Pasteur Institute (France), the European Molecular Biology Laboratory (Germany), Celera Genomics (USA), the ONSA network (Brazil) and others. TDR contributed US$ 250 000 for the creation of the gene libraries and databases to house the sequence data, while other consortium members contributed a total of US$ 9 million to complete the project. In October 2001, TDR and the Pasteur Institute announced the formal launch of the initiative, although in fact work was already underway. In 2002, just one year later, results were ready to be published. Although TDR’s monetary investment in the effort was relatively small, this initiative provides an example of how strategic leadership and leverage at a critical moment can stimulate a much broader effort that involves intensive investment and yields scientific breakthroughs.

“*In the same week, Science published the results of the *A. gambiae* genome sequencing project and *Nature* published a report on the sequencing of the *Plasmodium falciparum* genome,*” recalls Morel. “*So we had the full genome information of both the main malarial parasite and its vector.*”

Meanwhile, the road map of research to develop a transgenic mosquito, spearheaded by the Tucson meeting in 1991, had made enormous progress, aided by the new knowledge of the *A. gambiae* genome sequence. By 2001, TDR had supported more than 100 projects in 19 countries to identify parasite-inhibiting genes in mosquitoes; to genetically modify mosquitoes; and to drive selected genes into natural populations. As these advances paved the way for field trials, TDR initiated discussions on the ethical, legal and social implications of testing and evaluating transgenic mosquitoes (Macer, 2003).

In addition to genetic modification of vectors, genomic data can be mined and applied to a wide range of research endeavours from drug discovery research to improved diagnostics. However, this

"What I tried to imprint in TDR was to use the best sciences available in genomics and molecular biology to study and develop tools against disease that affect poor people."

requires proficiency not only in molecular biology and genetics, but also in sophisticated computer programmes that can examine and manipulate genomic data. To this end, TDR is now supporting training and networks in bioinformatics and genomics applications. A South–South Initiative for Tropical Diseases Research (SSI) was launched in 2001 so that researchers in developing countries could share resources and support in applied genomics research. The initiative promotes collaborations among scientists and institutions in Asia, Africa, South America, and with partners in developed countries. Annual training courses, proposal development assistance and grants are provided, with a website linking the far-flung groups and knowledge gathered.

**Discovery research — facilitating global networks**

The huge advances in understanding of vector and pathogen biology would, in turn, shape and influence TDR discovery research strategies. The challenge is to harness that knowledge to the search for novel lead compounds that can form the basis for innovative disease treatments. While PPPs and other partners assumed greater responsibility for the development of particular drugs and diagnostics for specific diseases, TDR would cast its net into the sea of compounds that had so far not been explored, searching broadly but systematically for novel leads. Alongside traditional whole-parasite screening techniques, this effort would harness the new tools of genomics, combinatorial chemistry and robotics to full advantage.

Three decades earlier, the TDR network approach had proved itself with ivermectin. It was a TDR screen of the drug's efficacy in cattle — innovative at the time — that confirmed the potential efficacy of ivermectin against human onchocerciasis. Now, the TDR compound-screening network was revitalized and expanded to include a broader range of academic and research institutes, and also industry partners. Along with this, new research networks for medicinal chemistry, pharmacokinetics, drug target portfolios and helminth drug discovery were created to cover other stages of the drug discovery process in a more integrated manner.

TDR's development of formal collaborations for drug discovery with industry has greatly enhanced the capacity of these networks. The high-tech, automated laboratories of industry can screen hundreds or thousands of compounds simultaneously for activity against a target protein or enzyme. Major industry collaborators have opened their vast medicinal chemistry libraries (for example, those at Pfizer, Merck-Serono and Chemtura) to the research efforts. And certain pharmaceutical firms are training developing country scientists in their laboratories, under TDR auspices. This will help build capacity and foster scientific leaders in the countries where neglected tropical diseases pose the greatest burden. TDR's discovery research programme has also supported the creation of a new global research tool, a Drug Target Database, to facilitate research on potential drug targets.

"This is the first time any group has assembled drug target information across multiple parasitic and bacterial diseases in a central location. The website is a global resource that will help in the selection and prioritization of targets for high-throughput screening campaigns. It will piggy-back onto work pharma has done," observes network coordinator, Dr Wesley Van Voorhis, of the University of Washington in Seattle.

