Making a Difference

30 Years of Research and Capacity Building in Tropical Diseases
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Dedication

This book was inspired by the 30th anniversary of TDR’s Joint Coordinating Board (JCB). TDR is the Special Programme for Research and Training in Tropical Diseases that is co-sponsored by UNICEF, UNDP, the World Bank and WHO. Without the long-term support and attention of the board participants from national governments, partner organizations and other committed individuals, the resulting critical innovations that have transformed the lives of millions of people would not have been possible. As TDR enters its fourth decade, the JCB has taken a leading role in developing a new 10-year vision and strategy for the programme, building upon TDR’s original mission of strengthening research capacity in disease-endemic countries and supporting the development of new tools and strategies for neglected tropical diseases. It is a time to look back in appreciation, and look forward with excitement.

Past and present directors of TDR

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Preface

I am honoured to be the Chair of the Joint Coordinating Board (JCB) at this time, and to be asked to write a preface for this book, which is dedicated to 30 years of TDR activities under the governance of the JCB.

I endorse the statement that when the JCB was established, it was ahead of its time. For the past three decades the JCB, representing a balance of donor and disease-endemic countries, has worked to monitor, advise and recommend actions to be taken by the programme to improve the health of the poor, many of whom suffer concurrently from more than one of the neglected tropical diseases.

Much has been achieved by TDR since its establishment and this book is testimony to those outcomes and their impact. In addition to the programme’s research and development achievements, which have helped to save and improve many lives, TDR’s work on capacity building should also be highlighted. I have heard many scientists attest to the fact that without support from TDR, they would not be in their current positions. Much of the early support helped to train scientists in disease-endemic countries who were able to take on challenges such as the emerging HIV/AIDS epidemic, and I look forward to monitoring further the impact of TDR’s capacity-building efforts as it builds on past successes to promote the empowerment of researchers and institutions in disease-endemic countries. Within my own country and its neighbours, I can see the impact of TDR’s work and opportunities for strengthening collaborations in the future.

I have been privileged to be a member of the JCB for many years and have great respect for its governance of the programme. The sense of commitment of the individual participants and their collective dynamics and willingness to reach a consensus for the global public good are to be commended and admired. In addition, the JCB has instilled a sense of rigour within TDR to report, assess and plan activities annually through the key Scientific and Technical Advisory Committee (STAC) and the JCB itself. The whole premise of the programme — from its individual projects to its overall direction — is based on sound peer review, ranging from the scientific experts who sit on the myriad of scientific committees to the governmental experts who sit on the JCB. TDR’s governance is a sound investment and it is only now that other programmes are taking a page from TDR’s book and setting up their own review and advisory committees.

I have greatly appreciated my term of office as Chair of the JCB at this important juncture for TDR. I am pleased to have been able to help TDR respond appropriately to its fourth external review, which in many ways was the most crucial of such reviews in view of today’s changing environment, with a greater range of partners now active in the field of tropical diseases. After 30 years, it is time for TDR to change, evolve and grow, and the important recommendations of the fourth external review committee are being built upon with the new strategy and vision for TDR. The stewardship function enunciated in TDR’s new strategy will play a major role in assisting all partners by providing much needed analyses of results, needs, gaps and opportunities, thereby enabling more strategic decisions and investments to be made.

As my term of office as Chair comes to an end, I look forward to continuing to work as a member of the JCB and to help TDR implement its new strategy. I take this opportunity to extend my deep gratitude to all who have supported me in my role, notably the Vice-Chairs, Dr Jacques Laruelle and Professor Rolf Korte; the Chair of STAC, Professor Peter Ndumbe; the three Special Programme Coordinators during my tenure, Dr Margaret Chan, now the Director-General of the World Health Organization (WHO), Dr Anarfi Asamoah-Baah, now the Deputy Director-General of WHO and Dr David Heymann, Assistant Director-General for Communicable Diseases; Dr Robert Ridley, current Director of TDR; and his capable staff with whom I have worked very closely, at times on a daily basis. Our collaboration has been excellent and was based on mutual trust, respect and cooperation.

My wish for the future is for TDR to continue to strengthen its important work in improving the health of the poor and for the JCB to sustain and increase its commitment, surpassing its historical level of support, to enable the new vision for TDR to be achieved and to foster an effective global research effort on infectious diseases of poverty in which disease-endemic countries play a pivotal role.

DR BIJAN SADRIZADEH, Chair of JCB (June 2005–June 2007).
A young boy has blood taken from his finger tip in a field study to detect the presence of trypanosomes, parasites that cause sleeping sickness (Ivory Coast • 1988 • WHO/TDR).
Introduction

Setting the scene: the 3 Ps — people, products and partnerships

Three decades of remarkable change — for our global village, for health, for scientific research and for TDR — give reason for reflection as TDR's governing body, the Joint Coordinating Board (JCB), celebrates its 30th anniversary. TDR was formed in an era of growing awareness of our world's interdependence. The programme came of age as social and economic development to bridge the gap between rich and poor countries became a mainstream UN endeavour. It has matured at the turn of the millennium, in a period of heightened recognition of our continued vulnerability to infectious diseases of all kinds — from TB, malaria and HIV/AIDS to lesser known parasitic infections. Yet there is also growing awareness of the potential for scientific research — undertaken in innovative public and private partnerships — to generate new knowledge of how to reduce these threats, particularly in countries bearing the greatest disease burden.

It was in the early 1970s when the vision of a global, UN-sponsored research effort to tackle some of the world's most neglected diseases was first formed. This was the end of the colonial era and a time when missions to the moon were giving rise to the popular concept of 'Spaceship Earth' — an awareness that we all lead interdependent and interconnected lives. As researchers in biomedical science made giant leaps forward in genetics, molecular biology and technology, and life expectancy improved dramatically in industrialized nations, reflecting a century of advances in public health and communicable disease control, attention turned to the plight of those in the less-developed world, where infectious diseases continued to cause enormous suffering and death, also slowing socio-economic development.

It was in this same period that a number of novel UN-based entities emerged to address a range of cross-border global problems. These new entities, sometimes described as 'Global Public Policy Networks', were innovative assemblages of governments, international organizations, the private sector, non-governmental organizations (NGOs) and other civil society groupings, brought together under a single organizational umbrella. A relatively open membership and varying degrees of partner involvement gave these organizations flexibility to address international issues. One of the first such entities was the Consultative Group on International Agricultural Research (CGIAR), which was created in 1971 when agriculture was becoming the key focus of development and the engine of Asia's Green Revolution.

The beginning of TDR

May 1974. The World Health Assembly calls for a programme to:

1. Intensify activities in the field of research on the major tropical parasitic diseases (such as malaria, onchocerciasis, schistosomiasis and the trypanosomiasis), taking into consideration that such activities should be carried out in disease-endemic areas whenever possible and feasible.

2. Define the priorities in research on the problem of tropical parasitic diseases in the various regions of the world, bearing in mind the primary needs of developing countries.

3. Extend cooperation with national institutions and other governmental and non-governmental organizations in regard to the coordination of research in this field.

4. Enlist extrabudgetary resources on a wider scale for these purposes.

Resolution WHA27.52.
Reproductive health was another emerging issue on the global agenda at that time, encompassing topics such as population growth, family planning, changing sexual mores and gender inequalities. The Expanded Special Programme for Research Development and Research Training in Human Reproduction (HRP) was formed in 1972 by WHO, together with two other United Nations agencies and the World Bank, as an instrument for research in that domain.

In the spring of 1974, the World Health Assembly called upon the Director-General of WHO to similarly intensify activities in tropical disease research, while strengthening research and training activities in developing countries. This call reflected a growing recognition that economic development had to go hand in hand with better health for the world’s poor. As WHO’s then Director-General, Dr Halfdan Mahler, was quoted saying at the time, TDR would help improve the health of developing countries so that they could produce the improved grains, tubers and animals developed by CGIAR’s research.

This set the stage for the Advisory Committee for Medical Research (now Advisory Committee for Health Research) to approve plans for a Special Programme for Research and Training in Tropical Diseases (TDR) in June 1974. In November of that year, a meeting of experts on leprosy launched TDR’s initial activities. This meeting not only spearheaded the eventual development of scientific working groups for other TDR-targeted diseases, it also brought together scientists, public health experts and institutions that were to play a key role in TDR for years to come. The gathering was supported by a US$ 25 000 grant from the Wellcome Trust as well as by the Government of Norway, which were among the institutions and governments that played a key role in TDR’s establishment and continuing support. The meeting was chaired by the renowned immunologist Professor Barry Bloom, then chairman of the Microbiology Department at Albert Einstein College of Medicine, Yeshiva University, and now Dean of the Harvard School of Public Health. Bloom would serve for many years on TDR scientific and steering committees, and then as Chairman of TDR’s Scientific and Technical Advisory Committee (STAC), the top scientific oversight body. The Swedish medical doctor and biochemist Professor Sune Bergström, who would later win a Nobel Prize, was also in attendance at the initial JCB meeting and would remain active in the programme for many years, prior to his death in August 2004.

The creation of the JCB

By January 1975, TDR had come into being as a programme entity. Over the next three years, its structure would be consolidated and its future assured. In 1976, the United Nations Development Programme (UNDP) formally joined WHO as a co-sponsor following its close
involvement with WHO in the development of the programme. In 1977, the World Bank also became a co-sponsor. In February 1978, a meeting of cooperating parties endorsed a Memorandum of Understanding on the administrative and technical structures of the programme. These included the JCB, the Standing Committee and the STAC. In November 1978, the first JCB session was held. The role of the JCB was — and still is — to review all TDR’s activities, evaluate its progress, decide on its budget, planning and execution, and approve arrangements for its financing.

The JCB comprises four groups: 12 members representing the various resource contributors to TDR; 12 members representing governments in the six WHO regions; and a representative for each of the co-sponsors. Other cooperating parties (initially three and expanded to six in 2006) are selected to serve on the board by the JCB itself, from among those governments, intergovernmental and other non-profit organizations that contribute financial resources, technical and/or scientific support to TDR. The creation of the JCB set a framework for TDR that was not only independent and transparent but also responsive to the needs of partner countries and institutions in both the developed and developing world.

The JCB determines TDR’s strategic direction. In reviewing and approving TDR’s strategies and goals, the JCB must maintain a harmonious balance between all aspects of the programme. TDR’s close liaison with a range of public, academic and private institutional partners worldwide requires board oversight to ensure that balance is retained between these institutions, and public interest remains pre-eminent at all times. Above all, the JCB is an advocate for the interests of the poor in disease-endemic countries, not only in terms of the priorities set but also for other issues such as the ethical conduct of clinical research.

Particularly at the time of its foundation, the JCB’s composition was innovative because it opened decision-making processes to equal participation by both donors and recipients, effectively breaking down those distinctions and creating a new partnership paradigm, whereby representatives from disease-endemic countries had a major role in determining TDR’s strategic direction.

Managing the science

In 1979, one year after the JCB was created, TDR’s STAC held its first meeting, taking over the responsibilities of the Technical Review Group, which had met from 1976 to 1978. STAC is composed of leading scientists from around the world. From its early days until the present, STAC has helped set the programme’s overall research priorities and goals in the form of recommendations to the JCB.

Other mechanisms of scientific peer-review extend deep into TDR’s operational structure. Each area of research activity is overseen by a specialized Scientific Working Group (SWG) led by a Steering Committee. Together with technical staff, the SWG selects research projects for funding and evaluates progress. Meanwhile, activities to train and strengthen institutions are guided by the Research Strengthening Group (RSG), which held its first meeting in 1977.

This peer-review system provides scientists worldwide with a say in TDR’s priorities and projects while also giving TDR both scientific credibility and organizational flexibility. As in the JCB, disease-endemic countries have scientific representation on each SWG. Coordination between TDR and WHO departments is facilitated by the participation of WHO expert staff and administrators in STAC, the SWGs and Steering Committees.

As the late Dr Goodman observed, “The concept of an independent STAC to oversee the plans and research results of the various SWGs gave research credibility to an international public health organization which had until then no great experience in running large international biomedical research projects.”

(TDR, 1987; TDR, 1995)

TDR’s first director, Dr Howard Goodman (who died in 1998), also noted that the “concept of an independent JCB of donors and participating countries to oversee the financial and administrative elements of the programme helped alleviate concerns among donors that decisions might otherwise be affected by political currents in WHO.” The drive for scientific integrity also was embedded in the structure of TDR, through STAC and the scientific working groups.
TDR governance – empowering developing countries

At the time of TDR’s foundation, there was no international framework for coordination of research to support infectious disease control, particularly in the developing world. Moreover, apart from their vote at the World Health Assembly, developing countries had little say in research priorities. The prevailing paradigm in research, as in development, was still one of donor and recipient. Activities were mostly ad hoc, determined by factors such as geographical proximity, common language, ex-colonial spheres of influence, specific problems or issues, available expertise, research equipment, databases and facilities, and transport and communication factors (Rand, 2001).

The concept of ‘empowerment’ had not yet permeated UN thinking. However, TDR’s design reflected an emerging philosophy — that disadvantaged populations, when properly enabled, would be capable of driving a ‘bottom-up’ development process, rather than passively awaiting ‘trickle-down’ benefits. The language may have changed over time, but the same basic vision still guides TDR’s operations today.

Defining priorities — addressing neglected priority needs

Fundamental to this approach was the research strategy and institutional framework that TDR adopted in the early days, which integrated diverse scientific viewpoints about TDR’s appropriate role. For instance, some founders and partners believed TDR should focus on basic biomedical research and research into new drugs and control tools. Others sought an emphasis on social science research that improved the use of existing tools in the field. At the same time, capacity building to foster research in developing countries was viewed as a critical function. Bringing together these diverse strategic points of focus into a single vision and framework ultimately gave TDR the potential to respond flexibly and in an innovative way to new research challenges that would emerge over time. TDR became a catalyst for high-level partnerships in discovery research and a pioneer in participatory and community-based field research at the grassroots level.

TDR’s key partners then and now include: control departments within WHO, as well as technical and policy echelons of its other co-sponsoring agencies; national governments and ministries; private foundations, beginning in the early days with the Wellcome Trust and Rockefeller Foundation; and partners in the scientific and research community as well as private industry. Notably, TDR was one of the first public organizations to engage with the private sector in public–private partnership activities, long before ‘PPPs’ became a popular institutional model (Lucas, 2000; Buse and Walt, 2000). Twenty-five years later, TDR helped create some of the first formalized PPPs for health research such as the Medicines for Malaria Venture (MMV) and the Foundation for Innovative New Diagnostics (FIND), in order to better harness global knowledge and resources for specific needs. Throughout TDR’s history, leading scientists from a range of institutions worldwide, including several Nobel Prize winners, have contributed to the constant peer-review of the programme’s work.

