CELEBRATING 40 YEARS OF RESEARCH

World Health Organization

40 YEARS TDR
For research on diseases of poverty
UNICEF • UNDP • World Bank • WHO

CELEBRATING 40 YEARS OF HISTORY

This timeline is the final result of the 2014 celebration of 40 years of achievements and impact.

In this publication, you will find examples of **visionary, long-term commitments** aimed at creating global, public health goods.

Some of these highlight the **new tools** that have been created – such as treatments for malaria, diagnostic tests for visceral leishmaniasis, and healthcare delivery strategies for remote, rural communities.

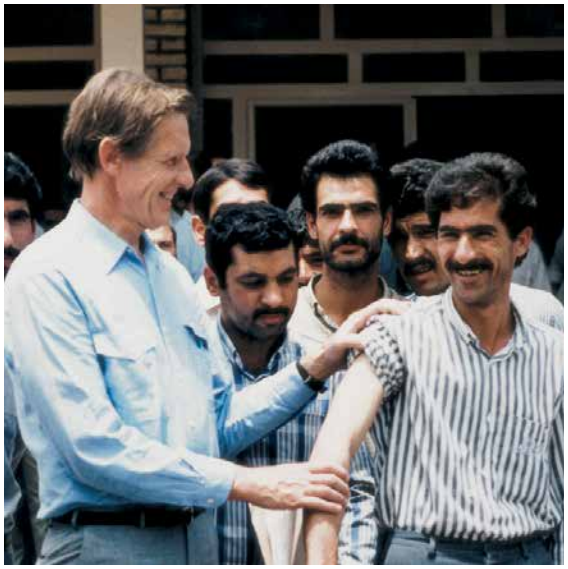
In other instances, the output takes the form of a **body of scientific knowledge**, such as the genome sequencing of parasites.

Since its inception, TDR has shown a remarkable ability to **stimulate pioneering partnerships and collaborations**, often between public and private sectors, leading to major advances.

Most importantly, there are numerous examples that show the value and impact of **building sustainable research capacity in low-income countries**. To be sure, the end goal is for these countries to be able to prioritize and conduct their own research.

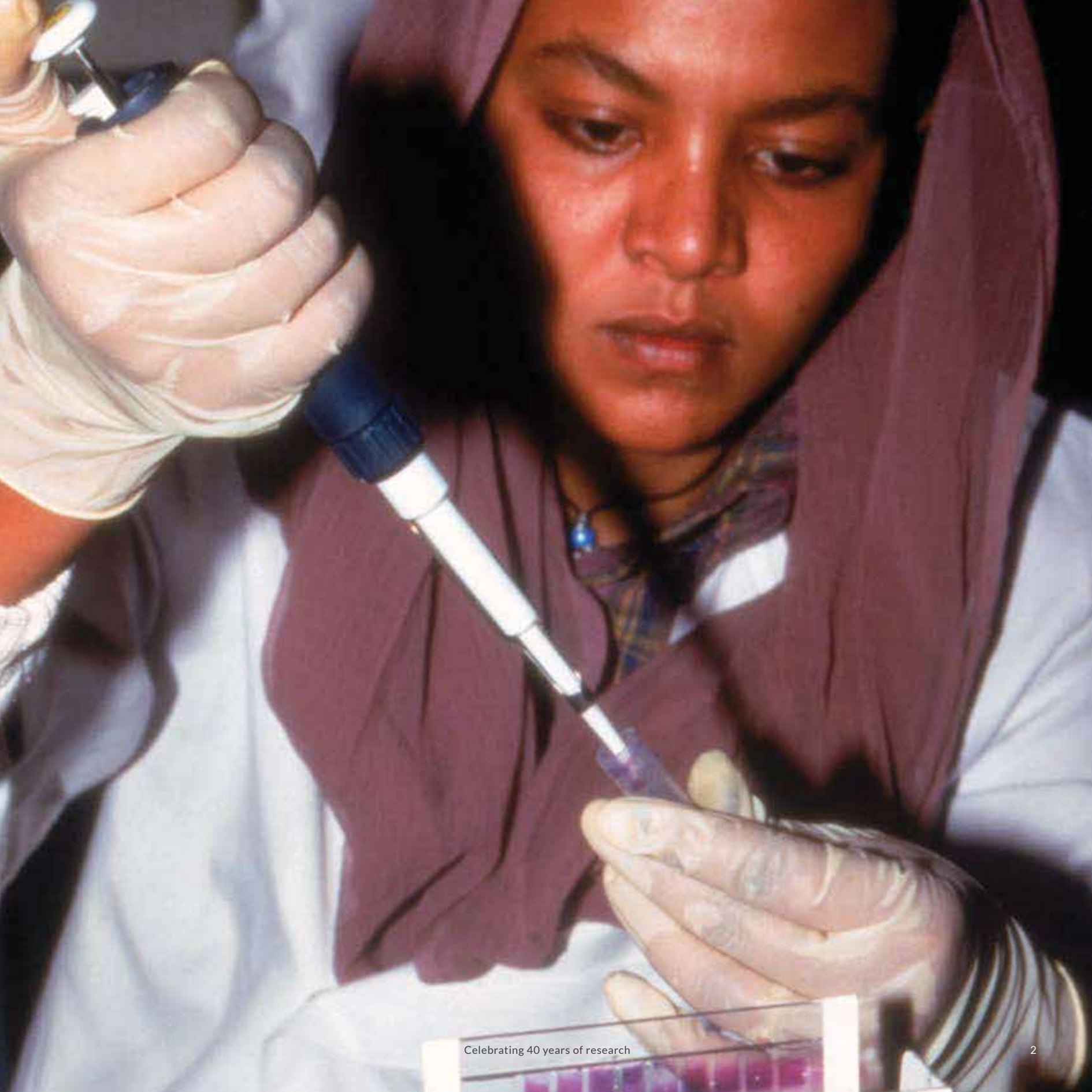
Over its 40 years, TDR has provided training and mentorship in basic research, product development for new tools, vector research to understand and cut patterns of transmission, social research to root out causes of stigma and discrimination and implementation research to improve delivery systems.