**Diagnostics — stimulating partnerships and products**

Responding to the concerns of disease control partners, TDR took on yet another critical unmet need — research into diagnostics. Effective diagnostics are not only necessary to guide individual treatment, they are equally important to the surveillance and monitoring of public health and the effectiveness of disease control measures. With parasitic and bacterial drug-resistance on the rise, getting good diagnostics to the field ensures that drugs are used only when necessary. In a sense, diagnostics replaced vaccines as the major thematic point of focus at TDR. TDR is both providing leadership and partnering directly with country control programmes for research into specific diagnostics — particularly at the village, home or a health clinic on the periphery of the health system.
Sexually transmitted diseases provided the initial focus of TDR efforts in diagnostics. At least 500,000 stillbirths and miscarriages occur every year as a result of congenital syphilis, as many babies are born with the disease. New rapid diagnostics are not uniform in quality, nor are they widely available in poor and remote locales. Research at TDR sites in Haiti, China, Brazil and Tanzania in which rapid syphilis tests were tested and their efficacy demonstrated has already stimulated several severely affected countries to increase prenatal screening for syphilis and foster initiatives for the elimination of congenital syphilis. Used widely in Africa, such diagnostics could help countries to reach the MDG goal of improving maternal health and reducing mortality of children under the age of five.

In 2003, TDR, together with the Bill & Melinda Gates Foundation, created the FIND, a PPP dedicated to the development of rapid, accurate and affordable diagnostic tests for developing countries. FIND and TDR have jointly launched projects to improve TB diagnostics.

**Research from bedside to bench — rectal artesunate**

The development of rectal artesunate for young children with severe malaria is another example of how TDR field research in antimalarials has led to the development of bottom-up collaborations in drug development. Rectal artesunate is intended to stabilize the condition of children who are so seriously ill that they are unable to take medication until they can get to a hospital. Anecdotal observations by TDR field researchers in the mid-1990s in Viet Nam who observed how artemisinin suppositories were being used to treat severe malaria stimulated TDR interest in development of a formal registered product, says TDR’s Dr Melba Gomes, then in charge of the Anti-Malaria (ANTIMALS) Task Force. The group proposed an assessment of artesunate suppositories. “Tore Godal, (then-director) at first argued against it,” recalls Gomes, “and then characteristically, after Christmas vacation (I believe he had been interviewed by a reporter) returned and said, ‘I want this developed for use in Africa.’” Clinical data from TDR supporting registration were approved by the US Food and Drug Administration (FDA) in 2002; outstanding work on the drug chemistry was submitted in 2006 by pharmaceutical collaborators Abbott, RP Scherer, Scanpharm and Solvias.
This could have a revolutionary impact on disease control as most of the estimated 9 million people who develop active TB every year are not diagnosed with sensitive and reliable tools, if they are diagnosed at all. A joint TDR–FIND TB Diagnostics Market Report, released in 2006, identified TB diagnostics as a major R&D opportunity in the diagnostics market.

Home management of malaria — diagnosis and treatment

Implementation research on home and community-based management of malaria became another key element of TDR’s programme in its third decade, continuing into the fourth. Home and community management involves the training of mothers, drug vendors, village volunteers and teachers in the first line of care for malaria when health clinics and health care providers are not accessible. The effectiveness of home management has been demonstrated by TDR over the past five years, reducing mortality by 40% or more in some studies (TDR, 2007). Further research is now underway to determine whether more complex artemisinin-based combination therapies (ACTs) can also be administered at the home and community level. More than 20 studies are examining health outcomes and overall feasibility of ACTs in home management. Preliminary results of a small study in Ghana using Coartem®, the only fixed-dose ACT currently available, show good results for community use. Meanwhile, research has also been initiated to determine whether rapid diagnostic tests for malaria can also be administered at community level by trained caregivers and whether use of diagnostics enhances the effectiveness of ACTs.

Mainstreaming social, gender and economic research for infectious disease control

Ever since its creation, TDR has been one of the few UN institutions to conduct research into health-related social and economic issues. In the programme’s first decade, this work had been conducted under the remit of the Social and Economic Research (SER) Steering
Eco-bio-social research — linking health and environment to dengue disease control

‘Eco-bio-social’ research has been another emergent sub-theme in social research at TDR. This identifies links between health, environmental and social factors that might be harnessed more effectively for disease control, particularly vector control. In contrast to genomics research (focusing on upstream technologies) and conventional vector control (focusing on single interventions such as vector traps or indoor residual spraying), eco-bio-social research looks in a multidisciplinary manner at how social, biological and environmental mechanisms can be harnessed for better disease control results, in a sustainable manner.

TDR-sponsored eco-bio-social research has focused so far on dengue. As there is no effective drug cure, integrated vector management (IVM) including vector control and appropriate diagnosis and rapid treatment, are recognized as the most promising strategies. A landmark TDR-sponsored multi-country study on dengue vector breeding sites set the basic research groundwork for better environmental management of dengue. The study tested the efficacy of a new ‘pupal productivity’ method for identifying the most prolific dengue vector breeding sites (usually domestic water containers). This, in turn, permits targeted vector-control measures (Focks, 2003; Focks & Alexander, 2006). Knowledge of how to identify and target breeding sites has helped drive more successful programmes of vector control in South East Asia and elsewhere (Nam, 2003; Kay, 2005).