In terms of its global outreach and organization, over the course of its first decade TDR moved away from the prevailing wisdom of identifying a few ‘centres of excellence’ in developing countries and concentrating vast amounts of resources into those few institutions. Instead, what developed over time was a network approach. Long
before the age of the internet and email, and before decentralization became popular, TDR was building dynamic ‘virtual’ networks of researchers and research institutions that were widely dispersed and often in remote locales. Revolutionary in its time, this approach proved to be both prudent and cost-effective. It empowered a broad variety of institutions and scientists in developing countries to identify their own problems, find novel solutions and press for the transformation of research knowledge into disease-control programmes. Today, as a new wave of science and technology investment aims again to foster centres of excellence in developing regions, the value of the TDR paradigm for sustainable development should not be ignored.

Building research capacity

From the beginning, a steady 25% of TDR’s total resources was earmarked for research capacity strengthening (RCS). Grants in this area were multi-faceted. There were training grants to support developing country researchers in their Masters, PhD and post-doctoral studies. Initially these grants were awarded for studies in institutions in developed countries, but later, as developing country institutions increased their academic capacity, most grants were awarded for studies locally or regionally. There were also ‘re-entry’ grants to facilitate the return of skilled scientists to their home countries, and thus reverse the ‘brain drain’ which has constituted one of the gravest socio-economic threats to disease-endemic countries over the past three decades. TDR offered various forms of grants and support to build research institutions in the countries where the diseases were endemic. Notably, grants were awarded directly to institutions or to principal investigators in developing countries, and not to agencies or consultants based elsewhere. Over 30 years, more than 4000 RCS projects in 80 countries have fostered and strengthened the capacity of over 200 institutions. TDR has sponsored training grants for more than 1500 young scientists worldwide, many of whom later became involved in other aspects of TDR research. An additional 5000 young scientists ‘nested’ their graduate training within other TDR grant formats. Indeed, despite the impressive list of milestones in product development and field research, in the eyes of its many partners and the broader public, one of TDR’s best known achievements is its capacity-strengthening efforts. These efforts acted as a catalyst for the development and growth of critically needed institutions, as well as professional and training networks, allowing the benefits of scientific knowledge in public health to be shared more evenly across the globe.

Taking stock

Fast-forward 30 years from the formation of TDR, and the world has seen dramatic and substantial advances in the fight against infectious diseases. TDR has played a major role in many of these advances, working with partners to provide research-based tools and evidence for control agencies to take forward into policies and programmes.

Spectacular advances have been made towards elimination of leprosy as a global public health problem. Onchocerciasis is under control in most of Africa, and has been eliminated as a public health problem in savanna areas of 11 West African countries. Following elimination campaigns begun in the 1990s, transmission of Chagas disease has been interrupted in several countries of Latin America, and large areas of the Southern Cone are virtually free of domestic infestation by the main triatomine insect vector (Remme et al., 2006). In addition, a Global Programme for Elimination of Lymphatic Filariasis (GPELF) has been established by WHO, as has a regional framework in WHO’s South-East Asia Region for the elimination of visceral leishmaniasis, signalling new potential to address these diseases.

“For TDR is] a global programme of international technical cooperation ... with the two interdependent objectives of developing improved tools for the control of tropical diseases and strengthening the research capability of affected countries themselves.”

Memorandum of Understanding on the administrative and technical structures of TDR, February 1978.
A cornerstone of such advances are new drugs, drug combinations and diagnostics; new evidence-based tools, methods and strategies for bolstering access to health care and treatment; and methods for the biological and chemical control of disease vectors, many of which have been developed and promoted through TDR-sponsored research and evaluation. Of the 18 new drugs or new drug combinations that have been registered for TDR-targeted diseases since the 1970s, more than half have been a result of TDR collaborations (see Appendix I) (Trouiller et al., 2002).

Yet some of TDR’s key achievements are by now so much a part of public health that the programme’s pioneering role in their development might well have been forgotten. The fact that TDR stimulated research into the first multidrug treatment for leprosy, which has reduced infections from over 5 million registered cases in 1985 to about 220 000 registered cases in 2006 (over 95% of which are cured within six months to two years), is little known to the broader public. Although the incidence of new infections is still significant in certain parts of Africa, Asia and Latin America, in many countries this ancient disease is on its way to becoming an artefact of history (WHO, 2005). TDR also helped support early research and collaboration with Chinese institutions into the artemisinin compounds that today are the basis for a malaria treatment, and coordinated the large multi-centre clinical trials that generated evidence of the value of artemisinin-based combination therapies (ACTs). Additionally, it led some of the first efforts to promote genetic research into the development of modified mosquitoes to control malaria, yet these efforts are largely unknown outside the genomics community.

In terms of its field and applied research, TDR played a key role in organizing and financing the large-scale trials of insecticide-treated bednets to prevent malaria transmission, which led to their introduction by WHO as a key disease-control intervention for malaria, one of the world’s biggest killers. Similarly, TDR supported research into and documented the efficacy of unit-dose packaging for home and community-based malaria treatment, as well as being involved in the development of appropriate dosing and packaging for effective use of the first internationally registered anti-malarial ACT, Coartem®. TDR-supported field research generated the first systematic mapping of the prevalence of Chagas disease and vector infestation across

“**Enthusiasts of basic biomedical research believed that the new advances in molecular biology, immunology, cell biology and biochemistry held the key to the development of new tools for the control of tropical parasitic diseases. At the other end of the spectrum were the sceptics who felt that the research effort should concentrate mainly on the better application of existing technologies rather than the search for new tools. The final decision was a compromise that took note of both sides of the debate.**”

endemic areas of Latin America, which was critical to subsequent disease-control efforts.

TDR’s engagement, stimulation and development of much of the evidence that forms the basis for the strategy of onchocerciasis control — from the early stages of the development of ivermectin to new rapid assessment methods for disease mapping, and ultimately to promoting community-directed interventions — has been critical for one of the biggest public health success stories in Africa, preventing and controlling river blindness in a population of over 60 million people. Of great significance to the onchocerciasis control effort has been the research underpinning the development of an innovative and cost-effective mass drug-delivery system, community-directed treatment, which became the backbone of onchocerciasis control programmes in the late 1990s. In the new millennium, TDR is building on this concept to assess its value in the effective co-implementation and integrated delivery of other critical health measures in Africa.

Diagnostics R&D is also playing a larger role in TDR’s research efforts, particularly for TB, malaria and sexually transmitted diseases. TDR is supporting both the development of new diagnostic tools and resources and the implementation of evidence-based guidelines for the evaluation of diagnostics. Improved diagnostic tests not only save lives at the individual level, they promote more cost-effective use of resources and blunt the build-up of drug-resistant microorganisms. At the policy level, TDR-driven research into, and validation of, rapid syphilis diagnostics has led to the development of elimination programmes for congenital syphilis in several countries.

All in all, over its 30-year history, TDR has supported nearly 9 000 R&D projects involving more than 7 000 scientists in 146 countries, mostly in the developing world. In many cases, however, practical, life-saving tools are still not being optimally used. For example, only 4–5% of children under the age of five in Africa sleep under insecticide-treated bednets, which TDR studies in the mid-1990s demonstrated could cut child mortality by 20% (UNICEF, 2006). TDR-supported research has demonstrated that in households where bednets are used, gender and social hierarchies can still leave the most vulnerable family members, such as pregnant women and children, unprotected.

So, while acknowledging the real gains that have been made, the dimensions of the infectious disease threat today remain significant and highly dynamic in a landscape of new social, economic and environmental drivers. In the early 1970s, it was estimated that 1 billion people out of a global population of about 3.9 billion were suffering from one or more tropical parasitic diseases. Today, while the world’s population had approximately doubled and the spectrum of disease threats has shifted, every year around 1 billion people in 149 countries still are victims of one or more neglected tropical diseases (WHO, 2006a). Climate change, large-scale migration, urbanization, irrigation and globalization also are changing the patterns of infectious disease and vector-borne disease transmission. Some diseases, such as TB and dengue, are resurgent while new diseases, such as HIV/AIDS and severe acute respiratory syndrome (SARS), have emerged.

As TDR enters its fourth decade there are formidable challenges ahead. Yet, acknowledging the successes that have been achieved to date can also inspire future efforts. No achievement could have been possible without collaborators, partners, donors and sponsors, notes Dr Howard Engers, former manager of TDR’s leprosy vaccine and malaria vaccine research programmes, and presently director of the Armauer Hansen Research Institute in Addis Ababa. “Far from trying to take all of the credit for TDR,” he says, “everything TDR has accomplished has been through partnerships.”

This book is dedicated to the JCB, which encompasses the key participants and representatives of TDR’s most vital partnerships, and which has been steadfast in its provision of oversight and guidance for the past 30 years.

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

(UNESCO Science Report, 2005).
Phase I
(1975–1986): Heroic goals

TDR took on eight of the world’s most neglected diseases, affecting millions of people in poor countries. Critically needed new drugs and drug combination therapies were developed for leprosy, malaria and sleeping sickness, and new diagnostics for other diseases. An innovative compound screening network identified the potential of ivermectin for onchocerciasis. TDR’s early support for Chinese research into artemisinin derivatives for malaria helped introduce an ancient remedy onto global research agendas. Pioneering field research and socio-economic research guided effective treatment of diseases, including those socially stigmatized (such as leprosy). At the same time, TDR supported long-term development of research institutions in disease-endemic countries, and high-level training of hundreds of scientists.
Advances in basic research, such as the development of monoclonal antibodies in 1975, opened up the possibility of developing more sophisticated diagnostic tools, as well as progressing in vaccine and drug research. An improved understanding of the fundamentals in immunology, cell biology and molecular biology, including the development of techniques for the genetic manipulation of organisms, paved the way for gene sequencing and an increased understanding of the biology of many of the major pathogens responsible for tropical diseases, their vectors and their hosts.

At the same time, it was becoming increasingly clear that the great strides in public health that had been made in developed countries since the beginning of the century were not occurring in poorer nations at the same pace. Many, if not most, major disease-control initiatives in the least developed countries were driven vertically by donors, and once these campaigns ended, any public health improvements were at risk. The capacity to conduct research to support and sustain public health initiatives was similarly weak. Private sector pharmaceutical firms based in developed countries had little incentive to invest in research into drugs and tools needed by poor countries that could ill-afford to pay for them.

It was against this background that then WHO Director-General Dr Halfdan Mahler articulated a vision of WHO as a global ‘health conscience’, acting as a countervailing influence to the narrower commercial interests of the marketplace (WHO, 1979). This followed the 1978 ‘Health for All’ Declaration, which was adopted at the International Conference on Primary Health Care in Alma-Ata, organized by WHO. This conference emphasized that improving primary health care was key to public health advances in poor countries, as well as being key to social and economic development. Although primary health care, as such, was anchored in the health care system, home-directed and community-based treatment would emerge as innovations of the late 1980s with the same philosophical basis, emphasizing good local use of technology and knowledge.
In TDR — the needs were great

TDR’s initial focus was on eight of the most serious and most neglected tropical diseases: malaria, leprosy, schistosomiasis, visceral and cutaneous leishmaniasis, onchocerciasis, lymphatic filariasis and the two diseases caused by parasitic trypanosomatid protozoans — Chagas disease in the Americas and human African trypanosomiasis (HAT), popularly known as sleeping sickness, in Africa. These particular diseases were targeted both because new drugs, vaccines and vector-control methods were desperately needed, and at the same time, basic research advances had opened up new possibilities for finding solutions. Scientists had just managed to culture *Plasmodium falciparum* in the laboratory, the most deadly of the four *Plasmodium* species to cause malaria in humans. The bacteria responsible for leprosy, *Mycobacterium leprae*, which would not grow in artificial cell-culture medium, had just been cultured in armadillos, paving the way for research into new drugs and diagnostics for this ancient malady.

Strikingly, in this pre-AIDS period, TB was not included in TDRs targeted diseases. The scourge associated with the crowded housing and work places of the early industrial era was not regarded as a major public health challenge in the 1970s. This would change by the turn of the millennium, when both TB and dengue would be added to the programme’s portfolio, reflecting the re-emergence of TB as a serious problem in HIV-infected populations and the epidemic growth of dengue in fast-developing urban areas of Asia and Latin America.

Early successes in drug development — leprosy, river blindness, malaria and HAT

One of the first achievements of note was the leadership role taken by TDR in the search for a new leprosy treatment. Early in its first decade, TDR helped demonstrate that drug resistance to dapsone, the prevalent treatment for leprosy at the time, was a real and growing problem, as was the lifelong course of treatment required.

“TDR, like other programmes in UN agencies, had to contend with political realities, especially at a time when the world was sharply divided into two major power blocks. TDR adopted a policy of providing a neutral platform on which scientists from all over the world could work together against diseases that were the common enemies of all human beings. Scientists responded admirably to this approach.”


TDR’s experts and advisers pointed out that several compounds had shown potential activity against *M. leprae* in laboratory tests, but they had not yet been properly evaluated for use in humans. More generally, scientists were beginning to investigate how multidrug therapy (MDT), when two or more drugs act in unison against different chemical targets in a given parasite or pathogen, might be more effective than monotherapy.
Eliminating leprosy

“Until the mid-1970s, leprosy was a disease more or less beyond hope. The bacterium was developing resistance to dapsone monotherapy — which was a lifelong treatment. Some 10 to 12 million people were estimated to have the disease. Then … WHO took the daring decision to advise a simple regimen of therapy with three drugs to combat resistance — multidrug therapy or MDT. By then, TDR had mapped and quantified the main areas of dapsone resistance, developed clinical protocols for MDT in different parts of the world, and established widespread ‘post-marketing’ surveillance of MDT. By the end of 1994, the global number of registered patients was 1.3 million — a fourfold decrease — with 560 000 new cases being detected annually.”


“The MDT for leprosy must be one of the top five achievements of TDR for the first decade. Although it should be emphasized that it was leprosy clinicians who were doing the work, with TDR support. But the development of MDT was, in fact, one of the reasons TDR’s work on leprosy vaccines ceased. We realized that MDT was going to solve the leprosy problem and we did not need a vaccine.”

DR HOWARD ENGERS, Director of the Armauer Hansen Research Institute, Addis Ababa, Ethiopia (TDR manager of vaccine research, 1987–2004).