It is this long-term, multi-disciplinary approach, developed in partnership with communities and many types of organizations, that distinguishes TDR.



TDR's major contribution is to have brought much of the absolute best, cutting-edge science to tropical diseases, to a field that could not have been further behind most areas of other biomedical research in 1975.

Dr Barry Bloom, former Dean, Harvard School of Public Health (TDR, 1995)



1975 – 1984

A NEW KIND OF ORGANIZATION

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.

Dr Adetokunbo Lucas, TDR Director, 1976–1986

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.

Dr Javid Hashmi, Chief of Research Capability Strengthening, TDR, 1986–1995

TDR Directors

Dr Howard C. Goodman (1975–1976)
Dr Adetokunbo O. Lucas (1976–1986)

Scientific highlights

- Leprosy multidrug therapy
- Onchocerciasis drug (ivermectin) and free distribution
- New anti-malarials (mefloquine and artemisinin derivatives)
- Development of a new drug, DFMO (eflornithine®), new vector control tools, and new diagnostics (CATT — card agglutination test) for sleeping sickness
- Diagnostics for schistosomiasis, malaria and lymphatic filariasis
- Multi-country studies on Chagas disease prevalence, protocols for Chagas diagnosis and field research on new vector-control tools
- Vector biocontrol (for example, use of Bacillus thuringiensis serovar israelensis [H-14] for onchocerciasis)
- Creation of public registries and repositories for reagents and other materials (such as monoclonal antibodies to parasite antigens)
- Innovative social and economic research of diseases and interventions.

1975 - 1984

The beginning of TDR – a new kind of organization

In the early 1970s, there was no international research framework for infectious disease control in the developing world – that is, until TDR.

In May 1974 the World Health Assembly called for a programme to define the research priorities of these developing regions and help build the human and capital infrastructure to bring new solutions that met their health needs.

The United Nations Development Programme (UNDP) and the World Bank formally joined WHO as co-sponsors, and UNICEF came on board in 2003.

Innovative from the outset – and standing up for the interests of the disadvantaged in disease-endemic countries – the Joint Coordinating Board is TDR's strategic driver. It ensures initiatives retain balance and harmony, and fosters close, beneficial partnerships with public, academic and private institutions worldwide.

TDR has had throughout its history two intertwined missions – to build research capacity in the countries where these diseases burden so many, and to help prioritize and fund the research needed. Today the first generation who got their start at TDR are now leading research institutions and ministries of health.

What was put in place 40 years ago now provides the foundation for several elimination campaigns and for a growing body of researchers and institutions capable of identifying research priorities and carrying out a range of studies, from clinical trials to implementation research to policy development.