Recently, TDR and the Canadian-based International Development Research Centre (IDRC) embarked on a multi-country initiative to examine a broad set of eco-bio-social factors affecting dengue transmission. The TDR/IDRC initiative includes six studies in high-endemic South and South East Asian countries. They examine how environmental factors, including climate and the urban environment, contribute to vector density and disease transmission and how socio-economic disadvantage can inhibit vector-control efforts. Through this research, more effective interventions for specific ecological settings will be identified.

In the early part of the last century, before the widespread availability of chemical control tools, vector control through environmental management and modification was the first-line strategy for malaria disease control, often achieving impressive results. (Utzinger et al., 2001; 2002). Vector control was also important to TDR research in the early days, and critical to the control of onchocerciasis in West Africa, as well as to Chagas, sleeping sickness, schistosomiasis and other diseases. At the same time, challenges exist in finding the right mix of innovations for different kinds of diseases, communities and needs, and in scaling up such innovations in a cost-effective manner.

For many years research in this area was neglected, despite the threat of increased vector resistance to many drugs, and the impacts of climate change, agriculture, irrigation, dams and urbanization on patterns of vector-borne disease transmission. However, recent WHO-sponsored research has indicated that a large fraction of the burden of the major vector-borne diseases could be reduced through better ecosystem management (Prüss-Üstün & Corvalán, 2006). This, in turn, could help support the judicious use of available chemical tools and preserve their long-term efficacy.
Committee. But in the mid-1990s, social research was integrated into the work of various TDR task forces, a positive development in some cases but also blurring the programmatic focus. In 2000, however, the creation of a new steering committee for Social Economic and Behavioural research (SEB) signalled a renewed emphasis on social research as a distinct endeavour.

“Until this period, social research was more of an accessory to field research,” recalls Morel, who took the initiative. “I wanted an SEB committee that was associated with basic strategic research, and I wanted the social scientists to be masters of their own minds and projects. Many people are reluctant to understand the importance of social sciences. We helped to put it in the spotlight, and I consider this one of my biggest accomplishments in TDR.”

At the strategic level, social research has recently looked at a broad array of social, political, economic and gender-related barriers to access or use of disease-control interventions, and pathways for the more efficient diffusion of technologies. The ethical, legal and social implications of biotechnologies (ELSI) have been another focus, as well as health sector reform and health economics. At the field level, and in the context of implementation research, social research has addressed gender disparities, as well as social and economic forces that limit the effectiveness of a particular diagnosis and treatment.

For instance, TDR social research found that access to anti-malarial drugs can be improved by supporting the rights of mothers to have a say in drug purchases in households where such decisions can be traditionally the domain of men. In the case of congenital syphilis, TDR has documented that the partner’s response to diagnosis and treatment is vital to ensure that a pregnant woman who receives treatment is not re-infected. And, in TB, gender research has explored why fewer women than men are diagnosed with TB, on the one hand, while, men, on the other hand, are more likely to have problems starting and completing treatment. Social research has also examined how factors such as sub-optimal drug supply mechanisms and non-adherence to treatment schedules can influence the strategic level of disease control and drug resistance. TDR has sponsored some 40 studies on various aspects of health sector reform relevant to tropical disease control.

“In the past several years, TDR has explored how a successful model for addressing one disease, onchocerciasis, can be used effectively to address multiple disease problems, in a single comprehensive strategy of community-directed interventions. The model, which has been tested initially in the APOC countries of Africa, demonstrates how TDR research can support the future scale-up of other critical interventions in a range of settings and locales.”

DR ROBERT RIDLEY, TDR Director, 2004–present.

Although the past decade has brought social research more to the fore of TDR emphasis, a challenge for the coming decade is its true integration into the research mainstream, says current TDR director, Ridley. “Recently, we have re-emphasized social and economic research, but the challenge of the coming years is to mainstream it.”

The next wave of implementation research — community-directed models for other health interventions

A decade ago, TDR and its research partners helped demonstrate how insecticide-treated bednets could dramatically reduce deaths from malaria. The programme also helped document how new anti-malarial combination treatments and unit-dose blister packs could improve the efficacy and delivery of anti-malarial drugs, particularly by caregivers and trained members of the community.

But implementation of these and other basic health measures remains a great challenge in many parts of the developing world. Only 4–5% of Africa’s youths currently sleep under bednets (UNICEF, 2006). Many do not have access to anti-malarials. Immunization campaigns often miss their targets. Health systems in developing countries are
frequently stymied over how to deliver treatment at the grassroots level in an efficient and integrated manner.