In July, 1978, scientists at the US-based laboratories of Merck, who had been researching ivermectin for several years, sent the compound to the TDR-supported drug-screening facility at James Cook University of North Queensland, Australia. Such screening, which tested ivermectin’s effectiveness in cattle harbouring a zoonotic strain of the filarial *Onchocerca* parasite responsible for river blindness, was regarded by scientists as the best predictor of how a compound would act against human onchocerciasis. Results showed the drug was ‘highly effective’ against the microfilariae, or infant larvae of the parasite, although it did not, in fact, seem to kill the adult worm. This screening test was part of a broader TDR effort to intensify the search for a new onchocerciasis drug, which had been established at considerable expense.

“The two drugs we had for onchocerciasis at the time were notorious poisons,” recalls Lucas. “We were really desperately looking for a new drug. When we visited the major drug companies, it was clear they
were not interested in this disease. No one was screening any compounds. We thought that perhaps there was a compound on the shelf that had not been discovered. The strategy put forward was to open a compound-screening network."

Along with James Cook University, the network involved researchers at the University of Georgia (USA); the University of Giessen (Germany); the Wellcome Trust (UK); the London School of Hygiene and Tropical Medicine; and the University of Tokyo.

“We asked industry to give us compounds to test,” continues Lucas, “and we would give them the results. We offered this free of charge and confidentially. We had thousands of compounds sent through small animal screens in the broader network. But since these often yielded false positives, the most promising compounds were sent to the cattle screen, which had been set up by TDR in order to expedite the search for a new drug for onchocerciasis. It was much more expensive, but also potentially more accurate. Among the first compounds to go through the cattle screen was ivermectin.”

Merck’s scientists were enthusiastic but TDR less so because the ultimate TDR goal was to identify a ‘macrofilaricide’, a drug that would sterilize or kill the adult parasite and not just the larvae, and thus cure an infected person rather than just control the disease. Merck proceeded independently to Phase I clinical trials. Serious TDR–Merck collaboration, however, resumed in the later stages of clinical trials, as ivermectin’s efficacy as a treatment and control measure became more evident. TDR contributed to the design of study protocols and definition of dosage and facilitated Merck’s links to collaborative networks in the Onchocerciasis Control Programme (OCP) of 11 West African countries (TDR, 1998).

In February 1986, as the drug was about to be registered, Lucas and Dr Brian Duke, head of WHO’s Filariasis Unit, held a decisive meeting with then Chief Executive Officer of Merck, Dr Roy Vagelos. Merck had been negotiating with development and donor agencies over the purchase of ivermectin, but had received little response. The TDR and WHO officials came ready to drive a hard bargain over pricing for developing countries: “Vagelos made us cups of coffee in his office,” recalls Lucas. “Then, as we sat down to talk, he told us that he had not gotten any response from the donors. He said wanted to see the drug widely used, so he had decided to donate it. But at the time, this remained confidential. In June 1986, as Lucas was about to conclude his ten-year term with TDR, he contacted Vagelos and Merck once more. “I asked them if I could make public Merck’s offer to donate ivermectin at the upcoming JCB meeting — the last one that I would attend as Director.”

The result was the 20 June telex to TDR. Vagelos was later awarded a medal by the Prince Mahidol Foundation for his “bold and unprecedented” decision. Lucas and his successor, Dr Tore Godal, received the same medal jointly for their contributions to TDR.

Following Merck’s announcement, TDR helped move rapidly with partners in OCP, WHO and elsewhere to translate the donation offer into policy action. Large scale trials were launched to determine safety and effectiveness of mass drug administration. Subsequent research helped define a public health rationale, epidemiological evidence and strategies for an unprecedented programme of community-directed treatment with ivermectin. Over the next two decades ivermectin (mectizan®) would reach some 60 million of the 100 million people at risk in endemic areas in sub-Saharan Africa. Although not a perfect solution, annual treatment gradually brought onchocerciasis under control in most areas reached, and contributed to the elimination of onchocerciasis as a public health problem in savanna areas of West Africa.

### Ivermectin comes free

“Merck and the WHO have collaborated extensively on the development of ivermectin for onchocerciasis … The special circumstances associated with this disease and the interest of several organizations and governments have caused Merck from the outset to consider ways of accommodating a variety of objectives. First and foremost is ensuring that the drug will be put to optimum use for the benefit of onchocerciasis patients and others who may be at risk. Consequently, 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 TDR Director Adetokunbo Lucas, 20 June 1986.
Paving the way for new malaria drugs — artemisinin

Malaria remained the biggest killer worldwide, and it was here that a new initiative, led by Chinese scientists and supported at an early stage by TDR, helped to pave the way for significant breakthroughs in malaria treatment. This initiative was research into the anti-malarial properties of the indigenous Chinese plant known as qinghao or sweet wormwood (*A. annua*). The plant had been used historically in traditional Chinese medicine, and Chinese researchers had identified its active compound, artemisinin, as potentially effective against parasites. Interest in new anti-malarials was high as parasite resistance was developing against most other available drugs, some of which had substantial side effects.

TDR, whose far-flung networks already included collaborations in China, would be among the first international institutions to dispatch scientists to China’s artemisinin research facilities, appreciate the value of the endeavour, and transmit that to colleagues elsewhere. Research cooperation into the properties of artemisinin, in an era when the Cold War was still a dominant feature of international politics, involved some delicate diplomacy. But overcoming the obstacles was a shared scientific quest — a better treatment for one of the world’s deadliest diseases and a modern use for an ancient Chinese herbal remedy.

“The Chinese scientists who were working on artemisinin contacted the malaria section of WHO,” recalls Lucas. “They were very anxious to have the drug registered and widely distributed. We said it needed more workup, including pre-clinical laboratory testing of toxicity. Part of that was done through the TDR network.”

“TDR helped to get researchers outside of China involved in artemisinin and get it on the research agenda.”

A kilogram of artemisinin

“In 1979,” relates Dr Wallace Peters, former Chairman of TDR’s Steering Committee on Drugs for Malaria (CHEMAL), “we went to Beijing to meet the Chinese (researchers doing artemisinin research and development) at the government’s invitation. We visited the labs at the Centre for Traditional Medicine and at the Second Military College in Beijing. The Chinese were very open. They were making it and growing it, and wanted to supply and sell it. It was just at a time, after the Cultural Revolution, when the Chinese wanted more dealings with the rest of the world, and wanted international recognition.

“China recognized that the toxicity standards were not detailed enough and requested assistance. CHEMAL supported inspection of the production plant by the US Food and Drug Administration (FDA) in 1982. Training fellowships were offered to the Chinese ... from the western regulatory point of view, there were big gaps in the Chinese toxicity and efficacy studies ... but China wanted the drug sold and used, and was uncomfortable about TDR taking over this development work.” (TDR 12th Programme Report, 1995).

Although TDR fully recognized the rights of the Chinese to develop artemisinin, validating the safety and efficacy of a drug with potential to improve malaria treatment worldwide required a broader testing effort. TDR sought to obtain a kilogram of purified artemisinin to allow the substance to be tested through its network of partner laboratories. When obtaining even a kilogram of purified artemisinin from Chinese sources proved difficult, Lucas decided to look elsewhere. TDR commissioned researchers at Mississippi University to grow the plant A. annua, and extract the sought-for kilogram of the purified artemisinin. This proved expensive as the yield was quite low and considerable acreage had to be cultivated. However, shortly after TDR had commissioned this work, a kilogram of artemisinin from Chinese collaborators did indeed arrive (Lucas, 2007).

By 1992, the first oral artemesinin-based combination therapy (ACT) of artemether and lumefantrine was registered in China. In 1994, Novartis formed a collaborative agreement with the Chinese Academy of Military Medical Sciences (AMMS), Kunming Pharmaceutical Factor (KPF) and the China International Trust and Investment Corporation (CITIC) for further development of the same combination, eventually leading to international registration of Coartem® and Riamet® (Olliaro, 2003).
Many other public and private partners across Asia, Europe and North America would soon take the lead in development of the main artemisinin derivatives (artemether, artesunate and arteether) and ACTs. TDR’s role would evolve into more supportive and focused endeavours, such as research into the development of injectable artemisinin derivatives for severe malaria; field trials demonstrating the value of ACTs in general; and field trials that demonstrated the safety of ACTs in young children. TDR-supported research for *in vitro* testing of anti-malarial drug resistance would help to develop a global map of parasite resistance to other drugs then in common use.

TDR’s early appreciation of, and response to, the innovative Chinese research into artemisinin demonstrated leadership in the initial phase of exploration, bridging barriers of geography and political mistrust to benefit public health.

DFMO — the ‘resurrection’ drug for sleeping sickness

Towards the end of the first decade came the discovery that d,l-α-difluoromethylornithine (DFMO), originally developed as an anti-cancer compound, could be used to treat HAT. HAT is popularly known as sleeping sickness because of the extreme fatigue and disorientation...
A tsetse fly trap being sprayed. Rural populations are most at risk of sleeping sickness. Even during daily activities, villagers may be exposed to tsetse flies, the vectors of sleeping sickness parasites. Easily erected insecticide-impregnated traps placed in tsetse habitats or around village perimeters help to reduce disease transmission (Ivory Coast • 1992 • WHO/TDR/EDWARDS).
that incapacitates victims before death. DFMO was initially developed by Marion Merrell Dow Pharmaceuticals (now Sanofi–Aventis). With TDR support, Phase III clinical trials of the drug began in 1987, and the rapid response of patients even in late stages of Trypanosoma brucei gambiense sleeping sickness gained DFMO the nickname the ‘resurrection’ drug. DFMO, or eflornithine® as it was licensed, was the first new drug for sleeping sickness in 40 years. It is noteworthy that Sanofi–Aventis now makes the drug available through a donation programme under a WHO Memorandum of Understanding.

Pioneering field research and social science research

In terms of field research, emphasis was being placed on vector control, particularly for diseases where the promise of new and more effective drugs was still remote. Reducing insect vector populations through environmental management or manipulation has historically been recognized as an important aspect of disease prevention, and knowledge of how certain species act as predators on vector populations was expanding. Interest was also growing in biological vector-control tools that might replace chemicals to which parasites or vectors had developed resistance, as well as chemicals increasingly recognized as posing long-term risks to health and the environment, such as dichloro-diphenyl-trichloroethane (DDT).

TDR thus supported research into ‘larvivorous’ fish species that prey upon the larvae of malarial insects living in both water containers and flooded agricultural fields. It also supported research into the use of the bacterium Bacillus thuringiensis israelensis H-14 (Bti) to control larvae of mosquitoes and other vectors. Bti was incorporated into control programmes by 1982 and was soon followed by another bacterial vector control tool, Bacillus sphaericus (Rowe, 1984). Bti, in particular, would play an important role in controlling the blackfly vector for
onchocerciasis in the savanna regions of sub-Saharan Africa in the mid-1980s, where vector control was the main means of disease control and the synthetic larvicides available at the time were losing their impact. In the case of onchocerciasis, Bti was later superseded by other synthetic formulations, but it remains an important tool for mosquito control in the USA. Elsewhere in Asia, Africa and the Americas, Bti and B. sphaericus have been used successfully in a range of field trials and pilot control efforts, and larvivorous fish have been deployed against malaria vectors in rice fields and water containers, although such tools are still not widespread in mainstream vector control or vector-borne disease-management programmes (Walker, 2002).

Also in the mid-1980s, TDR-supported field research trials of HAT vector control began to demonstrate the efficacy of pyramidal tsetse fly traps for control of the vector population, in the absence of better drug treatment.

Across nine countries in Latin America, an unprecedented series of epidemiological studies supported by TDR between 1980 and 1985 helped develop a standardized protocol to determine the prevalence of Chagas disease and accurately map the patterns of infestation by the insect vectors of the Trypanosoma cruzi parasite. One aspect of successful prevalence mapping was a TDR capacity-strengthening effort that helped scientists and laboratories in endemic countries to standardize their serological techniques and criteria for diagnosis of the infection.

“It was the first time that disease prevalence information was generated in a way that was truly comparable,” notes Lucas. “That generated a first-ever map of Chagas prevalence in all of the endemic areas of Latin America.”

In this decade and the next, TDR also supported field research on the effectiveness of various vector-control tools, including vector detection sensors, insecticidal paints, fumigant canisters and housing improvements, as well as measures to halt Chagas transmission through blood banks by improving serological screening. Together, the new diagnostic, screening and vector-control tools would help provide the evidence base for the Southern Cone Initiative. Launched in 1991, the initiative was a regional strategy for control of Chagas disease, coordinated by the WHO Regional Office for the Americas. It was followed in 1997 by similar initiatives in Central America and the Andean Pact regions (now the Andean Community). The results have been impressive; large areas of the Southern Cone region are now free of domestic vector infestation, and disease prevalence more generally has been reduced (Remme et al., 2006).

Social research was another area in which TDR would be called to innovate. In 1976, WHO Director-General Dr Halfdan Mahler had emphasized that “TDR was not designed simply to advance medical technology, but rather as a contribution to the promotion of human welfare in the widest sense in the context of a new international order in economic and social affairs.”

With no social research community and no significant tradition to build upon, it was another three years before the first TDR Steering Committee for Social and Economic Research (SER) became operational. Over time, the output from this effort began to support other aspects of biomedical research and assist in translating new interventions into implementation. In the area of leprosy, for instance, social science research began to uncover the social stigma that prevented many women from being diagnosed and treated for leprosy, owing to the fear that they would be unable to marry. These findings would later become important for the implementation of MDTs for leprosy and their broad public acceptance. In the 1990s, research into the socio-economic impacts of onchocerciasis, including the economic loss due to human migration away from disease-endemic, but fertile, river valleys, and the social stigma associated with onchocerciasis-related skin and eye conditions, would be critical in convincing policy makers of the importance of mass ivermectin administration.

“Ultimately, tropical diseases must be controlled by endemic countries. Even when an experimental tool fails, there will be trained men and women who are capable of developing a new one.”

DR FARROKH MODABBER, Consultant DNDi; Coordinator RCS and Manager Leishmaniasis Vaccine initiatives, TDR, 1984–2000.
Building research capacity

An early emphasis of research capacity strengthening (RCS) was on long-term grants to support the construction of research institutions in disease-endemic countries, more so than on targeted scientific priorities. The basic instrument was a non-competitive long-term grant that was designed to help an institution acquire or upgrade existing research facilities. Although part of the grant requirement was a programme of scientific research, scientific merit was still secondary to institution building. The programme involved capital grants for initial investigation, research and follow-up, so that funding could continue for a prolonged period of a decade or so. A major RCS review by TDR’s Scientific and Technical Advisory Committee (STAC) in 1992 noted that proposals for RCS institutional grants in

Critical action at a critical moment

“The TDR grants to the molecular biology and immunology departments were critical action at a critical moment, important to the rebuilding of FIOCRUZ in the late 1970s,” says former TDR Director Dr Carlos Morel.