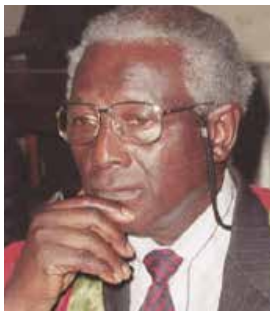
> *[TDR is] a global programme of international technical cooperation … with the two interdependent objectives of developing improved tools for the control of tropical diseases and strengthening the research capability of affected countries themselves.*
>
> Memorandum of Understanding on the administrative and technical structures of TDR, February 1978

1975

- TDR established at World Health Organization with "Special Programme" designation
- Dr Howard Goodman becomes first TDR director

1976

- Dr Adetokumbo O. Lucas becomes second TDR director



- United Nations Development Programme (UNDP) formally joins as co-sponsor

1977

- World Bank becomes co-sponsor

THE WORLD BANK
IBRD • IDA | WORLD BANK GROUP

1978

- Joint Coordinating Board meets for first time as TDR's top oversight body, comprising equal representation among low-, middle- and high-income countries

1979

- Scientific and Technical Advisory Committee holds its first meeting

A workshop on in vitro microtest of drug sensitivity of Plasmodium falciparum at a WHO/TDR Collaborating Centre for Malaria, Schistosomiasis and Filariasis, China, 1979. (WHO/TDR)

Building individual and institutional research capacity

One of TDR's first steps was to put in place a research capacity-strengthening programme to increase institutional capacity and train individuals to tackle immediate and serious health issues.

To ensure a prolonged (up to ten-year) period of funding, the programme involved capital grants for initial investigation, research and follow-up. Initially, TDR focused on non-competitive long-term grants to help construct or upgrade research facilities, and grew into increasingly competitive grants.

At Brazil's Oswaldo Cruz Institute FIOCRUZ, grants helped build a new biochemistry and molecular biology department, and supported the work of Dr Bernardo Galvão Castro, who would become the first scientist in Latin America to isolate the HIV virus. At Thailand's Mahidol University, Dr Yongyuth Yuthavong was supported to put together a course on molecular biology.

By the mid-1980s, 98 institutions had benefitted from TDR support. It had issued over 700 training grants and launched more than 10 MSc courses in entomology and epidemiology in Asia, Africa and Latin America.

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.

TDR began by highlighting this resistance and supporting research to identify several potential new compounds. Clinical trials followed to test new combinations, of dapsone, rifampicin, clofazimine and acedapsone, called multidrug therapy (MDT), in Mali and India.

The success of these trials is one of TDR's top achievements in its first decade, leading to a landmark WHO recommendation in 1982 for MDT treatment of leprosy.

At the same time, 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.

By the mid-1990s, the global number of registered patients had decreased fourfold, with TDR's work on MDT effectively eradicating the need to continue searching for a leprosy vaccine.

1981

Multi-drug therapy for leprosy recommended by WHO

A village chief sticks an MDT poster to his truck before driving around his remote community to mobilise people to attend the local health post for diagnosis and MDT treatment, Sudan, 1997. (WHO/TDR/Crump)

1982

As part of the OCP, helicopters and fixed-wing aircraft are used to spray insecticides (chemical and biological) on rivers and fast-flowing water where larvae of the blackfly, Simulium damnosum, breed. The fly transmits the parasites which cause onchocerciasis, or river blindness, West Africa, 1990. (WHO/OCP/Ward)

Biological control methods of blackfly identified that can replace larvicides for which resistance had developed

1984

Mefloquine and Mefloquine plus sulphadoxinepyrimathamine registered by Hoffman-LaRoche

1985 – 1994

MORE MEDICINES, DIAGNOSTICS AND VECTOR CONTROL

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, former representative to the JCB, Government of India

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.

Dr Winston E. Gutteridge, Coordinator, TDR Product Research and Development, 1996–2001

TDR Director

Dr Tore Godal (1986–1998)

Scientific highlights

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

1985 - 1994

Helping millions of Africans avoid the scourge of onchocerciasis

Since its foundation, TDR has been at the forefront of a global fight to combat and eradicate onchocerciasis (river blindness).

TDR effectively became the research arm of the Onchocerciasis Control Programme (OCP) in West Africa, and then the African Progamme for Onchocerciasis Control (APOC).

Research on how to curb disease transmission in broad savanna regions of West Africa led to the breakthrough innovation of incorporating the Bti bacterium to control insect larvae, including that of the blackfly, in 1982.

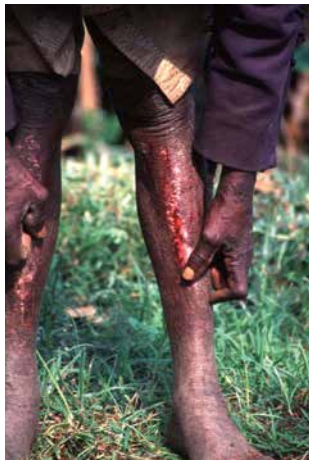
At around the same time, scientists at the US-based laboratories of Merck sent a little-known agent called ivermectin to a TDR-supported compound screening process, which showed the agent's efficacy against the infant larvae of the onchocerca parasite.