The community-directed treatment (ComDT) strategies used to control river blindness have, however, indicated one potential response to these challenges. The ComDT programme for onchocerciasis control is perhaps the most successful model of a disease control and drug administration strategy in Africa today. The secret of its success lies in the system of treatment, where communities themselves manage the distribution and administration of the drug ivermectin. ComDT is now well established in hundreds of thousands of African communities, with a total population of 60 million people. By the year 2010 coverage will increase to 100 million people — nearly one-sixth of the population of sub-Saharan Africa. ComDT therefore represents a powerful model for delivery of other interventions.

Recognizing the potential of this tool, and at the request of the board of APOC that includes 19 African health ministers, TDR in 2004 launched a multi-country study to examine to what extent a community-directed approach could be used for the integrated delivery of other needed drugs and tools. This study into what were termed ‘community-directed interventions’ (CDI) tested how the distribution of interventions such as bednets and anti-malarials, along with ivermectin, could be controlled and managed by community members in the regions where ComDT was well established.

Results from the second year of the study from 40 health districts in Nigeria, Cameroon, Uganda and Tanzania indicated that indeed, the community-directed approach has potential for broader applications. The percentage of people covered by insecticide-impregnated bednets and home-administered anti-malarials doubled or tripled in the CDI-administered locales. This is in comparison to control districts that received the same amount of intervention materials, but where delivery was by conventional means. Preliminary economic data also indicated that the total cost of delivery was similar in the CDI and control districts, suggesting that CDI was more cost-effective.

“This is something that comes out of our long experience in onchocerciasis control,” says TDR research coordinator Dr Hans Remme, “where ComDT is now a proven strategy that is working very well, with good treatment coverage sustained in most areas. In some communities there is 10 years of experience and it is still going strong.

“The theory was that this same approach would be useful for other interventions, and we built upon it. This is not your standard community-based intervention, where you use a few local people to carry out an intervention. It is really a process where you put the community in charge from planning to execution. The community collectively decides if it wants to do the intervention, and if so, how to go about distributing it: where, when and to whom.

“It is an amazing development, and what we have seen is that it has potential for other applications. The study has also shown that the addition of other interventions was not detrimental to ivermectin treatment; quite the contrary, ivermectin coverage improved even further. Presented with the evidence of the effectiveness of CDI, the board of APOC has now strongly recommended it should be used on a wider scale.”

From products and partnerships to disease elimination

At the close of the programme’s third decade, four of the original eight TDR diseases — leprosy, Chagas disease, onchocerciasis and lymphatic filariasis — were advancing towards regional or global elimination as public health problems. Spurred by new drug innovations and other breakthroughs, WHO and partner countries India, Nepal and Bangladesh drafted a framework for the elimination of visceral leishmaniasis as a public health problem on the Indian subcontinent by 2015. The elimination strategies are diverse and include mass administration of TDR-evaluated drugs, often offered at preferential prices by pharmaceutical companies; increased use of multidrug combinations rather than monotherapies; and finely tuned strategies for drug administration that harness not only health systems but also the resources and interest of the communities themselves. Although elimination programmes are designed and carried out by WHO together with the countries themselves and not TDR, they are often underpinned by TDR research.
“TDR research has helped get to the stage of disease elimination,” says Ridley. “Continued TDR research is needed to make sure elimination happens and is sustained.”

**Leprosy.** The World Health Assembly resolution setting leprosy elimination as a goal was adopted in 1991. By 2006, the number of registered cases had fallen from 5.4 million in 1985 to approximately 220,000. Although several hundred thousand new cases of leprosy are still reported every year, most are cured within six months to two years (WHO, 2005). More than 80% of cases today occur in just a few countries (including Brazil, India, Madagascar, Mozambique, Nepal and the United Republic of Tanzania). Still, there is no question that shortly after the turn of the millennium, the elimination of the ancient scourge of leprosy as a public health problem has advanced dramatically. A cornerstone of that advancement has been the development of TDR-recommended multi-drug therapy. An innovation that was tested in the 1970s became the cornerstone of elimination efforts in the 1980s, implemented by national control programmes, non-governmental organizations (NGOs) and WHO, with the results accumulating over subsequent decades.