Founded in 1900, the Oswaldo Cruz foundation (FIOCRUZ) underwent a major institutional and financial crisis in the early 1970s. In 1978, Morel, who had done his PhD thesis work at the Swiss Cancer Institute in Lausanne, Switzerland, joined the FIOCRUZ faculty to build a new biochemistry and molecular biology department. At approximately the same time, Dr Bernardo Galvão Castro (who later would become the first scientist in Latin America to isolate the HIV virus) took over as head of the immunology department. Both of them received institution-building grants from the TDR RCS programme. Castro received a long-term grant, while Morel received a US$ 100 000 grant to develop a course on genes and antigens.

“These were a small drop in the budget of FIOCRUZ,” observes Morel. “But they were critical to getting international support in two key areas of science that had been neglected. It was not only a question of money, but of prestige, leadership and international recognition.”

At about the same time, on the other side of the globe, another young scientist, Dr Yongyuth Yuthavong, was building another course on molecular biology at Mahidol University in Thailand, also with support from a TDR grant. Both Morel’s and Yuthavong’s efforts yielded manuals that in the 1980s became standard reference works for students of molecular biology in many developing countries. While Morel would later become president of FIOCRUZ, prior to assuming the Director’s post at TDR, Yuthavong would become Thailand’s Science Minister.

Oswaldo Cruz Foundation (FIOCRUZ) in Rio de Janeiro, which has benefited from TDR research capability strengthening (RCS) support (Brazil • 1992 • WHO/TDR/EDWARDS).
TDR’s research capability strengthening (RCS) programme has supported capacity building activities in field research and in the knowledge of disease impact and control at the community level, as in the training course portrayed here in Ndola (Zambia • 1980 • WHO/TDR).
this first phase tended to be “ambitious development plans, often carrying requests for expensive laboratory equipment and proposals for research projects in several diseases or more than one disciplinary area.” (TDR 12th Programme Report, 1995). This approach was judged to be successful in various external reviews both in terms of scientific output and in terms of increasing the capacity of key institutions at a time when such support was needed. But by the late 1980s, RCS grants evolved into increasingly competitive formats reflecting, indeed, the increased capacity of the research institutions in disease-endemic countries. Two examples of institutions that benefited from early TDR support were the Oswaldo Cruz Institute (FIOCRUZ) in Brazil and Mahidol University in Thailand, both now internationally recognized centres for tropical disease research. TDR also played a critical role in fostering a major malaria research centre in Mali, the Malaria Research and Training Centre, which today is doing “some of the most advanced malaria research on the continent,” in the words of Lucas. “There are other institutions in Africa doing comparable work, of course”, he says. “However, the Mali institution is truly an example of an African institution that was developed by TDR.” By 1986, TDR had supported 98 institutions, issued more than 700 training grants and launched more than 10 MSc courses in entomology and epidemiology in Asia, Africa and Latin America. One third of TDR-sponsored publications were authored or co-authored by scientists from disease-endemic countries (TDR, 1987).

### TDR/JCB institutional milestones

- **1974**
  - World Health Assembly calls for an intensification of research on major tropical parasitic diseases (WHA27/52).
  - World Health Assembly requests WHO’s role in the development and coordination of biomedical research (WHA27/61).
  - WHO Advisory Committee on Medical Research recommends the institution of an expanded WHO programme for research and training related to tropical communicable diseases and agrees on objectives for the expanded programme.
  - First TDR Steering Committee Meeting (IMMLEP Project Group).
- **1975**
  - TDR commences formal operations.
- **1976**
  - UNDP becomes a co-sponsor of the Special Programme.
- **1977**
  - First meeting of the Research Strengthening Group.
  - The World Bank joins UNDP and WHO as co-sponsors of the Special Programme.
  - World Health Assembly adopts goal of ‘Health for all by the year 2000’.
- **1978**
  - Meeting of Cooperating Parties endorses the Memorandum of Understanding on TDR’s Administrative and Technical Structures.
  - First meeting of the Standing Committee (comprising representatives of the three co-sponsoring agencies).
  - First session of the Joint Coordinating Board (JCB).
  - WHO Alma-Ata Declaration on Primary Health Care is identified as best strategy for meeting health for all goal.
- **1979**
  - First meeting of the Scientific and Technical Advisory Committee (STAC).
- **1980**
  - World Health Assembly endorses certification of smallpox eradication.
- **1982**
  - Submission of the First External Review Report to JCB (5).
- **1983**
  - TDR resource contributors adopt procedures for the selection of JCB members by the contributors (paragraph 2.2.1 of the Memorandum of Understanding).
- **1984**
  - First session of the JCB held outside WHO HQ — JCB (7) held in Bangkok, Thailand.
At a field survey to detect schistosomiasis, an infected child demonstrates that he has swallowed the medicine given to cure his infection. Children are weighed and the correct dosage of drugs (Praziquantel) is also prescribed by weight. (TANZANIA • 1988 • WHO/TDR/MORENA).
A man blinded by onchocerciasis (Haute-Volta • 1975 • donation from the Private collection of the late Dr Uwe Brinkmann, Harvard School of Public Health).
“When I got to my position as director of research in the Ministry of Health, I received information on what TDR was doing in Cameroon. I realized that when I was a young guy, TDR was conducting a study on onchocerciasis in the region where I was going to primary school, and maybe I was part of one of the trials with kids in that primary school.”

DR PIERRE ONGOLO-ZOGO, Chief, Division of Operational Health Research, Ministry of Public Health, Cameroon and representative to the JCB, Government of Cameroon.
Microscopic examination of blood samples and improved serodiagnostic tests such as the Card Agglutination Test for Trypanosomiasis (CATT) allow for a large number of people to be screened for gambiae sleeping sickness infection in a relatively short time (IVORY COAST • 1992 • WHO/TDR/EDWARDS).

“TDR has achieved so much with so little, thanks to partnerships and cooperation with many other players in the field of research and control of tropical diseases.”

Tsetse fly ecology; Tsetse flies in a test tube awaiting dissection after being trapped in a field near the river Comoe. Tsetse flies are the vectors of the parasites which cause sleeping sickness (Burkina Faso • 1990 • WHO/TDR/Baldrey).
Jiangsu province: A couple set fish traps in water close to a ruined building. Areas such as this are regularly flooded when rivers rise following heavy rains. The flooding means that intermediate host snails can re-invade areas previously cleared, parasites can develop, and the waters can become sources of infection for anyone living nearby (China • 1999 • WHO/TDR/Crump).
“TDR supports research on schistosomiasis in many ways using a holistic, long-term strategy, targeting all the facets of the parasite life cycle as well as the behaviour of people living in the endemic areas, an approach which is now starting to pay off in a big way.”

Research capability strengthening: Laboratory practice during a 1978 workshop on enzyme-linked immunosorbent assays (ELISA) at the Institute of Parasitic Diseases, Chinese Academy of Sciences, a WHO/TDR collaborating centre for malaria, schistosomiasis and filariasis (China • 1978 • WHO/TDR).
“Since its very inception, TDR’s active and ever evolving engagement ... has been a model for accelerated capacity building. TDR has not only served to transfer state-of-the-art technologies and knowledge to scientists in these countries, but it has also helped create an environment that has instilled respect for scientific rigor and merit.”

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.
In the world

If the first decade of TDR’s history was supported by general optimism regarding what could be accomplished by international development, the second decade saw the gap between ‘haves’ and ‘have-nots’ remain as wide as ever. Events such as the prolonged drought in Sudan and Ethiopia in the mid-1980s brought the plight of the poor into the homes of television viewers in the developed world, and generated widely publicized relief efforts. Yet, in the aftermath of such emergencies, the long-term trend was a decline in overseas development aid, particularly to the least developed countries, which saw overseas development aid drop from US$ 16.6 billion in 1992 to US$ 12.1 billion in 2000 (UN, 2001a).

China’s doors were now open for trade and the old Cold War blocs were crumbling, giving rise to new globalized economic markets and industries and, at the same time, increasing the importance of regional diplomacy and regional development policies. This period also saw the increased democratization of political systems across Latin America, Africa, Europe and Asia; the collapse of apartheid in South Africa; and the Madrid Peace Conference in October 1991, which launched peace talks for the Middle East. Yet at the same time, civil wars and regional strife, movements for independence and autonomy and border conflicts would continue to leave large populations, mostly poor, in the grips of violence, which, regardless of the motive or cause, prevented serious focus on health and development. In 1992, the Rio ‘Earth Summit’ would put environmental issues in the global spotlight, highlighting for the first time risks to human health from unsustainable development and global environmental change.

In public health

The crises of wars, floods, earthquakes, drought and famine pushed emergency responses to health crises higher up the public health agenda (Neelakantan, 2006). New long-term public health challenges were also emerging on the horizon, particularly the AIDS pandemic, prompting the creation of the Joint United Nations Programme on HIV/AIDS (UNAIDS) through a 1994 resolution of the UN Economic and Social Council. UNAIDS was an example of how TDR’s innovative partnership and governance model would be replicated by others: the governing body, the Programme Coordinating Board (PCB), was modelled after TDR’s Joint Coordinating Board (JCB), and included representatives of 22 governments, UN co-sponsors, the World Bank and non-governmental organizations (NGOs).

The period was marked by declining industry engagement in tropical disease research, even as a grave new health threat to developing countries emerged, HIV/AIDS. Declining industry involvement in drug development contrasted with the major advances in basic research. The sequencing of entire genomes of microorganisms in the mid-1990s was to pave the way for a new approach in the quest for drug leads, new vaccines and other disease-control measures. Until now, drug research had been largely based on serendipity. Now, while empirical observations continued to play the dominant role in drug discovery, a more rational approach would become feasible, at least in theory. This approach involved development of lead drug compounds aimed at molecular-level targets in the organism of interest.
In a period when competition for limited public health funds continued to increase, more focused health services that could leverage and stimulate broader changes became the theme. The concept of targeting health care and research investment on the basis of systematically and rationally defined priorities was introduced by the World Bank’s World Development Report in 1993 (World Bank, 1993) and reinforced by the 1996 WHO Ad Hoc Committee on Health Research (Godal et al., 1996), which TDR helped initiate.

In TDR — new emphases and reorganization: applied field research

By the beginning of TDR’s second decade, dozens of new products and innovations were in various phases of R&D 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 external review determined it should be a top priority with a focus on:

- The realities of disease control, prioritizing outcomes that had actual impact on disease, coupled with expansion of field testing.
- Intensified and extended socio-economic research.
- The creation of field research expertise in disease-endemic countries.

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’s experience was anchored in the laboratory, where his work had led to the development of monoclonal antibodies for leukaemia and lymph node cancer. But he would tackle the challenges of applied field research with characteristic fascination, energy and vigour.

“Health systems are evolving to leave even more responsibility at the ‘end of the track’. It is thus crucial to develop means of two-way communications with these communities. To learn more directly of the real problems people face and how they can be solved or ameliorated with the minimum of external resources. This was how Uche Amazigo discovered the importance of onchocercal skin disease (onchodermatitis) in communities in northern Nigeria in 1991. And in subsequent multi-country studies social scientists, dermatologists and epidemiologists worked hand in hand to confirm and quantify the impact of the disease from individual, clinical and epidemiological perspectives.”


By 1994, the budget for field research activities had approximately doubled (TDR, 1995). A major reorganization of TDR in 1994 also led to a shift away from the disease focus of previous years to functionally led groupings and interdisciplinary task forces. Over time, field research would undergo increased refinement, with emerging sub-themes. These included intervention studies to test the health outcomes of new drugs, diagnostics, tools and new strategies in community settings as well as studies to identify health risks, barriers to access or use of particular interventions and opportunities for improved service delivery. At the same time, the JCB called for social and economic research to receive greater emphasis, examining broad issues such as gender discrimination, violence and poverty. In 1988 a fixed-term post for social and economic research in TDR was approved (Lucas, 2001; TDR, 1987; TDR, 1995).
Applied field research was a complex endeavour, involving multiple participants and disciplines, coordinated by TDR task forces which also liaised with WHO control departments (for example, TDR’s Integrated Management of Childhood Illness (IMCI) Task Force linked to the broader IMCI effort at WHO). Despite the challenges, some of TDR’s most significant breakthroughs in its second decade emerged from applied field research initiatives. These included community-directed treatment for onchocerciasis; the introduction of insecticide-treated bednets; 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). The work of the task forces rapidly identified measures and evidence for effective, simplified treatment that could empower people in homes and communities to prevent disease and protect their own health.

“There is also much promise, through the increasing engagement of the disease-affected communities themselves. In Africa, around 80% of malaria cases are dealt with at home.”


Field research takes centre stage — insecticide-treated bednets

In early 1992, striking results were obtained in a modest TDR-supported trial study in The Gambia: a 63% reduction in child mortality as a result of the use of insecticide-treated bednets. The findings spurred TDR to embark on one of its most ambitious research programmes ever — to establish unequivocal evidence of what role this new tool could play in 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, a unique blend of a rigorously controlled scientific trial and operational research. A range of prominent international experts were involved in the design, including scientists from the London School of Hygiene and Tropical Medicine. The broad participation not only ensured rigour, but enabled the findings to be taken seriously by the scientific community and policy makers. The trials were cluster randomised. Bednets were distributed free of charge to children in trial villages, compared with control villages. The use of bednets was not rigorously supervised, although when the study team discovered that in some households adults were using the
nets instead of children, a decision was made to distribute nets to all household members, just to ensure that children had access.

The choice of the indicator that would measure success was difficult. Some scientists wanted to measure malaria mortality only. But this was very difficult to measure in rural Africa, argued Jacqueline Cattani, a professor from Harvard seconded to TDR and head of TDR’s Applied Field Research in Malaria Steering Committee (FIELDMAL). She maintained that since malaria was such a major cause of death, the number of lives saved by preventing malaria would be reflected by a drop in all-cause mortality. In retrospect, this proved to be the correct approach, she says, noting “nobody can argue with a death.” The multi-country studies demonstrated that insecticide-treated bednets could reduce overall childhood mortality by an average of around 20% (Cattani et al., 1998).

New drug treatments for malaria — combining field research with product development

The chemotherapy equivalent of FIELDMAL was CHEMAL, the steering committee that funded TDR research on malaria chemotherapy. 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 artemunate and artemether in China, therein describing what some regarded as the most significant advance in the treatment of malaria 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 supported drug development and partnerships to register these drugs in developed

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 trials, village to village comparisons of different vector- and malaria-control strategies. Just this 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 expatriates and the wealthy. But in The Gambia they had some tradition of use, which was why they did the 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 enough population in a rigorously designed trial over time. I would never have dreamed that TDR would be willing to put in the kind of money needed 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.