As clinical trials progressed, ivermectin's potential became more evident. TDR contributed to the design of study protocols and dosage, and connected Merck with the OCP networks.

In 1986, with the drug about to be registered, CEO of Merck Dr Roy Vagelos made the momentous decision to donate the drug to whoever needed it, as long as it was needed. TDR and partners set up large-scale community trials under field conditions to move the drug from individual treatment in hospitals to mass drug administration, strengthening the value of ivermectin in the onchocerciasis control strategy.

To support this mass drug administration, a new model was proven that empowered communities to put in place their own system for ivermectin distribution and administration, with health services offering support and training.

Today, 98 million people in 31 sub-Saharan African countries receive annual treatments through this system.



Onchocerciasis, Kanungu district, Uganda, 2001. (WHO/TDR/ Crump)

1985

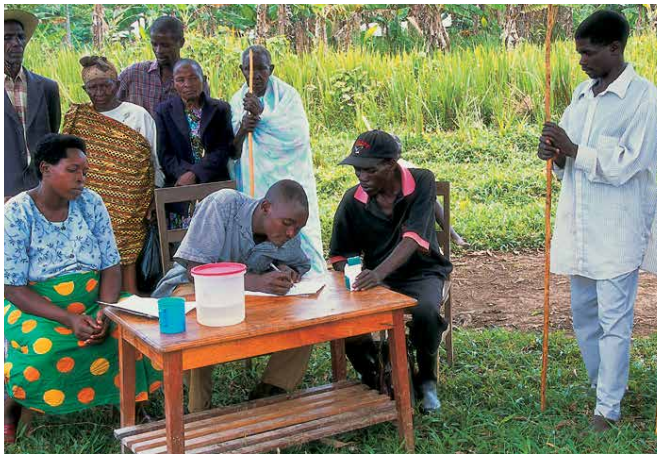
Microtest kit for measuring *P. falciparum* sensitivity to anti-malarial drugs in disease control use

1986

Dr Tore Godal becomes TDR's 3rd director

1987

Clinical trials of ivermectin lead to registration and free donation programme by Merck, bringing onchocerciasis control to most areas across Africa



Rukungiri: A local health worker (seated with cap) arrives in a remote pygmy village. He delivers ivermectin tablets to the community-directed distributors and supervises their activities during central point distribution. (WHO/TDR/Edwards)

> *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.*
>
> TDR, Third External Review, 1998

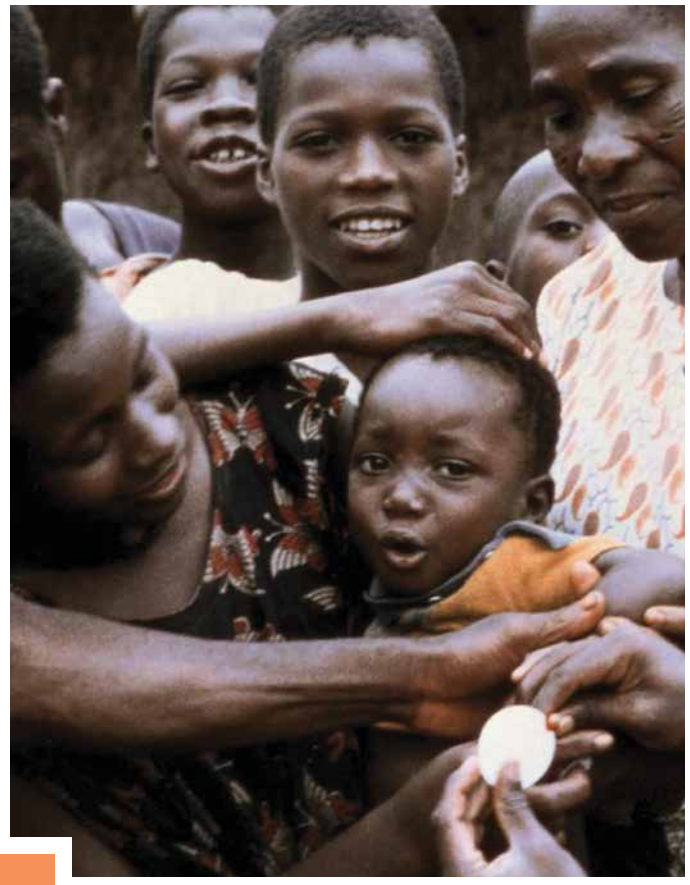
Controlling human African trypanosomiasis

Human African Trypanosomiasis (HAT) – also known as sleeping sickness due to the extreme fatigue that afflicts sufferers before death – is particularly prevalent in rural regions, where villages are at daily risk from exposure to tsetse flies, the vectors of sleeping sickness parasites.