**Chagas disease.** The TDR-supported epidemiological surveys of Chagas disease undertaken in the 1980s documented the true scale of this disease for the first time, building political will to address the issue. In addition, field testing of vector-control tools, and support for improved and standardized methods of disease diagnosis and blood-blank screening, helped set the stage for regional disease elimination initiatives in the 1990s, and a rapid decline in the overall incidence of Chagas disease ever since. Vast areas of the Southern Cone are now virtually free of domestic infestation by the main disease vector. Deaths from Chagas declined from an estimated 45,000 in 1991 to approximately 13,000 in 2001 (Remme, 2004). In 1998, the World Health Assembly approved a resolution confirming the interruption of transmission of Chagas disease in several countries of Latin America (WHA51/7). However, Chagas elimination still faces a variety of challenges. Domestic vector-control methods used in countries of the Southern Cone region are not appropriate for Central America where transmission is maintained by peridomestic and sylvatic triatomine vectors. Vector re-infestation has also been an issue in some areas that were previously declared free of transmission, and good surveillance remains critical. In the new TDR strategy, research into new and improved methods for controlling Chagas vectors is to be a focus in the area of innovative vector-control interventions.

**Onchocerciasis.** The elimination of river blindness as a public health problem has advanced in two major phases, firstly in the savanna areas of the 11 west African countries in the Onchocerciasis Control Programme in West Africa (OCP). The OCP was dissolved in 2002 after elimination was achieved, due to the combined use of innovative vector-control tools such as *Bacillus thuringiensis* serovar *israelensis* H-14, diagnostics supported by TDR, and ivermectin. In the second stage of efforts, ivermectin administered through community-directed treatment (ComDT) has eliminated onchocerciasis as a public health problem in regions of the African Programme for Onchocerciasis Control (APOCH) where it has already been administered annually for a number of years. Treatment has prevented debilitating itching, disfiguring skin lesions, visual impairment and blindness — an annual saving of some 1 million disability-adjusted life years (DALYs). However, ivermectin is a ‘microfilaricide’, which kills the parasite offspring, but not the adult worm. Therefore, except in locales with favourable entomo-epidemiological conditions (for example, endemic areas of Latin America and some foci in Africa), disease transmission cannot be permanently interrupted with ivermectin, and so annual treatment must continue for an indeterminate length of time, placing a considerable burden on health systems.

There also is the risk that parasites could develop resistance. This has made the continued search for a ‘macrofilaricide’ (capable of killing or sterilizing adult worms more effectively) a compelling research issue. One potential drug is moxidectin, owned by Wyeth Pharmaceuticals, and currently the focus of a TDR-sponsored Phase II clinical trial in Ghana involving 192 infected people. Final data from this study will be available in 2008–2009. If the drug is demonstrated to be efficacious and safe in this and additional clinical trials, it could pave the way for onchocerciasis eradication.

**Lymphatic filariasis.** In 2000 the Global Programme for Elimination of Lymphatic Filariasis (GPELF) was established by WHO and national partners, reflecting the new opportunities for eliminating this disease as a public health problem. The definition in the mid-1990s of a simple, single-dose diethylcarbamazine (DEC) treatment,
or DEC plus ivermectin, as effective on the basis of TDR research that compared this with longer treatment, helped stimulate the elimination campaign. WHO’s Department of Neglected Tropical Diseases (NTD) has led this effort along with national health services and communities, while TDR field research has been critical in guiding implementation strategies.

Lymphatic filariasis is endemic to 83 countries with 1.1 billion people living in areas at risk of the disease. In its severe form, the disease causes elephantiasis and hydrocele, and lifelong conditions of disability. It has been estimated that 119 million people are infected worldwide. Although countries like China and Egypt have already seen dramatic reductions in infection, India and Africa, the most endemic areas of the world, witnessed little change until recently (Remme et al., 2004). However, donations of ivermectin by Merck for use in Africa and another new drug, albendazole, by GlaxoSmithKline, have spurred dramatic increases in treatment coverage. TDR-supported research also played a critical role in stimulating the interest of national policy makers in lymphatic filariasis, documenting the economic cost of the disease and the cost-effectiveness of mass drug administration. Dr Kapa Ramaiah and colleagues at the Vector Control Research Centre in Pondicherry (an institute of the Indian Council of Medical Research) estimated that in India alone, economic losses due to lymphatic filariasis disease amount to nearly US$ 1 billion each year. (Ramaiah, 2007). As a result of the new developments, hundreds of millions of people in at-risk areas are now receiving annual treatment. Questions regarding how many annual doses are needed to break transmission have also been addressed through ground-breaking longitudinal studies supported by TDR between 1995 and 2005. These studies concluded that the 4–6 year time frame initially estimated for mass drug administration programmes would be insufficient. The studies also documented the importance of high coverage to move elimination forward.

Visceral leishmaniasis. The development of new tools and rapid diagnostic techniques for treatment of visceral leishmaniasis (known as Kala azar), which was supported by TDR, have strengthened the political will on the Indian subcontinent to eliminate this disease as a public health problem. Endemic countries and the WHO Regional Office for South East Asia (SEARO) have developed a framework for the elimination of visceral leishmaniasis by 2015. Visceral leishmaniasis is a fatal disease with an estimated incidence of 500,000 cases per year, 60% of which occur in India, Nepal and Bangladesh.