“Malaria remains the great challenge. But at the household level, we are learning how to ensure anti-malarials are well used with blister packs.”

countries. Together with Kunming Pharmaceutical Factory (KPF) and the French-American pharmaceutical firm Rhone-Poulenc Rorer (now Sanofi-Aventis), CHEMAL would foster the development of injectable artemether for severe malaria, leading to its registration in France on a named-patient basis in 1996, and elsewhere soon thereafter. TDR also collaborated with the Dutch company Artecef and the Walter Reed Army Institute of Research (WRAIR) to develop a second injectable artemisinin derivative for severe malaria, beta-arteether (artemotil®), which was registered in 2000.

Particularly in Asia and South East Asia, artemisinin derivatives had rapidly become a popular treatment therapy. Viet Nam, still isolated from the global market economy (although this would change rapidly over the course of the decade) had the highest levels of severe malaria in its history, and began producing artemisinin compounds in oral and suppository formulations and distributing them widely within the country in community-based programmes.

It was here in South East Asia in the mid-1990s that TDR and its partners would undertake field research on how to improve the use and distribution of anti-malarials in rural areas. The research was led by TDR's Anti-Malaria Task Force (ANTIMALS), in a small but innovative series of trials. Some of the first anti-malarial drugs in easy-to-administer unit-dose ‘blister packs’ came out of this initiative. Such innovations set the stage for broader advocacy of community-based and home-based malaria treatment models, particularly in Africa. A few years later, the approach became a key component of WHO global strategies on malaria. Effectively, unit-dose packaging was the breakthrough that empowered schools, community workers and, most of all, mothers and caregivers to administer life-saving treatment to children without relying on hard-to-access health centres. The ANTIMALS research also led to a subsequent TDR decision to develop for formal registration one popular artemisinin derivative, artesunate in a rectal formulation, as a pre-referral treatment for severe malaria in children.

While the new artemisinin-based drugs were increasingly popular, concerns were also growing that widespread use of such compounds on their own could foster parasite resistance that would undermine the impact of a remarkable drug discovery. The most common artemisinin derivative, artesunate, was widely sold as a monotherapy in Asia, and seldom regulated. The development of ACTs thus emerged as a global public health priority. In the mid and late 1990s, TDR would lead large-scale, multi-centre clinical trials with various international partners to demonstrate the fundamental efficacy of oral ACTs. Trials in South East Asia funded by the Resistance and Policies (RAP) Task Force documented how combination therapies, using two or more drugs at the same time, could improve cure rates and reduce the resistance of malaria parasites to any one drug formulation. TDR-sponsored studies in the mid and late 1990s tested a wide range of ACTs including: amodiaquine plus artesunate; artemether plus lumefantrine (Coartem®); chloroquine plus artesunate; and mefloquine plus artesunate. 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.

A range of public and private agencies across Asia, Europe and North America were meanwhile moving various artemisinin derivatives (artemether, artesunate and arteether) towards international registration, alone and in combinations. In 1998, Novartis, in collaboration with KPF and the Chinese Academy of Military Medical Sciences (AMMS), registered the first formal fixed-dose ACT, lumefantrine plus artemether (Coartem®) in Europe. The drug is available at a preferential price to developing countries under an agreement negotiated by WHO. Oral, fixed-dose ACTs are the fastest-acting anti-malarials available today — destroying parasites in approximately 48 hours on average — with high documented cure rates. Following the initial registration of Coartem®, TDR research helped define appropriate unit-dosing and packaging. And in the programme's third decade, TDR helped demonstrate the efficacy and safety of Coartem® for infants over 5 kg in weight, leading to the formal extension of the label in 2004 for such use.

Although cases of malaria in Africa continued to rise markedly throughout the 1990s, the development of a new generation of anti-malarials undoubtedly contributed to strategies for halting what would have been even sharper increases in malaria mortality. ACTs can at least blunt the development of parasite drug resistance, effectively buying more time for the development of future disease- and vector-control tools, strategies and innovations.
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 savanna region, where gradual progression to blindness can occur. TDR’s vision that ivermectin could be used on a mass scale, beyond the therapeutic treatment of infected individuals, led to the community-based trials and eventually established convincing evidence for the present role of ivermectin in the mass-treatment strategy for onchocerciasis control.

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 ‘for as long as is needed’, questions still remained as to how to use this new drug most effectively. The trials leading to registration had shown that ivermectin treatment in infected patients prevented ocular lesions leading to blindness. However, many believed that in order to reduce the broader range of symptoms and burden of disease, the drug should be distributed prophylactically through a system of mass administration, and not only for treatment of individual cases. To do so, however, urgent information was required on how safe the drug was for large-scale administration, and how effective it could be in reducing onchocerciasis transmission. New TDR Director Dr Tore Godal would move quickly to answer those questions — and translate Merck’s donation into meaningful action. 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 examining safety and efficacy of ivermectin in annual mass drug administration and, in some cases, ivermectin alongside ongoing vector control programmes (TDR, 1995).

Trial data was integrated into a new and sophisticated computer simulation model, OCHOSIM (developed by Erasmus University, Rotterdam, together with OCP). The model predicted trends in infection prevalence, morbidity and disease transmission. Results indicated that a combined strategy of vector control plus drug treatment would reduce the projected timeline for bringing onchocerciasis under control, and for the elimination of onchocerciasis as a public health problem in the OCP region. However, actual interruption of disease transmission might not be feasible in many hyper-endemic areas. Effectively, in such areas, annual ivermectin treatment would have to be sustained almost indefinitely (Remme, 2004). This posed a significant challenge to disease control.

By the mid 1990s, as field trials had well established the safety and efficacy of annual ivermectin treatment in prevention of many disease symptoms, OCP sought to incorporate drug distribution into its operations, alongside vector control. But actual field distribution of the drug still remained limited. Getting the drug to the people who needed it in remote areas year upon year was a significant challenge.

Meanwhile, there was also mounting pressure to tackle the disease in areas outside of the OCP regions of West Africa. In fact some 80% of the population at risk for onchocerciasis lives outside of West Africa. In these other African regions, the disease presents different features, and control presented different challenges. Disease vectors breed in forests along small streams and rivers, making vector-control programmes of the kind that had been successful in West Africa’s savanna, even prior to ivermectin, impractical. In addition, in forested areas, the main disease symptom is skin lesions rather than blindness.

It was therefore clear that to expand ivermectin distribution to non-OCP areas, and to optimize its distribution in remote OCP regions, critical questions still needed to be answered, including: how to justify massive control in forest areas where the main disease symptom was less pathogenic to the eye; where to target control; and how to create a system of annual drug distribution and treatment. In a series of discussions with the World Bank, other donors, WHO and African governments, a ‘wish list’ of research needs was generated and TDR was asked to help come up with the answers (Remme, 2004).

The World Bank offered US$ 1.2 million to accelerate operational research. The research effort would guide and support a new regional organization to control onchocerciasis on the rest of the continent. In December 1995, this new umbrella organization, known as the African Programme for Onchocerciasis Control (APOC), was created in 19 central, southern and eastern African countries. Concurrent with this, TDR launched its special initiative for Onchocerciasis Operational Research.

To determine the health, social and economic importance of skin disease in the forest areas of Africa, TDR had already begun to document the burden of disease from onchocerciasis-related dermatitis (AFR Reports/TDR, 1995). Findings on the profound psycho-social and economic impacts of this skin disease, indeed, provided convincing policy
justification for extending onchocerciasis control to forest areas where the pathology of the disease had not previously been appreciated.

TDR-supported research also provided timely new tools for the rapid epidemiological mapping of onchocerciasis (REMO) based on a simple examination for palpable onchocerciasis nodules in sample communities that was then extrapolated to an epidemiological map of a broader region. This facilitated the rapid identification of areas where mass treatment with ivermectin would be needed (Ngoumou et al., 1993).

Finally, in 1994 TDR-supported researchers launched a multi-country, multi-disciplinary study to answer the key question in disease control — how to distribute the drug most effectively. Early in the study, the researchers discovered that the so-called ‘community-based’ approaches being used by NGOs, with very mixed results, were not really anchored in community decision-making.

The teams developed a new framework for ‘community-directed treatment’ (ComDT) that put communities directly in charge of ivermectin administration. The rationale was simple. Communities empowered to organize their own system would do so in a manner best suited to them, with health services providing necessary training. A second phase demonstrated that ComDT was feasible and effective, and led to greater treatment coverage. 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 coverage to more than 45 million people in Africa out of an ultimate target population for treatment of approximately 70 million. In collaboration with APOC and local research institutions, TDR has continued to play a supportive research role. Research over the past decade helped fine-tune ComDT methods. TDR supported the development of yet another rapid mapping method (RAPLOA) to identify areas of co-infection by Loa loa parasites, the causative agent of another filarial infection of humans. In these locales, ivermectin treatment requires closer supervision due to the higher risk of adverse reactions.

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 to make ivermectin distribution one of the most successful programmes of mass drug administration in history, and one of the biggest public health successes in Africa.

The picture has never been all rosy. Serious problems were encountered in sustaining drug distribution when wars and instability struck various endemic countries. In October, 2001, a detailed review of the
APOC and OCP experiences with onchocerciasis control concluded that while onchocerciasis was well under control as a public health problem in the 11 original OCP countries, it could not be eradicated using the currently available tools. The development of a drug that can kill or sterilize the adult onchocercal worm living inside infected individuals remains a top priority.

At the same time, more recently, TDR investigators have begun to appreciate how ComDT strategies could have other, far-reaching applications. TDR has begun to investigate how ComDT might be used for the integrated delivery of a range of critical public health interventions, including, but not limited to, home treatment with anti-malarial drugs and insecticide-treated bednets.

Setting health priorities in research and control

Setting health priorities was another area in which TDR would provide a platform for new ideas, in this case standardized methods of assessing disease burden that would make it easier for policy makers and the public to evaluate the need for, and cost-effectiveness of, particular health care investments. The Ad Hoc Committee on Health Research, initiated by TDR under WHO auspices in 1994, would make the case for greater evidence-based allocation of investments in health care and health research, anchored in careful measures of the relative burden of disease posed by particular diseases, and the relative savings in burden that could be gained from investment in particular areas of disease control or research (WHO, 1996).

To compare investments more accurately across all types of disease, injury and disability conditions, the committee’s final report promoted a disease burden measure, the disability-adjusted life year (DALY), already familiar to many health economists but not then well known to the broader community of health policy makers. The DALY represents a weighted measure of deaths and morbidity. This measure more accurately reflects the true socio-economic and health impacts of many parasitic diseases, such as onchocerciasis and filariasis, which have high morbidity but low mortality. The measure provides a standardized basis for evaluating the cost-effectiveness of health interventions, through an examination of the DALYs gained or lost per unit cost of investment (WHO, 1996).

The DALY analysis thus supports the prioritization of research needs as well as investments in health care and disease control. If a very large disease burden could be reduced in a cost-effective manner through existing disease-control measures, then research efforts should be focused on more efficient health systems or health service delivery. But if cost-effective interventions were absent, then biomedical R&D was needed to identify new, or more cost-effective, interventions.

The committee’s report also highlighted key neglected health risks. Pneumonia and diarrhoeal disease (linked to environmental risk factors such as air pollution, unsafe water and poor sanitation), represented 15.4% of the disease burden in 1990, but only 0.2% of spending on R&D. Traffic injury, another major cause of death, had similarly been ignored (WHO, 1996). In subsequent years, both issues would receive substantially greater attention. While such methods for quantifying the health burden and cost-effectiveness of interventions using DALYs or similar measures were already known to experts, the committee’s work helped introduce these concepts to the global health community.

The work of the Ad Hoc Committee led to the creation of the Global Forum for Health Research. Key participants involved with the committee’s work later helped stimulate initiatives such as the formation of the WHO Commission on Macroeconomics and Health, and a major WHO initiative to define the global and regional burden of all major diseases systematically in terms of DALYs, along with the cost-effectiveness of key interventions. The findings were represented in the 2002 World Health Report (WHO, 2002; Ezzati et al., 2004). Methods to estimate the burden of disease are now being shared with many countries and regions worldwide, where they are becoming increasingly popular among health policy makers who must justify their health investments in terms of costs and benefits.
Social and economic research — the gender dimension

Another area of research in this period was gender and tropical diseases, under the auspices of the TDR Social and Economic Research (SER) Steering Committee. In 1991, women and tropical diseases was singled out as a specific area of work but by 1992, the focus had shifted from ‘women’s issues’ *per se* to the broader concept of gender, which considered issues relating to both men and women. From 1994 to 1999, the Task Force on Gender and Tropical Diseases served as TDR’s leading expert committee on gender-related issues. It funded more than 77 projects and its work resulted in the development and publication of the *Healthy Women’s Counselling Guide* and *Gender and Tropical Resource Papers* series. A small grants scheme, co-funded by the International Development Research Centre (IDRC), supported more than 20 research proposals on the impact of tropical diseases on women. In 1997, the Task Force on Gender-Sensitive Interventions was set up. In 1999, both Task Forces were discontinued and their responsibilities were transferred to the newly established Steering Committee for Social, Economic and Behavioural Research (SEB), for which gender-sensitive interventions have continued to be an explicit area of focus, along with inequality of access, health economics, conflict and infectious diseases, globalization and the ethical, legal and social implications (ELSI) of biotechnology.

Harnessing genomic knowledge

Since the technological breakthroughs of the early 1980s, the fields of genomics and molecular biology had grown exponentially. TDR was helping to harness this knowledge in practical ways. One of the
Early applications of this emerging knowledge was the routine use of polymerase chain reaction (PCR) in the entomological evaluation carried out by the OCP in West Africa. This new technique amplified tiny amounts of specified DNA to detect onchocercal parasites in blackflies in areas which had been cleared of the disease, and to distinguish non-blinding and animal forms of the parasite from the blinding human form. The technique was developed by TDR, jointly field-tested by TDR and OCP, and then transitioned to OCP, involving the establishment of a molecular biology laboratory in the programme’s headquarters in Ouagadougou, Burkina Faso.

By 1986, scientists in Latin America had begun to make progress in sequencing the Trypanosoma cruzi genome. This research had rapid practical results; it led to the identification of key T. cruzi antigens that could

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**Leveraging the sequencing of the Tritryps**

In 1994, Dr Carlos Morel, later to become TDR Director, was both president of FIOCRUZ and a member of TDR’s Scientific and Technical Advisory Committee (STAC). At the time FIOCRUZ was among those institutions leading ground-breaking research into the molecular biology of tropical disease parasites and their vectors. Morel, a molecular biologist himself, suggested that TDR undertake a project for the sequencing of the Tritryp genomes, and offered to host and co-fund the meeting at FIOCRUZ in Brazil. The photograph here was published, along with the three completed genome sequences, in Science magazine in 2005.