Easily erected insecticide-impregnated tsetse fly traps that had been tested in TDR's first decade were by now halting the epidemic in southern Uganda.

Another important step forward was the use of d,l-α- difluoro¬methylornithine (DFMO). Originally developed by Marion Merrell Dow Pharmaceuticals (now Sanofi-Aventis) as a compound to treat cancer, DFMO showed distinct potential in the treatment of HAT. In 1987 TDR supported Phase III clinical trials that proved its efficacy, with patients even in later stages of the disease responding rapidly.

It was the first new treatment for sleeping sickness in four decades, and is now made available by Sanofi-Aventis through a donation programme under a WHO Memorandum of Understanding.



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. (WHO/TDR)

1988

Partnership grants initiated for collaborations between low- and middle-income countries and advanced research institutions

1989

Insecticide-impregnated tsetse fly traps become control tools for sleeping sickness

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, 2002. (WHO/TDR/Edwards)

1985 - 1994

Testing new malaria treatments: mefloquine, artemisinin and Coartem®

Mefloquine was a malaria treatment initially overlooked as both unpatented and expensive. However, TDR's work with pharmaceutical experts and its sponsorship of more than twelve clinical research studies in Latin America, Zambia and Thailand, helped find a more cost-effective way to synthesise the drug.

TDR was one of the first foreign institutions to explore first-hand the work of scientists at China's artemisinin research facilities. Research into this indigenous plant used in traditional Chinese medicine showed its active compound was potentially highly effective against parasites. So TDR led large-scale, multi-partner clinical research into their oral use, testing various combinations (called ACTs) of artemesinin with other active compounds: amodiaquine plus artesunate; chloroquine plus artseunate; mefloquine plus artesunate; and also artemether plus lumefantrine (Coartem®).

Further research into packaging that could be understood with pictures, and doses put into blister packs, provided effective and safe use of Coartem® for infants over 5 kg in weight. This broad research approach would provide key evidence for the World Health Organization promotion of ACTs as a fundamental part of malaria treatment policy and negotiated preferential rates.

Developing countries could then benefit from the fastest-acting anti-malarials available – destroying parasites in approximately 48 hours on average – with high documented cure rates.

TDR's Dr David Davidson inspecting production facilities for artemisinin-derivative anti-malarial drugs in China, 1991. (WHO/TDR)

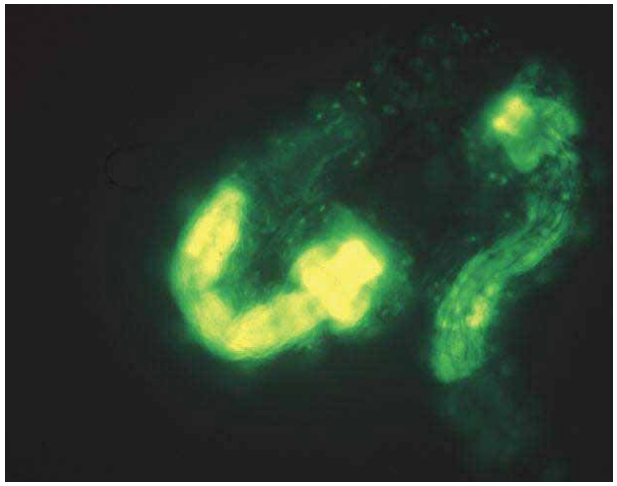
1990

- Eflornithine (DFMO) registration by Marion Merrel Dow for treatment of late-stage sleeping sickness
- Fumigant canisters, insecticidal paints and boxes to detect the Chagas disease triatomine bug put into control use

Fumigant canisters that release insecticidal smoke when lit and control the triatomine bugs that transmit Chagas disease. (WHO/TDR)