New drugs available include the TDR-fostered miltefosine, an oral formulation which avoids injections, and paromomycin, an injectable drug, whose development was initiated by TDR and then taken up by the Institute for OneWorld Health. The registration of miltefosine in India in 2002 and Germany in 2004 was achieved as a result of a special capacity-strengthening partnership between TDR, Zentaris, the Government of India, and investigators from the Bihar region where visceral leishmaniasis is endemic. Staff in four hospitals participating in the miltefosine trials underwent training and new research facilities were built, so Bihar now has a self-sustaining research centre. Integrating drug development with capacity strengthening and engagement of national control groups created a ‘complete package’ for the drug’s development, and helped build political will for the disease elimination campaign, notes Ridley. Many hurdles are yet to be overcome in advancing elimination. Post-registration Phase IV safety trials of miltefosine are still ongoing. TDR is also
“The development of miltefosine was, in my view, one of the major successes of TDR in this period. It was the first oral drug for VL, it involved an excellent partnership between TDR, the Indian authorities and the private sector. And the initiative involved capacity building with the Indian hospitals involved in the drug trials.”

DR CARLOS MOREL, former TDR Director, now leading the creation of the new Centre for Technological Development in Health at FIOCRUZ in Brazil.
supporting a major programme of implementation research to develop cost-effective strategies for case detection and management of visceral leishmaniasis patients in poorer socio-economic strata, and in communities where public health services are weak. Issues being addressed include health-seeking behaviour (interaction with the private sector is often preferred by patients) and compliance issues. TDR has also supported studies into integrated vector management to support visceral leishmaniasis elimination.

Research capacity strengthening (RCS) — networks for training

Informal partnerships between institutions and individuals have always been integral to RCS. The last decade, however, witnessed the development of major new networks and regional training centres to build capacity in various facets of research, as well as short courses and training programmes in targeted areas of need.

These new networks and training formats build clinical and research skills and awareness not only among scientists and PhD students, but also among diverse groups of health workers, such as nurses and laboratory technicians, and in other contexts, among policy makers and control officers. They thus complement the ongoing traditional grant programmes for institution-building and for academic support and training.

Regional training centres have provided hands-on training in new technologies such as genomics and bioinformatics and in specific disciplines such as the social sciences and natural products R&D. Short courses have been developed to improve planning of research projects, Good Laboratory Practice, Good Clinical Practice and for appropriate ethical review of research involving human subjects. TDR also fostered regional and global ‘train-the-trainer’ networks and expert networks around specific themes to further embed practices and procedures into academic curricula and national codes and guidelines.

In many cases, initial TDR efforts catalyzed or supported new capacity-building partnerships that are now led by others. Key examples include SIDCER (Strategic Initiative for Developing Capacity in Ethical Review); FAME (Forum for African Medical Editors); and the South–South Initiative for Tropical Diseases Research. Other important partnerships partially supported by TDR include the PSSMC (Partnership for Social Sciences in Malaria Control), ACTMalaria (Asian Collaborative Training Network for Malaria) and RNAS (Regional Network for Asian Schistosomiasis) to name but a few.

Today, SIDCER, which TDR helped to establish in 1999, boasts five regional forums in Asia, Africa, Latin America, North America and Eastern Europe. The forums bring together governments, researchers, members of ethics committees, and representatives of educational institutions to develop national guidelines and local standard operational procedures. One of the regional forums, the Forum for Ethical Review Committees in Asia & the Western Pacific (FERCAP), has stimulated China and Thailand to further improve their own ethical research guidelines. All in all, over 1100 people have been trained in the new format of short courses between 2000 and 2005, along with the continued support for degree students.
In terms of institution-building per se, TDR turned its attention to long-term support in the least developed countries where research capacity is weakest. Here, too, more attention was placed on promoting and enabling quality research environments in addition to institutional development. Proposal development workshops have thus been developed to help research teams develop fully-fledged research proposals out of letters of intent. When funding is granted, TDR provides subsequent training in good research practices. A third strand of effort has been investment in partnerships between researchers and disease control officers and policy makers.

TDR training grants for academic studies at Masters and PhD levels, likewise, have evolved from the early days when they were merely another form of scholarship to enable students from developing countries to attend university abroad. Today, 80% of holders of TDR-supported training grants pursue their research and training in local or regional institutions, contributing to institution development and sustainability. Training grants are now regarded as a managed human resource development tool, where decisions on a research focus as well as how and where to train are made jointly with TDR. The chosen research themes must fit into the general context of a priority discipline for developing countries and be relevant to a priority disease control effort.