Why did sequencing of the Tritryp genomes take 11 years to complete — far longer than the sequencing of the Anopheles gambiae genome, which would be started later and completed in less than two years?

“In the beginning we thought that the Tritryp genomes would be sequenced by a consortium of several institutions,” explains Morel. “But then the technology was being advanced so quickly, we saw it was better to engage one of the big sequencers. So we convinced NIH, The Institute for Genome Research (TIGR; now the J. Craig Venter Institute), and the Wellcome Trust Sanger Institute among others. But it also proved challenging to convince these big sequencers, because people soon had a long list of genomes they wanted to sequence — the honey bee, fish, the chimpanzee — and so the genomes for three neglected tropical diseases were not very high on the list. That is why TDR was so important … one scientist alone would not have the leverage. TDR has to be seen as the organization that made the critical difference.”

Partners in the Tritryps genome sequencing projects:

**Trypanosoma brucei**: Wellcome Trust Sanger Institute (UK) and TIGR (USA).

**Trypanosoma cruzi**: TIGR, Seattle Biomedical Research Institute (USA) and Karolinska Institute (Sweden).

**Leishmania major**: Wellcome Trust Sanger Institute, Seattle Biomedical Research Institute and EULEISH (a consortium of 10 European laboratories).

The genome projects were funded by The Burroughs Wellcome Fund, The National Institute of Allergy and Infectious Disease, NIH, the Wellcome Trust, WHO/TDR and the European Commission.
then be produced in the laboratory by recombinant DNA technology, creating improved diagnostic reagents. By 1994, a far more ambitious effort involving the same parasite family would get under way, once more in Latin America, and co-sponsored by TDR and FIOCRUZ. At a meeting at FIOCRUZ the plan was laid for a ‘pump-priming’ discovery effort to sequence the genomes of the three related trypanosomatid parasites responsible for Chagas disease (T. cruzi), HAT (Trypanosoma brucei) and leishmaniasis (Leishmania major). The plan, dubbed the Tritryps project, involved researchers from both developed and developing countries, supported by the Wellcome Trust, the European Commission, the US National Institutes of Health (NIH), and national research institutes. In a parallel move, supported by TDR, Brazil made major investments in genomics, extending work to a Schistosoma genome. Meanwhile, in 1991, a global gathering of scientists held an initial meeting on a related endeavour — an ambitious plan to genetically engineer an Anopheles gambiae mosquito to make it incapable of transmitting malaria parasites. The meeting in Tucson, Arizona, sponsored by TDR and the MacArthur Foundation, would set out a 20-year research plan that would become a road map for efforts both in TDR and globally, with tangible results apparent by the turn of the millennium (Morel et al., 2002).

Vaccine initiatives — some challenges are bigger than others

Most of the stories discussed in this book relate successes with clearly identifiable products. However, the record of achievement in terms of vaccine development is more problematic. Research into vaccines for a wide range of TDR diseases was a major thrust of TDR efforts from the time of its creation until the end of this second decade. Then, in the late 1990s, most of TDR’s vaccine research responsibilities were shifted to the WHO-based Initiative for Vaccine Research (IVR), which plays a coordinating role, rather than funding directly vaccine discovery research. Also in the same period, the Global Alliance for Vaccines and Immunisation (GAVI Alliance), based at UNICEF, was established.

Despite considerable efforts by TDR and others worldwide, a major vaccine breakthrough has continued to elude most tropical disease researchers. Additionally, development of effective drug therapies (for example, for leprosy) made the need for a vaccine a low priority. For other parasitic diseases such as visceral leishmaniasis, lymphatic filariasis, Chagas disease and onchocerciasis, new drugs and control measures have advanced elimination agendas without a vaccine breakthrough. However, an underlying challenge of vaccine research for complex parasitic diseases is not only the fact that a plethora of other drug and elimination options might be available, drawing interest and investment, but also the complexity of the immune response to parasitic infections compared with certain other infectious diseases for which vaccines have been developed.

“Technically,” says Dr Robert Ridley, current TDR Director, “most vaccines that we have mimic the natural immune response. If you get measles or mumps and you do not die, then you are immunized against the infection. The measles and mumps vaccines simply mimic the body’s natural immune response in advance of getting the disease so that the body develops its defences early. In the case of parasitic diseases, immunity is not acquired in the same way. If you get malaria you are not automatically immune from further infection and so a vaccine that merely mimics the body’s response to the disease is insufficient if you want to prevent infection. For a malaria vaccine or schistosomiasis vaccine we have to get the immune response to do something it is not naturally programmed to do. So the search for a vaccine in the case of parasitic diseases is a much more complex process.”

Despite the difficulties of research into vaccines for parasitic diseases, TDR succeeded in raising the profile of the issue. Many of the linkages and collaborations that TDR facilitated and fostered through its steering committees continue to bear fruit. Several malaria vaccine public–private partnership (PPP) initiatives are now in place, and some candidates have shown promise in clinical studies. A new wave of initiatives to develop an improved vaccine for TB is underway. Since the shifting of vaccine research responsibilities to WHO/IVR, TDR has continued to play a collaborative role in particular aspects of vaccine research, where promise or need was evident. In particular, TDR has supported continuing development of a therapeutic vaccine for leishmaniasis. Work in this area began with the testing of a whole-cell inactivated vaccine, developed initially by the Razi Vaccine Institute in Iran. Although the initial results proved insufficient for continued development as a preventive vaccine, the same vaccine candidate was recently tested by Sudanese researchers.
as a potential therapy for a type of leishmaniasis termed post-Kala azar dermal leishmaniasis (PKDL). The initial results from this are promising, and other groups are now interested in developing a therapeutic vaccine to complement leishmaniasis chemotherapy. In many ways, the Sudanese investigations have influenced the way leishmaniasis vaccine development is now viewed internationally. If success can be demonstrated with this or another candidate therapeutic vaccine, then it will provide a strong platform from which to promote the development of prophylactic (preventive) leishmaniasis vaccines.

It should also be noted that TDR’s engagement in vaccine research has enabled investigators in disease-endemic countries to play a major part in vaccine discovery efforts. Two projects now being advanced by the Malaria Vaccine Initiative have lead investigators from China and India. Both of these projects had their origins in research that was sponsored and coordinated by TDR. A novel peptide-based malaria vaccine candidate also emerged from Colombia in the late 1980s. Although not directly involved in this research, TDR helped facilitate links between the vaccine developer and others in the international vaccine community to facilitate a full evaluation of this vaccine candidate. Unfortunately, the data generated did not justify further development. However, this should not detract from the effort made by Colombian institutions and other partners in both developed and developing countries, which enabled large-scale testing of this candidate vaccine.

In drug development, the ‘low-hanging fruit’ were disappearing

Significant challenges were also becoming apparent in drug development during the second decade of TDR operations. This period saw registration of important products that had been developed in the first phase. These included DFMO (eflornithine®) for sleeping sickness, liposomal amphotericin B for visceral leishmaniasis and the artemisinin derivative artemether for malaria. Still, some of the key opportunities for using existing drugs that were already on the shelves but were inadequately tested for other potential indications had largely been exploited — as in the treatment breakthroughs for leprosy and sleeping sickness. In other cases, drug development projects initiated in this period would ultimately be transferred in the next decade to new PPPs specifically designed to manage targeted product development. Increasingly then, the challenge for TDR as this decade came to a close would be how to lead the search for new innovations, and foster the discovery of new lead compounds specifically designed for TDR-targeted diseases.

Innovations in capacity building

Changing global priorities drove shifts in research capacity strengthening (RCS) strategies in this period. Beginning in the late 1980s, science-driven, three-year institutional grants of US$ 250 000 were offered to achieve targeted objectives in institutional capacity-building. Programmes in malaria research, the social sciences and biotechnology were supported through three grant cycles and were regarded as highly successful. During this same period, TDR teamed up with the Rockefeller Foundation in an innovative formula to partner research institutions in developed and developing countries. TDR provided grant support to institutions in developing countries, while the Rockefeller Foundation supported the parallel programme or project in a developed country institution, cementing the partnership. Towards the end of this period, the number of institutional grants was reduced, and support was focused on very promising institutions in less-developed countries to assist their emergence as leaders in particular fields of endeavour. Meanwhile, as prominent institutions with high-quality PhD programmes began to emerge in developing countries, more and more applicants for TDR training grants were encouraged to pursue their studies and research in their home countries or regions, while increased attention was given to the integration of both institutional and trainee research projects and programmes to both TDR disease priorities, and local research needs.

**TDR/JCB institutional milestones**

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<th>Year</th>
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<td>1995</td>
<td>Second session of the JCB held outside WHO/HQ — JCB (18) in Luxembourg.</td>
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“Like the vectors and the parasites it attacks, the programme is constantly adjusting to its environment. TDR’s changing environment is that of science, the evolving parasites and vectors themselves, the affected communities, the endemic countries and their economic and political development, the changing priorities of its partners and contributors. TDR’s environment is the whole world environment.”

“In the areas of implementation, you have new thinking, new products, we’ve tested it and it works much better than anything else, but then nothing happens. So before you have reached a level where people take the new product or approach, TDR plays a big role in translating that into real life and that’s very, very exciting.”

OK PANNENBORG, World Bank representative to the JCB, 2001–present.
Inside a village school classroom. Many of the children show signs of onchocercal skin disease on their legs. Infected children cannot pay proper attention due to constant scratching of their itching skin (Nigeria • 1998 • WHO/TDR/Crump).
Larva of the onchocerciasis (river blindness) vector, the blackfly (Simulium damnosum) (GHANA • 2002 • WHO/TDR/STAMMERS).
Health workers and Onchocerciasis Task Force members study local maps showing rivers and villages to help identify communities most at risk and which may be approached to participate in community-directed treatment with ivermectin (Mali • 1996 • WHO/TDR/CRUMP).

“REMO (rapid epidemiological modelling for onchocerciasis) and RAPLOA for Loa loa co-infection conceptualized rapid, simple epidemiological assessment methodologies now used on a much broader scale in the health sector. This was something that came out of the TDR corner.”

DR BERNHARD LIESE, Chair, International Health Programs, Georgetown University and former World Bank representative to the JCB.
Recording the temperature of a child during the pioneering studies in The Gambia on the effectiveness of insecticide-treated bednets in lowering child mortality from malaria. In this initial study, which preceded the larger scale TDR-supported clinical trials, children were diagnosed as having a clinical episode of malaria if they had a fever (a temperature of 37.5 degrees centigrade or more) plus malaria parasites in their blood. Such measurements were carried out weekly on around 2,000 children during the study (The Gambia • 1991 • WHO/TDR/Lindsay).
A health worker checking the identity of children during a clinical survey at the completion of the initial study in The Gambia investigating the effect of using insecticide-treated bednets. The study showed that child mortality caused by malaria could be substantially reduced by the use of the nets (The Gambia • 1991 • WHO/TDR/Lindsay).
A photomicrograph of anopheline mosquito larvae. The larvae have been genetically modified to incorporate a gene for the enhanced green fluorescent protein which causes the larvae to glow. The introduction of such genes, to effect stable transformation of mosquitoes, is one effort among many in the global genomics research effort to create a transgenic mosquito, initially fostered by TDR. This research opens up the prospect of modifying mosquitoes so that they become unable to transmit malaria parasites (UK • 2001 • WHO/TDR/Stammers).

“...You can look at the science developed by several of the major players in science today, look what they do now and where they started, and you will see TDR’s role. A little grant here and there, and they were able to leverage more money. A lot of these people came out of TDR research.”

DR RODRIGO CORREA DE OLIVEIRA, Centro de Pesquisas Rene Rachou, Oswaldo Cruz Foundation (FIOCRUZ) and representative to the JCB, Government of Brazil.
Artemisinin derivatives extracted from Artemisia annua are being tested as potent new anti-malarials. Experiments at the University of Geneva, under the guidance of Dr A. Benakis, are being carried out using radioactive labelling to investigate artemisinin extraction processes. Plants are sealed within this growth chamber and then exposed to radioactive carbon dioxide gas (Switzerland • 1993 • WHO/TDR/Crump).

“TDR’s outstanding legacy goes beyond the many drugs it helped develop, to the formation of the first independent PPP dedicated to a particular product for a specific disease. Its leading role in the formation of the new MMV not only established a portfolio of malaria R&D projects necessary to secure the required supply of new antimalarial drugs, but also pointed the way for other similar partnerships.”

Sapa, Chungh Trai commune. Health workers carry out medical examinations and distribute drugs to infected patients, including artemisinin derivatives (artesunate) to combat malaria (Viet Nam • 1994 • WHO/TDR/MA&RS).
Medics administering anti-worming treatment to an infant Yanomami, one of the indigenous communities of the Amazon. Members of this community regularly receive medical examinations (particularly for signs of malaria or onchocerciasis) at CAICET hospital Parima B, Niyayobaten village, Territorio Federal Amazonas (VENEZUELA / BRAZIL • 1992 • WHO/TDR/EDWARDS).
Field research on patterns of Chagas vector infestation supported by TDR and involving workers from the national control programme (Honduras • 1991 • WHO/TDR/Ponce).

A SUCAM (Brazilian Ministry of Health) officer treats the interior of a corn crib in Posse, Goia, with a low-toxicity anti-insecticidal powder and exterior walls with an insecticidal paint. Such products, developed by national agencies with TDR support, are applied to houses and peridomestic buildings to control the triatomine vectors of Chagas disease (Brazil • 1991 • WHO/TDR/Oliviera-Filho).

"The interruption of Chagas disease transmission has been achieved in three countries, namely Uruguay in 1997, Chile in 1999 and Brazil in 2006. TDR played a major role in the validation and evaluation of new control tools through the standardization of protocols for applied epidemiological research."

DR ALVARO MONCAYO, Secretary General, National Academy of Medicine, Bogotá, Colombia and former Manager of the TDR Task Force on Chagas Disease 1979–2001.
“TDR took up some of the most neglected and difficult diseases. Because of its connection to WHO, it could interact with these countries, which others could not.”

DR NIRMAL K. GANGULY, Director-General, Indian Council of Medical Research and representative to the JCB, Government of India.

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. gambiae* 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 resurfaced on the back of increased 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
“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, 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.”


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. In fact, new partnership formulas have enhanced TDR’s ability to make an impact, says current TDR Director Dr Robert Ridley, a biochemist with experience in Africa, academia and industry, who took over from Morel in 2004. For instance, TDR fostered two new drugs for visceral leishmaniasis 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.