1991

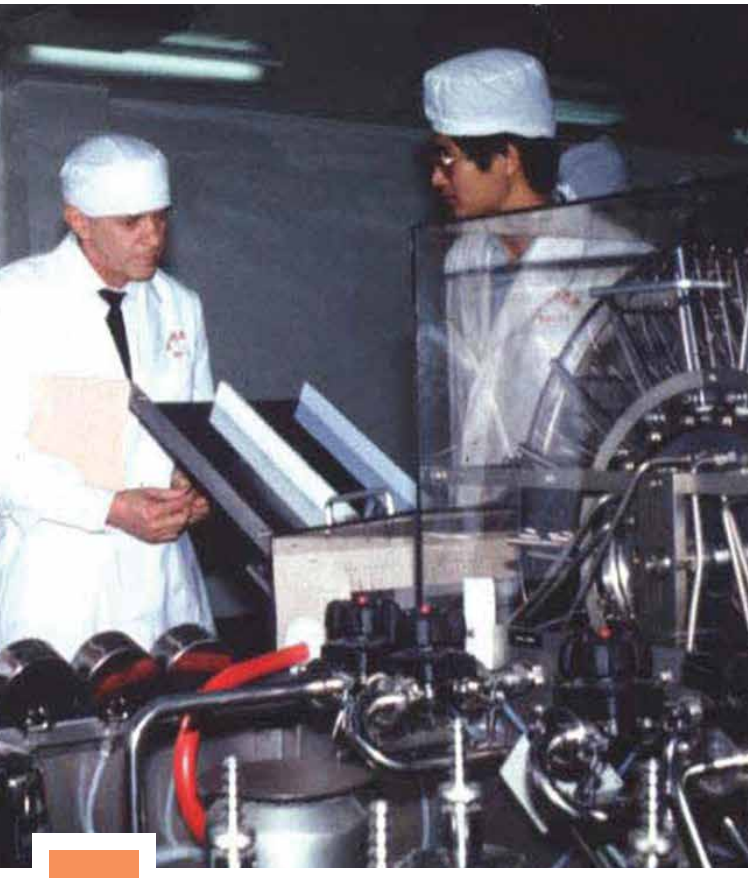
- Initiative launched to control malaria by genetically engineering the *Anopheles gambiae* mosquito to interrupt transmission
- DNA probes for detection of Onchocerca volvulus in black flies in control use



Photomicrograph of *Anopheline* mosquito larvae. The larvae have been genetically modified to incorporate a gene for the Enhanced Green Flourescent Protein which causes the larvae to glow. (WHO/EURO)

1992

- Small grants scheme initiated



Genetic modification of mosquitoes

At a meeting in Tucson, Arizona in 1991, TDR joined the MacArthur Foundation in calling for the genetic engineering of A. gambiae, the mosquito that transmits the malaria Plasmodium parasite. Thus started a major effort requiring extensive partnerships and collaborations.

The TDR Molecular Entomology Committee was created to develop tools for this genetic modification. A 15-year programme was agreed to identify the modifiable genes that carried the parasite, develop methods for spreading these genes in wild mosquito populations, and field-test control methods.

TDR gathered together a consortium of high-level international organizations, including the National Institutes of Health (USA), the Pasteur Institute (France), the European Molecular Biology Laboratory (Germany), Celera Genomics (USA), the ONSA network (Brazil) and others, to initiate the sequencing of the A. gambiae genome. While TDR's monetary investment was relatively small, it provides an example of how strategic leadership and leverage at a critical moment can stimulate a much broader effort.

Just one year after the initiative was formally launched, the A. gambiae genome sequencing project was published in Science, and Nature issued a report on the sequencing of the Plasmodium falciparum genome.

By 2001, TDR had supported more than 100 projects in 19 countries on this work, and then started to focus on the ethical, legal and social implications of testing and evaluating. This included training and networks in bioinformatics and genomics applications to increase the capacity of scientists in low- and middle-income countries to conduct this kind of research and surveillance, and in 2014, a guidance framework with proposed standards for safety was published.

1993

- Rapid epidemiological mapping of onchocerciasis (REMO) in disease control use
- Social surveys in India identify community-level gender differences in stigma related to leprosy

1994

- Effectiveness of mass drug administration with ivermectin demonstrated to prevent eye disease and blindness in longitudinal studies in Africa
- Parasite genome sequencing project launched in Brazil
- Meeting on genomics launched a new era in basic research, starting with the sequencing of the parasites responsible for leishmaniasis, sleeping sickness and Chagas disease
- Leishmaniasis direct agglutination diagnostic test (DAT) and standard leishmanin skin test antigen put into control use
- Liposomal amphotericin B for visceral leishmaniasis registered by NeXstar
- Single-dose treatment with DEC or ivermectin+albendazole for new global lymphatic filariasis control strategy

Maharashtra: Indian field researchers comparing notes during a social survey, India, 1993. (WHO/TDR/Vlassoff)

1995 - 2004

COMMUNITY AND SOCIAL RESEARCH

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, Former Chair of TDR's Scientific and Technical Advisory Committee

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, former representative of UNICEF to the JCB

TDR Directors

Dr Carlos M. Morel (1998–2004)
Dr Robert G. Ridley (2004–2011)