Applications for training must be proposed as an integral part of a programme that clearly documents a career development path. Following training, grantees are expected to exhibit scientific expertise in their chosen field, promote the development of the research environment at their home institute, provide training opportunities, be conversant with information and communication systems and to develop collaborations with scientists and institutions in their own country and with other countries where possible.

Just counting the thousands of Masters and PhD students, other scientists, clinicians and support staff who have been trained and sponsored over the past three decades by TDR, in both formal programmes and in short courses, provides one indicator of the cumulative impact of RCS. Another indicator would be the balance of R&D grants awarded recently by TDR — some 70% of the R&D partners engaged by TDR between 2000 and 2005 were from developing countries. However, such measures fail to capture the multi-dimensional impact of RCS activities over time, notes Dr Bernhard Liese, Chair of International Health Programs at Georgetown University and the World Bank’s former representative on the JCB.

“Twenty-five years ago, if you went to Africa to do research, you would be running into a lot of expatriates,” Liese observes. “Today, if TDR organizes a meeting in Africa, it will be mostly African scientists attending, and sharing a common scientific culture and perspective about disease control problems that need to be addressed — and much of that is due to TDR’s influence. TDR, in effect, trained two generations of African scientists. What an achievement that is in capacity building. Perhaps you can measure it in terms of heads trained, but that still misses part of the story.”

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<th>TDR/ JCB institutional milestones</th>
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<td><strong>1999</strong></td>
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<td>• TDR disease portfolio expanded to include tuberculosis and dengue.</td>
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<td><strong>2000</strong></td>
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<td>• JCB conditionally approves sexually transmitted infections diagnostics pilot project in the TDR portfolio.</td>
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<td><strong>2003</strong></td>
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<td>• Third session of the JCB held outside WHO/HQ — JCB (25) in Delhi, India.</td>
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<td>• UNICEF joins TDR as the fourth co-sponsor.</td>
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<td><strong>2006</strong></td>
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<td>• Two high-level ministerial meetings on health research held in Ghana and Nigeria, supported by TDR and WHO, to develop global perspective and priorities for health research in developing countries.</td>
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<td>• Fourth session of the JCB held outside WHO/HQ — JCB (29) in Accra, Ghana.</td>
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<td>• JCB (29) receives recommendations from the Fourth External Review.</td>
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<td>• Special Stakeholders and JCB session held in Geneva, which supports new TDR 10-year vision and strategy.</td>
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**Fostering excellence in achievement**

Over the years TDR has supported individual career development and institution-strengthening grants involving over 400 research groups and institutions in about 80 disease-endemic countries. TDR has thus contributed to the formation of a new generation of public health leaders, many now directing major national and international disease control and research efforts. Below are just a few examples of past and current TDR Research capacity strengthening (RCS) grant recipients.

**Dr Sima Rafati:** head of the Department of Immunology at the Pasteur Institute in Tehran and recipient of the Institute Pasteur/UNESCO medal for her research into leishmaniasis vaccines and isolation/identification of genes from the parasite. She has been the recipient of three successive TDR grants since 1996 for research training, research group development and vaccine discovery research.

**Dr Rodrigo Correa Oliveira:** head of the Laboratory of Cellular and Molecular Immunology at the Oswaldo Cruz Institute (FIOCRUZ), a leading expert on immune system response to schistosomiasis, and a member of the JCB. He first received a TDR grant to pursue his doctoral training more than 20 years ago, and has received two other RCS grants and awards.

**Dr Francine Ntoumi:** a researcher from the Republic of Congo, currently the European Coordinator for the European and Developing Country Clinical Trials Partnership (EDCTP). She was the recipient of four TDR research training, re-entry and research grants between 1993 and 2002 for her work on the molecular biology of malaria parasites and genetic factors in the immune response to malaria.

**Dr Zhou Xiao-Nong:** deputy director of the Chinese Centres for Disease Control—Parasitic Diseases. He received two RCS training and applied field research grants for his work in China on schistosomiasis, including development of GIS and remote sensing tools to map key schistosomiasis snail habitats and ‘hot spots’ for transmission.

**Dr John Gyapong:** manager of the Lymphatic Filariasis Control Programme in Ghana and director of the National Health Research Unit. Since 1993, he has received two research training and re-entry grants as well as 10 R&D grants for his work involving lymphatic filariasis elimination.

**Dr Aboulaye Diomde:** head of the Molecular Epidemiological and Drug Resistance Unit at Mali’s Malaria Research and Training Centre. He has made a significant breakthrough in the fight against drug-resistant strains of malaria parasites, one of the major threats to malaria control today, and he received two RCS research training and re-entry grants between 1996 and 2002.