**MIM — extending the partnership model**

The Multilateral Initiative for Malaria (MIM) was launched in 1998 by TDR, the US Department of Health and Human Services, National Institutes of Health, the Wellcome Trust and the Pasteur Institute, to strengthen malaria research and training in Africa. The effort includes: internet and/or library access (MIMCom) through the US National Library of Medicine; a Malaria Research and Reference Reagent Resource Centre (MR4) and the MIM/TDR task force, to support international, cross-regional and research-policy collaborations. African investigators in 24 countries have thus received support for research on: formulation and update of drug policies; improved vector control and use of bednets; indigenous plant products; and strategies to improve access to community-level health systems. MIM/TDR grants also support North–South research partnerships. At the time of their institution, the grants set a precedent in the donor world by awarding funds directly to African research partners, rather than channelling the money through a developed country institution. The MIM-sponsored conference on malaria in Africa, staged once every three years, has become one of the largest malaria research events in the world, attracting policy makers and politicians as well as scientists.
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 Tritryps, 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.

*A baby with severe malaria who was given rectal artesunate at home to stabilize his condition until his mother could carry him for several hours to the nearest hospital. Local mothers were trained to give the artesunate as part of a study of the TDR-fostered drug formulation to see if this could increase the number of children treated early and effectively. (Tanzania • 2006 • WHO/TDR/Craggs).*
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 (APOC) 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.

Teenage boy suffering from visceral leishmaniasis at the Medecins Sans Frontieres (MSF), Holland clinic at Umkara. The boy exhibits splenomegaly, distended abdomen and severe muscle wasting (SUDAN • 1997 • WHO/TDR/CRUMP).
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.”

### TDR/ JCB institutional milestones

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<th>Year</th>
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<tr>
<td>1999</td>
<td>TDR disease portfolio expanded to include tuberculosis and dengue.</td>
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<td>2000</td>
<td>JCB conditionally approves sexually transmitted infections diagnostics pilot project in the TDR portfolio.</td>
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| 2003 | Third session of the JCB held outside WHO/HQ — JCB (25) in Delhi, India.  
UNICEF joins TDR as the fourth co-sponsor. |
| 2006 | 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.  
Fourth session of the JCB held outside WHO/HQ — JCB (29) in Accra, Ghana.  
JCB (29) receives recommendations from the Fourth External Review.  
Special Stakeholders and JCB session held in Geneva, which supports new TDR 10-year vision and strategy. |
**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 Rafat**: 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 Filaria 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 Diimde**: 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.

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* 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.
Patients awaiting attention outside the Filariasis Clinic at the Vector Control Research Centre (VCRC) (India • 1993 • WHO/TDR/CHANDRAN).
“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.

Pondicherry: Health workers distributing medicines (DEC and albendazole tablets) to members of a household in a rural village. The work is part of research into mass drug administration methods to combat lymphatic filariasis (India • 2001 • WHO/TDR/Cremer).
Phase IV (2007–future): Research that makes a difference

When TDR was established, it was on the cutting edge of innovation, not only in science but institutionally — creating global partnerships between rich and poor and empowering those affected by some of the world’s most deadly and debilitating diseases. Three decades later, TDR’s commitment to research that makes a difference in disease-endemic countries remains unwavering. The core values that shaped the programme’s first thirty years are robust and enduring. TDR’s new strategy, endorsed by its Joint Coordinating Board, offers renewed vigour. As the UN system’s lead agency for research in neglected diseases of poverty, TDR is planning dynamic collaborations and innovations in the new environment of private and public partnerships.
Our global ‘spaceship earth’ — to use the term coined in the 1970s — is hurtling into the future at an ever-quickening pace. New scientific knowledge is constantly unfolding. Geographical and cultural distances between far-flung reaches of the planet are shrinking, giving rise to the global village concept of interdependency. And yet the gaps between rich and poor remain enormous, including large disparities in disease burden and access to health care.

To address new and emergent problems in disease control while remaining innovative, TDR’s strategic focus is undergoing a metamorphosis. From a programme of tropical disease research, TDR’s new strategic vision has been defined as ‘fostering an effective research effort on infectious diseases of poverty in which disease-endemic countries play a pivotal role’.

Emphasis will be placed on fostering leadership among researchers and public health experts in disease-endemic countries, and addressing the most neglected aspects of infectious disease control. This new strategy responds to changing patterns of disease epidemiology, socio-political environments and institutional alignments.

The changing landscape of health and research

The epidemiology of infectious diseases, including those most associated with poverty, has changed. Some diseases, including leprosy, Chagas disease, onchocerciasis, lymphatic filariasis and visceral leishmaniasis, are now moving towards regional or global elimination, while other diseases have emerged or re-emerged, including TB, HIV/AIDS and dengue. These diseases pose risks first of all to those living in poverty, who comprise TDR’s core constituency, and also to the broader global community.

The factors affecting health are highly dynamic and include urbanization, agriculture, deforestation and climate change. Increased mobility and globalized economies accelerate cross-border transmission of communicable diseases.

The potential severity of new and unforeseen disease threats underlines the importance of rapid and accurate responses from both disease control officials and researchers. Yet many of the poorest countries still lack good health care and research capacity. Laboratories, hospitals and other facilities do not have essential hardware for research, education and treatment, and doctors, laboratory technicians, nurses and scientists often feel compelled to seek better economic opportunities elsewhere.

There are reasons for optimism, nonetheless. Our basic scientific knowledge about the agents of disease and the disease vectors has progressed by light-years in just the past 30 years. Advances in genomics, molecular biology, biotechnology, vector entomology and multiple other fields have created vast new possibilities for innovation in research for new drugs, diagnostics and vector-control tools. IT and communication technologies have made it easier to map and track disease trends geographically and share knowledge more equitably around our global village.

Many disease-endemic countries are strengthening their research institutions and investing in researchers, scientists and health care
The fashion today is ‘output-driven’ projects. But if you only look at the achievements of TDR, if you only make a list of all the products that have been developed, it would truly miss the point. The point is this: TDR developed a culture for research-based decision-making and a functioning network organization. This is a rare thing in an international organization. Of course you need the products. But there is more to it than that. You have to look at the catalytic function of TDR as one of its main strengths.”

DR BERNHARD LIESE, Chair, International Health Programs, Georgetown University and former World Bank representative on JCB.

Policy makers, often with support from TDR. In developed countries, a broad new array of public–private partnerships (PPPs) have emerged, harnessing private-sector resources and a public-minded sense of accountability to these new endeavours.

TDR’s new approach

The multiplicity of new participants provides new momentum but also leads to a more complex research environment. The views of researchers and policy makers in disease-endemic countries themselves are still under-represented in global priority setting. Research needs are unequally covered and certain critical research areas remain neglected.

More than ever, stewardship is needed to bring diverse organizations and interests together in coherent, operational research programmes that are supported by — and inform the decisions of — both disease-endemic countries and global health agencies.

More than ever, the global public health sector needs to provide leadership for a coherent approach to priority setting, so that the most serious infectious disease threats are addressed and the needs of the most vulnerable populations are not overlooked. A public sector ‘convenor’ of disparate groups and interests is essential to ensure independent analysis, evidence-based guidance and meaningful involvement of disease-endemic countries in research that can make a difference to health policy as well as to actual practice in homes and communities.

As the main UN agency for research in tropical diseases, TDR has played this kind of role for over three decades. In the coming decade, TDR will scale up its activities significantly in these areas, in respond to the changing health and research environment.

Needed: smart investments in health research

In 1975, the estimated global annual research budget on tropical infectious diseases was only about US$ 30 million (WHO, 1975), with TDR’s US$ 20 million annual budget representing two thirds of the total global expenditure. Then as today, investment in research on neglected tropical diseases was woefully disproportionate to the need.

Over the past 30 years, global spending on health research has increased sharply and drug development costs have risen, on average, four-fold, from roughly US$ 230 million per drug in the 1970s–1980s to as much as US$ 800 million or more today (Rawlins, 2004).

TDR’s budget growth has been far more modest, increasing from US$ 20 million at the time of its establishment to about US$ 50 million in 2007. Yet in this environment of rising costs, and operating with only a modest budget, TDR has played a pivotal role in tropical disease research achievements, as documented in this historical account.

As noted in the first chapter, more than half of the new drugs for tropical diseases to have come on the market in the past three decades were supported by TDR. The corner has been turned for five of the
eight diseases that were part of the programme's original portfolio, namely lymphatic filariasis, visceral leishmaniasis, onchocerciasis, Chagas and leprosy. Malaria remains one of the world's most serious killers, but new tools, including bednets and artemisinin-based combination therapies, offer greater hope for bringing the disease under control — particularly if operational research can show us how to use those tools most effectively in homes and communities. Meanwhile, new attention is being focused on sexually transmitted diseases, re-emerging dengue and TB/HIV co-infections, while diseases such as human African trypanosomiasis (sleeping sickness) and schistosomiasis still require much more attention.

TDR cannot and does not claim credit for those accomplishments on its own — only on behalf of the many partners and collaborators who pushed this work forward. Yet it is fair to say that if TDR had not played its role, the burden of disease would have been even higher, the threat even more sinister.

In terms of cost-effectiveness, TDR's record over the past 30 years remains unmatched. This is true not only in terms of its record in leveraging partnerships to develop new and more efficacious drugs and control tools, but also in terms of capacity building and intervention studies that identified simple and inexpensive measures for putting drugs and tools to better use.

Involving thousands of scientists, control officers and community members, in endeavors ranging from field innovations — such as fixed-dose packaging of anti-malarials and insecticide-treated bednets — to global initiatives in genome sequencing, TDR has repeatedly demonstrated its organizational strengths as a leader of partnerships.

TDR's new 10-year strategy, endorsed by its Joint Coordinating Board (JCB), will better position TDR to play its role with renewed vigour — as the UN system's lead agency for research in neglected diseases of poverty — in a dynamic environment of PPPs (TDR, 2006). Strategic goals include:

- Stewardship for research on infectious diseases of poor populations: as facilitator and knowledge manager to support needs assessment, priority setting, progress analysis and advocacy, and to provide a neutral platform for partners to discuss and harmonize their activities.
- Empowerment of researchers and public health professionals from disease-endemic countries, moving beyond traditional research training to build leadership at individual, institutional and national levels so countries can better initiate and lead research activities, develop a stronger presence in international health research and effectively use research results to inform policy and practice.
- Research on neglected priority needs that are not adequately addressed by other partners. In terms of diseases addressed, TDR's focus will be redefined to include not only the 10 diseases now in its portfolio but infectious diseases of poverty more broadly, including a limited number of well-defined activities within this broader disease scope.

The new strategy thus formalizes TDR's expanded disease scope to include aspects of research in TB, HIV/AIDS and sexually transmitted diseases, and focuses programme activities on two contrasting areas of the research spectrum:

- Implementation research to evaluate the use of new drugs and tools in real-life settings and enhance access to interventions (TDR, 2005).
- Innovation-driven leadership of discovery research for the next generation of new drugs and products.
WHO is placing a renewed focus on primary health care and on access to health care services in the spirit of the ‘Health for All’ Alma Alta charter, with a special focus on Africa and vulnerable populations, particularly women. TDR’s new strategy will support this global focus, while reinforcing strategic links with co-sponsoring agencies, including WHO.

**Research in real-life settings — relevant to the broader health agenda**

Inexpensive and effective disease control interventions, such as insecticide-treated bednets and anti-malarial drugs, remain underused in most developing nations (Donaldson & Banatvala, 2007). Implementation research is anchored in the recognition that drugs or control tools function very differently in the field than in controlled trials or laboratory settings, and research on how to improve access, distribution and use of available tools can make a critical difference to health and to health systems. Social and behavioural research is also gaining recognition as another means of identifying and overcoming gender and socio-economic barriers to effective access to, and use of, tools and treatments (Irwin, et al., 2006; Sachs et al., 2001).

In the coming decade, TDR will build upon its track record in implementation research and socio-behavioural research, exploring how vital interventions can be scaled up and fine tuned effectively in real-life settings. For instance, recent TDR research in communities with experience in community-directed treatment for onchocerciasis has now etched a model for integrated delivery of multiple drugs and tools, beyond the annual ivermectin dose.

Such research indicates that community-directed models can potentially increase access to health interventions among poor rural populations. Integrated delivery also has the potential to achieve greater cost-efficiencies (Brady, Hooper & Ottesen, 2006). Future research will develop and test such community-directed models more widely in various African settings, exploring where such approaches are most suitable, how they might be upscaled, and with what kinds of interventions.

### Innovation in product development and discovery

Despite the drug innovations seen in recent years, parasitic diseases still affect one in six people worldwide, killing more than 500,000 people every year. There is a continuing need for new drug innovations to improve drug safety and efficacy, and overcome parasite resistance to older compounds. While new PPPs are playing an important role in product innovation, the vital role of the global public health sector in promoting a high-level research agenda based upon objective criteria and needs cannot be ignored. A global public health institution is best positioned to convene relevant stakeholders, help link networks and partnerships, gather the most relevant evidence based on broad expert consensus, gain the broad cooperation of governments and agencies for testing and scale-up, and promote coherent guidelines for use.

The development and expansion of TDR’s discovery networks and diagnostic research frameworks are indicators of the role that TDR has recently had in this arena. Other planned and future TDR activities include research into the treatment and care of patients that are co-infected with TB and HIV/AIDS, innovative vector-control interventions and a new helminth drug development initiative.

The renewed emphasis placed by WHO on these diseases through its Neglected Tropical Disease Department also provides an important point of public health focus. TDR’s new strategy will simultaneously support WHO’s control efforts, stimulate research and foster research leadership for product development in disease-endemic countries.

### People, products and partnerships

From leprosy treatments to insecticide-treated bednets; evaluation of diagnostics for TB, malaria and syphilis; home management of malaria and other innovations; TDR has seized upon small stories of success and built them into much larger experiences.
TDR’s role as a leader, convenor and innovator in research over the past decades is well documented. As an instrument of the international community, TDR promoted goal-oriented, merit-based research institutions, focusing on capacity strengthening in the least developed nations where the need was greatest but where the research could be shared for the benefit of all.

Its success is unmatched in bringing together experts from poor and rich countries, from top scientists to trainees, from industry to the public sector, and from countries in disparate social, geographical and political settings, in the battle against diseases of the poor. Of necessity, the creation of new knowledge and understanding is a public good, and so requires public involvement and investment. Funds have been provided to TDR by an unfaltering core group of governments, public sector agencies and foundations all committed not just to improving health but also to ameliorating poverty, the twin objectives of the Millennium Development Goals.