Scientific Highlights

- Incubation and foundation of Medicines for Malaria Venture (MMV) and Foundation for Innovative New Diagnostics (FIND)
- Support for creation of TB Alliance and Neglected Diseases Initiative (DNDi)
- Establishment and transition of several anti-malarial drug development projects to MMV and DNDi
- New drug discovery networks
- Miltefosine for visceral leishmaniasis
- Tools and field research supporting visceral leishmaniasis/lymphatic filariasis elimination campaigns
- Validation of syphilis diagnostics for elimination efforts
- Validity of ACT use in home management of malaria
- Rapid assessment (RAPLOA) of onchocerciasis/Loa loa co-endemicity
- Extension of community directed interventions beyond onchocerciasis
- *Anopheles gambiae* and Tritryps genome collaborations
- Partnering Multilateral Initiative for Malaria (MIM)
- Establishment of Strategic Initiative for Developing Capacity in Ethical Review (SIDCER)
- Thousands of people trained in new Research capacity strengthening (RCS) short courses
- 70% of R&D partners engaged are from developing countries
- WHO recommendation to stop using single-drug treatments for malaria and move to only artemisinin-combination therapy (ACT), supported by TDR studies.

1995 - 2004

Eliminating lymphatic filariasis

Happily, by the end of TDR's third decade, lymphatic filariasis was one of four original TDR-targeted diseases heading towards regional or global elimination.

At its worst a cause of elephantiasis, hydrocele and lifelong disability, the disease is indigenous to 83 countries, with 119 million people worldwide estimated to be infected.

In 2000, spurred by the recent introductions of diethylcarbamazine (DEC) and DEC plus ivermectin, WHO and its national partners established the Global Programme for Elimination of Lymphatic Filariasis (GPELF).

TDR field research and support not only played a key role in guiding implementation strategies, but also in highlighting to national policy makers the economic cost of the disease against the cost-effectiveness of mass drug administration.

TDR identified the number of annual doses needed to break disease transmission and helped rural communities manage their drug administration and treatment through community health care workers. Together with donations of drugs such as ivermectin by Merck, and albendazole by GlaxoSmithKline, hundreds of millions of people have received the treatment they desperately need.

A house-to-house community-based distributor of ivermectin treating members of a household: explaining the difference between the old 6 mg tablets and the new 3 mg ones. Nigeria, 1998. (WHO/TDR/Crump)

1995

- Method for rapidly identifying urinary schistosomiasis in highly endemic communities put into control use
- Onchocerciasis control extended to forest areas in Africa to address skin disease

1996

- Unit-dose packaging of artemether and lumefantrine improves adherence and suitability for malaria treatment
- New community-led approach for onchocerciasis annual mass drug treatment becomes mainstay of the African Programme for Onchocerciasis Control (APOC) delivery strategy
- Drug delivery strategies developed for lymphatic filariasis elimination in Africa

1997

- Improved multidrug therapy (ROM: rifampicin, oflaxacin and minocycline) for leprosy control
- Effectiveness to treat and prevent onchocerdermatitis demonstrated in field trials in Africa

Shertallai: Patients awaiting attention outside the Filariasis Clinic at the Vector Control Research Centre (VCRC), 1993. (WHO/TDR/Chandran)

Multilateral Initiative for Malaria builds research capacity among African scientists

In 1998, TDR helped establish a key platform for African-based researchers to strengthen malaria research and collaboration in Africa.

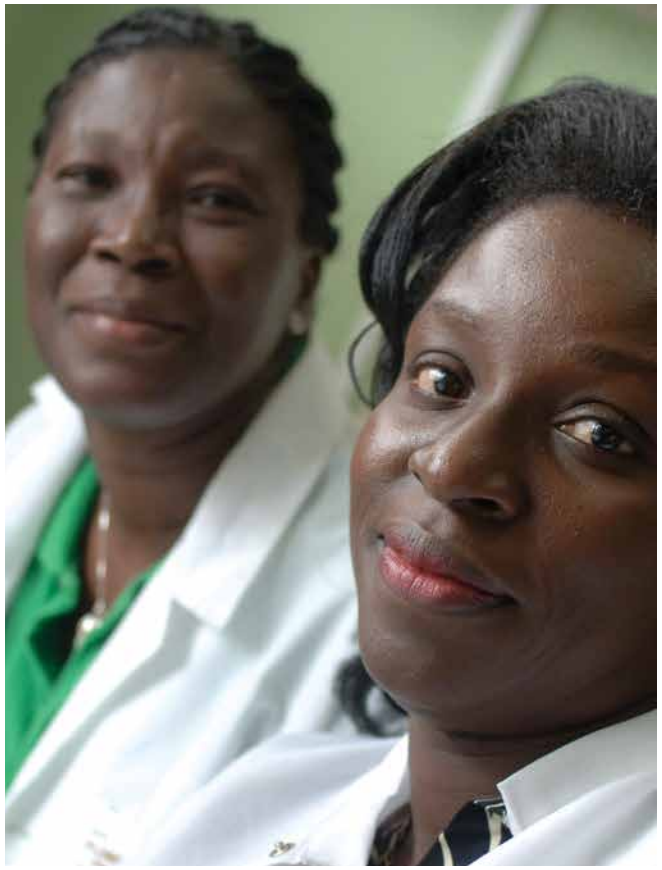
The Multilateral Initiative for Malaria (MIM) was launched in collaboration with the US Department of Health and Human Services; US. National Institutes of Health; the Wellcome Trust; and the Pasteur Institute in Africa.