**Dr Shyam Sunda:** of the Institute of Medical Sciences at India’s Banaras Hindu University. He is at the forefront of efforts to improve the diagnostics and treatment of visceral leishmaniasis. He received two TDR grants, one for project development and one for RCS between 1998 and 2002, and was a member of the project team that developed miltefosine, a new drug against visceral leishmaniasis.

**Dr Fred Binka:** currently head of INDEPTH (International Network of field sites with continuous Demographic Evaluation of Populations and their Health in developing countries). A medical doctor from Ghana and world leader in operational research, focusing on child health, case management and malaria, Binka was the driving force behind the 1992 establishment of the Navrongo Health Research Centre in Ghana, an endeavour supported by an RCS research training grant and numerous grants for research and development.

**Dr Abdul Faiz:** currently a professor of medicine at Dhaka Medical College, Professor Faiz established a TDR-supported malaria research group in Chittagong, Bangladesh, which carried out some of the clinical trials of rectal artesunate, the new emergency treatment for severe malaria. He has been the recipient of RCS and R&D grants since 1998.

**Dr Roberto Briceño-León:** a sociologist and director of the social science laboratory (LACSO) at Venezuela’s Central University in Caracas. He helped establish a dynamic and highly skilled scientific community of health and social science researchers in countries throughout Latin America in the 1990s through an innovative small grants programme funded by TDR.

**Dr Obinna Onwujekwe:** a Nigerian health economist. He established the Health Policy Research Unit at the University of Nigeria and co-founded the West African Health Economics Network, which brings together other TDR grantees. With support from several TDR research training and re-entry grants, he demonstrated the feasibility of a novel community funding system for mass distribution of ivermectin for the treatment of onchocerciasis as well as undertaking research on economic and financing aspects of malaria control.

**Dr Feng Zheng:** former director of China Centres for Disease Control — Parasitic Diseases (formerly Institute of Parasitic Diseases, Chinese Academy of Medicine). Supported by a TDR RCS grant, Zheng was a driving force behind the establishment in 1999 of the Regional Network for Asian Schistosomiasis (RNAS), which links disease control authorities and experts in five countries regionally, and experts globally.

* Excerpt from *Research Capacity Building in Developing Countries* (TDR/RCS, 2003)
“TDR is a tried and trusted friend of disease-endemic countries. Institutions have been built or strengthened, individuals have been trained and ministries of health have been given the tools to help them organize and manage research for health.”

DR PETER NDUMBE, Dean, Faculty of Health Sciences, University of Buea; Director, Centre for the Study and Control of Communicable Diseases, Faculty of Medicine, University of Yaounde I, Cameroon and Chair of TDR’s STAC.
A rapid syphilis test evaluated by TDR that is now being used more widely in Haiti. The test requires no electricity or water and can be delivered within 20 minutes instead of several days, resulting in many more women being tested and treated, particularly pregnant women, thus protecting their unborn children from the congenital form of the disease (Haiti • 2006 • WHO/TDR/Craccs).
“TDR is a very successful programme. The Pedro Kouri Institute has benefited from the RCS programme and, in turn, has itself been able to share this knowledge with others.”

DR GUSTAVO P. KOURI, Director-General, Institute of Tropical Medicine ‘Pedro Kouri’ and JCB Representative, Government of Cuba.
A health promoter for malaria at his reference centre outside his home, together with his daughter, who takes all the records and notes. People come from surrounding areas to be tested for malaria and to receive free anti-malarial treatment from the community-based promoters who are supported by the Ministry of Health (COLOMBIA • 1999 • WHO/TDR/CRUMP).
“TDR is the only public health research institution that is jointly owned by everybody ... all of the member states of the UN and the World Health Assembly own TDR and that is why it is unique. The smallest country in the world has a stake in it, the biggest country in the world has a stake in it. That to me is the comparative advantage of TDR: joint ownership.”

DR KAYODE OYEGBITE, representative of UNICEF to the JCB, 2004–present.
“The Global Programme for the Elimination of Lymphatic Filariasis (GPELF) of WHO stands as an evidenced-based monument to TDR’s field research, which directly contributed new and innovative tools towards the control and elimination of this disease of poverty.”

Professor CP Ramachandran (TDR-1976–1996)
“I had the unique opportunity to work with TDR as a scientist from a developing country. The financial and other relevant assistance helped us to enter into the science as a group (Malaria Research Group, Bangladesh). The group is now in a position to plan, implement, coordinate, supervise and monitor biomedical research of global importance in different countries, including Bangladesh.”

DR ABUL FAIZ, Professor of Medicine, Dhaka Medical College and JCB Representative, Government of Bangladesh.