While this commemorative history has illustrated the high points, every summit of achievement has been carved by as many or more valleys. These included institutional challenges as well as the scientific and technical challenges of the research — dead ends for promising endeavors, efforts that ran into unforeseen complications, initiatives that failed to yield conclusive results — positively or negatively.

Certainly there were also times when powerful interests sought to influence or intervene in the more objective processes of research. Amidst the pressures, TDR strove to remain above the fray as a trusted mediator and honest broker. Yet there were times when the programme’s own positions had to be re-examined. By remaining focused on a goal, identifying the concrete obstacles or issues and creating ‘learning’ solutions and systems that could be adapted or fine-tuned with more experience, many such hurdles were overcome.

“For every success that has been documented, there are numerous non-successes,” notes current TDR director, Dr Robert Ridley. “That is the nature of science and of research. Mistakes are made, and the failures, as much as the achievements, guide the next step that you need to take. But in the end, if the goals are solid, if the commitment of the partners, the governing board, and the individuals or investigators involved in implementation is solid, then that leads to success.”

Adds Liese, “Historically, you cannot ignore the more rocky times. These have included times when challenges were introduced by the donor community, when there were administrative hassles, when issues arose over the separation between research and disease control functions, and the more recent question of TDR’s future role and direction.

“But what makes an organization strong, is its internal capacity to adjust its course and deal with these issues. And if you look at the kinds of changes TDR has made over the years, the things it has taken on and phased out, it has done quite a lot. And responding to these questions is what the new strategy is all about.”

TDR is proud of the role it has played over the past 30 years — guided by the JCB and its scientific steering and technical committees — as a champion of research and training, as a facilitator and catalyst for action, and as a conduit for the voice of the poor and disadvantaged who still suffer the disproportionate burden from devastating diseases.

TDR has always been, and will continue to be, about people, products and partnerships — and how best to bring all three of these elements together in research to achieve the single, unifying common objective of better health and well-being for all.

“TDR was a gamble in many ways. We made up these rather awkward titles to emphasize that there was no hierarchy in TDR, only team members and the director. After 30 years the answer (as to whether this was successful) is self-evident.”

Institute of Endemic Diseases (University of Khartoum): A laboratory technician carrying out an electrophoresis test (SUDAN • 1997 • WHO/TDR/Crumm).
Dr Bijan Sadrizadeh, Chair of TDR’s Joint Coordinating Board (JCB), and WHO Director-General Dr Margaret Chan (then Assistant Director-General for Communicable Diseases), at the JCB meeting in Accra, Ghana in June, 2006 (GHANA • 2006 • WHO/TDR/Craggs).

Ambitious targets are underpinned by research promoted over the years by TDR and its partners. This work increasingly includes operational and implementation research aimed at improving access.”

“We greatly need research and development for innovative new tools, particularly for diseases like African trypanosomiasis, leishmaniasis, and Buruli ulcer.”

DR MARGARET CHAN, WHO Director-General; keynote address at the Prince Mahidol Award Ceremony, Bangkok, Thailand, February 2007.
“What are the most important lessons from the early history of TDR? To have the courage to experiment. Many aspects of the organization and management of TDR were untested and therefore experimental. Many of the experiments have proven successful, and less successful aspects were modified. To dare to keep science alive in a large bureaucracy: one constant danger was that the programme would be submerged in a sea of bureaucratic red tape. But despite all that, TDR has kept faith with the ideals and objectivity of science.”

Timeline — milestones in TDR collaborations

1979  
**African trypanosomiasis diagnostics** — Miniature anion-exchange centrifugation.

1980  

1981  
**Leprosy** — WHO recommendation for use of multidrug therapy (MDT) for leprosy following its registration in 1980 by Ciba-Geigy.

1982  
**Onchocerciasis** — Biological control of vectors, *Bacillus thuringiensis israelensis* H-14 in use for blackfly control of onchocerciasis at critical moment to replace larvicides for which resistance had developed.

1983  
**Leprosy** — Social research finds that the far lower rate of women diagnosed with leprosy reflects fears of stigmatization and loss of marriage options.

**African trypanosomiasis** — Card agglutination diagnostic test for trypanosomiasis (CATT) in disease control use.

**Schistosomiasis** — Diagnostic urine-filtration technique in disease control use.

1984  
**Leishmaniasis** — New regimen for antimony compounds in disease control use.

**Malaria** — Mefloquine and Mefloquine plus sulphadoxine-pyrimethamine registered by Hoffman-LaRoche.

1985  
**Malaria** — Microtest kit for measuring *P. falciparum* sensitivity to anti-malarial drugs in disease control use.

1987  
**Onchocerciasis** — Ivermectin registered by Merck, and donation programme begins.

1989  
**African trypanosomiasis** — Insecticide-impregnated tsetse fly traps in disease control use (biconical and monoconical).

**Chagas disease** — Improved agglutination blood test for rapid screening of transfusion blood in disease control use.

**Malaria** — Diagnostic monoclonal antibody-based (Zavala) test for species-specific detection of sporozoites in mosquitoes in disease control use.

1990  
**African trypanosomiasis** — Efornithine® registered by Marion Merrel Dow.

**Chagas disease** — Fumigant canisters, insecticidal paints and triatomine detection boxes in disease control use.

1991  
**Malaria** — New initiative launched to develop new control strategies for malaria by genetic engineering of mosquito to interrupt transmission.

**Onchocerciasis** — DNA probes for detection of *Onchocerca volvulus* in black flies in control use.

1993  
**Onchocerciasis** — Rapid epidemiological mapping of onchocerciasis (REMO) in disease control use.

Publication of a widely distributed Manual for the Use of Focus Groups.
1994
- **Chagas disease, sleeping sickness and leishmaniasis** — Parasite genome sequencing project launched in meeting in Brazil, co-sponsored by TDR and FiOCruz. Sequences published in 2005.
- **Filariasis** — Single-dose treatment with DEC or ivermectin is shown to be an appropriate treatment regimen, providing the basis for a new global control strategy based on mass drug administration.
- **Leishmaniasis** — Direct agglutination diagnostic test (DAT) and standard leishmania skin test antigen in disease control use.
- **Lymphatic filariasis** — Detection and monitoring of the adult parasite (*Wucheria bancrofti*) in humans by ultrasonography.
- **Onchocerciasis** — Effectiveness of mass drug administration with ivermectin in preventing posterior segment eye disease, visual impairment and blindness demonstrated in longitudinal studies in Africa.

![A bottle and packaging of 3mg ivermectin (Mectizan) tablets (Africa • 1999 • WHO/TDR/Merck/Scott).](image)

1996
- **Malaria** — Final results of large field trials of insecticide-treated bednets involving 400,000 people in Ghana, Burkina Faso, Kenya and The Gambia demonstrate that insecticide-treated bednets could reduce overall childhood mortality by around 20%.
- **Malaria** — Unit-dose packaging of Coartem® to ensure adherence and suitability for home management of malaria in collaboration with Novartis.
- **Malaria** — Intramuscular artemether for severe malaria registered by Rhone-Poulenc-Rorer.
- **Onchocerciasis** — Community-directed treatment (ComDT) of onchocerciasis with ivermectin becomes the mainstay of APOC mass drug administration delivery strategies following multi-country field studies testing the model’s efficacy.
- **Schistosomiasis** — Guidelines for diagnosis of female genital schistosomiasis completed.
- **Ad Hoc Committee Report on Health Research issues relating to resource prioritization for research and control leads to inclusion of TDR in Global Forum for Health Research.
- **Lymphatic filariasis** — Drug delivery strategies developed for lymphatic filariasis elimination in Africa.

1997
- **Leprosy** — Improved multidrug therapy based on rifampicin, ofloxacin and minocycline (ROM) used for leprosy control.
- **Onchocerciasis** — Effectiveness to treat and prevent onchodermatitis demonstrated in field trials in Africa.
- **Malaria** — A TDR-supported pan-African conference on research in Dakar, Senegal decides to create the Multilateral Initiative on Malaria.


1998 — *Lymphatic filariasis* — Diagnostic for disease mapping ICT (immunochromatographic test) recommended for use.

1998 — *Malaria* — Home management of malaria approach adopted as a strategy by WHO.


1998 — The Multilateral Initiative on Malaria (MIM) is formally launched.

1999 — Medicines for Malaria Venture (MMV) established with the support of TDR as a new public–private partnership to discover, develop and deliver new anti-malarial drugs.

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1999 — Manuals on Good Laboratory Practice and Good Clinical Practice published.

2000 — *Lymphatic filariasis* — Rapid mapping of filariasis in control use.


2000 — *Malaria* — Germline transformation of *Anopheles* mosquitoes.

2000 — HINARI, a partnership for Health InterNetwork Access to Research Initiative, is launched with TDR as part of the partnership in the area of research capacity building.

2001 — TDR initiates several partnerships for developing capacity in bioinformatics.

2002 — *Leishmaniasis* — Miltefosine for treatment of visceral leishmaniasis is registered by Zentaris in India (and in Germany in 2004) following successful completion of clinical trials.

2002 — *Malaria* — Genome sequencing of *Anopheles gambiae* completed by TDR-fostered consortium.

2002 — The Strategic Initiative for Developing Capacity in Ethical Review (SIDCER) is inaugurated.

2002 — The Forum for African Medical Editors (FAME) is launched.
2003 — **Lymphatic filariasis** — Lymphasim model established and utilized to predict the long-term impact of different control strategies for lymphatic filariasis.

- **Malaria** — Lapdap® (chlorproguanil and dapsone) registered for uncomplicated malaria by GlaxoSmithKline.
- **Lymphatic filariasis** — Longitudinal studies produce evidence that mass drug administration would be required for more than 4–6 years in most places to eliminate lymphatic filariasis.
- **Sexually transmitted diseases** — TDR-led evaluation of rapid syphilis diagnostic tests led to those with acceptable performance being placed on the WHO procurement list at negotiated pricing for member states, which in turn led to elimination programmes for congenital syphilis planned in several countries.
- The Foundation for Innovative New Diagnostics (FIND) is launched with the support of TDR to develop diagnostic tests for poverty-related diseases in the developing world.
- Drugs for Neglected Diseases Initiative (DNDI) is established with TDR as a founding partner.

2004 — **African trypanosomiasis** — International Glossina Genomics Initiative (IGGI) to fully sequence the tsetse fly genome launched.

- **Malaria** — Regulatory label extension is obtained for the use of Coartem® (oral treatment of artemether + lumefantrine) in infants and young children above 5 kg in weight.

2005 — **Visceral leishmaniasis** — The health ministers of India, Nepal and Bangladesh sign a Memorandum of Understanding pledging to eliminate kala azar (visceral leishmaniasis) from their countries by 2015.

**Visceral leishmaniasis** — Validation of RK39 as a diagnostic for use in India but not in Africa, incorporated into visceral leishmaniasis elimination programme.

- **Tuberculosis** — Studies completed demonstrating lack of effectiveness of 19 TB serological tests.
- **Onchocerciasis** — RAPLOA (rapid assessment procedure for determining areas of *Loa loa* endemicity) developed, validated and incorporated into disease control use.
- **Malaria** — Results from studies in Ghana indicate that the proportion of caregivers using ACTs correctly in terms of promptness, dosage and number of days is more than 90%, leading to reduced delay in seeking treatment.

2006 — **Dengue** — Multi-country studies validating pupal productivity survey methods for dengue vector control are published, demonstrating method effectiveness.

- **Visceral leishmaniasis** — Paromomycin is registered for use in India through the Institute for One World Health.

2007 — **Leishmaniasis** — Paromomycin is registered for use in India through the Institute for One World Health.
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| JCB(29) June 2006 | Chairperson: Dr A. N. Mohammed Suleiman (OMAN)  
Vice-Chairperson: Dr I. Larivière (CANADA)  
Rapporteur: Dr R. Korte (GERMANY) |

### Scientific & Technical Advisory Committee (STAC) — Past and Present Chairs

<table>
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<tr>
<th>Year</th>
<th>Chairperson</th>
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<tr>
<td>1979</td>
<td>Dr Pieter G. Janssens (BELGIUM)</td>
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<td>1980–1986</td>
<td>Dr Alexander B. Morrison (CANADA)</td>
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<td>1987–1989</td>
<td>Dr Diter Von Wettstein (DENMARK/AUSTRIA)</td>
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<td>1990–1995</td>
<td>Dr Barry R. Bloom (USA)</td>
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<td>1996–1998</td>
<td>Dr Carlos M. Morel (BRAZIL)</td>
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<td>1999</td>
<td>Dr Manikavasagam Jegathesan (MALAYSIA)</td>
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<td>2000–2005</td>
<td>Dr Graham F. Mitchell (AUSTRALIA)</td>
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<td>2006–present</td>
<td>Dr Peter M. Ndumbe (CAMEROON)</td>
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TDR Director: Robert Ridley
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Three decades of remarkable change have occurred in our global village, in health, and in scientific research as the joint UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) celebrates the 30th anniversary of the founding of its governing body, the Joint Coordinating Board.

TDR was formed in an era of growing awareness of our world’s interdependence. The programme came of age as social and economic development to bridge the gap between rich and poor countries became a mainstream UN endeavour. It has matured at the turn of the millennium, as the global community increasingly recognizes our continued vulnerability to infectious diseases of all kinds — from TB, malaria and HIV/AIDS to lesser known diseases such as dengue, schistosomiasis and sleeping sickness. Yet there is also heightened potential for scientific research — harnessed to new technologies and innovative public–private partnerships and networks — to reduce this vulnerability in disease-endemic countries.

The past 30 years have seen four of the original eight diseases targeted by TDR, namely leprosy, onchocerciasis, Chagas disease and lymphatic filariasis, advance towards elimination as public health problems. Additionally, there has been a recent commitment to the elimination of visceral leishmaniasis as a public health problem on the Indian subcontinent by 2015. Helping to drive many of these advances are new drugs, drug combinations and diagnostics as well as other evidence-based intervention approaches and strategies which have been developed and promoted through TDR-sponsored research partnerships, in which scientists and institutions in disease-endemic countries are increasingly taking a leading role.

As TDR enters its fourth decade there are formidable challenges ahead and the strategic vision and operational focus of the programme are changing in response. Yet the core values and commitment to address diseases of poverty remain unwavering. With this book, our hope is that acknowledging the successes that have been achieved to date will inform and inspire future efforts. No achievement, however, would have been possible without collaborators, partners, donors and sponsors — indeed, everything that TDR has accomplished to date has been accomplished through partnerships. This book is dedicated to TDR’s Joint Coordinating Board, which encompasses the key participants and representatives of TDR’s most vital partnerships, and which has been steadfast in its provision of oversight and guidance for the past 30 years.