African researchers were given access to technology, facilities and expertise; wider networking capability; and TDR grants that, uniquely for the time, went directly to researchers, rather than being distributed through a developed country institution.

Perhaps most significantly, the programme enabled breakthrough research on drug and insecticide resistance through an improved research infrastructure and new molecular genetics capability. Investigators in Ghana, Mali, Nigeria, Tanzania, and Uganda helped pool evidence of resistance to chloroquine and sulfadoxine-pyrimethamine, which eventually led to the introduction of more effective artemisinin-based combination therapies.

Within 10 years, 69 research grants had been awarded to principal investigators in 36 African-based institutions in 17 countries. Many grantees became internationally competitive and attracted large grants, and have gone on to lead major research institutions and programmes.

In a 2007 external review of the programme, one participant said, "The MIM/TDR grant is a life line; it has helped those of us with no big CVs to get grants and start our real research careers."



Nigerian researchers, 2006. (WHO/TDR/Craggs)

1998

Dr Carlos Morel becomes TDR's 4th director

Multilateral Initiative on Malaria (MIM) launched to strengthen collaborative research in Africa

Home management of malaria approach adopted as WHO strategy for community healthcare workers to diagnose and treat malaria

Initiating a worldwide genomic sequencing effort

Three of the world's most neglected tropical diseases are caused by parasitic trypanosomatids – African trypanosomiasis (sleeping sickness), Chagas disease and leishmaniasis.

In the mid-1980s, initial progress on sequencing the Chagas disease Trypanosoma cruzi genome demonstrated that antigens could be produced in the laboratory by recombinant DNA technology, creating improved diagnostic reagents.

A decade later, TDR and Brazil's Oswaldo Cruz Institute (FIOCRUZ) co-sponsored the 'Tritryps project' to sequence the genomes of the three related parasites. This brought together researchers from both developed and developing countries and was supported by the Wellcome Trust, the European Commission, the US National Institutes of Health (NIH), and national research institutes.

The Tritryp genomes were completed 11 years later, providing a first peek into the biology of the trypanosomatids and a blueprint for genome-wide studies that are starting to generate new products to fight these long-neglected diseases.

This work is another example of visionary, long-term commitments aimed at creating global, public health goods. In this case, it is a body of scientific knowledge that many others throughout the world are using to create useful health products.

1995 - 2004

ACT being provided in India. (Anita Khemka)

Supporting a paradigm shift in malaria treatment

It was 1998 and the world was in danger of losing an effective malaria treatment. Parasites were developing resistance to chloroquine, the major drug treatment for half a century, and its replacements, sulfadoxine-pyrimethamine and mefloquine. Evidence on new treatment options was urgently needed.

In the meantime, Chinese researchers had discovered a new class of potent antimalarials, the artemisinins, extracted from the plant Artemisia annua. Studies supported by the Wellcome Trust in the mid-90's had shown that the combination of an artemisinin derivative, artesunate, with mefloquine was highly effective in Thailand where mefloquine resistance was rampant. TDR coordinated a series of multi-country trials in Africa and Latin America between 1999-2001 comparing single-agent treatments with the medications then recommended (chloroquine, amodiaquine and sulphadoxine-pyrimethamine) to regimens where they were combined with artesunate. Collectively all these studies, together with further studies on their cost effectiveness, helped provide the evidence for a paradigm shift in malaria, from single-agent to combination therapy.

A technical consultation at WHO in 2000 reviewed these data and recommended to malaria endemic countries to stop using single-drug treatments and move to only artemisinin-combination therapy (ACT). A year later, a list of 4 recommended ACTs was distributed. These treatments have since become the cornerstone of malaria control and elimination, helping to reduce thousands of deaths and illnesses every year.

2000

- Manuals on good laboratory practice and good clinical practice published
- WHO recommends moving from single-drug treatments for malaria to only artemisinin-combination therapy (ACT)
- Germline transformation of *Anopheles* mosquitoes

Anopheles female mosquito, 2000. (WHO/EURO)

2002

- Milefosine registered by Zentaris for visceral leishmaniasis treatment in India
- *Anopheles gambiae* malaria parasite genome published
- Series of social research methodologies published

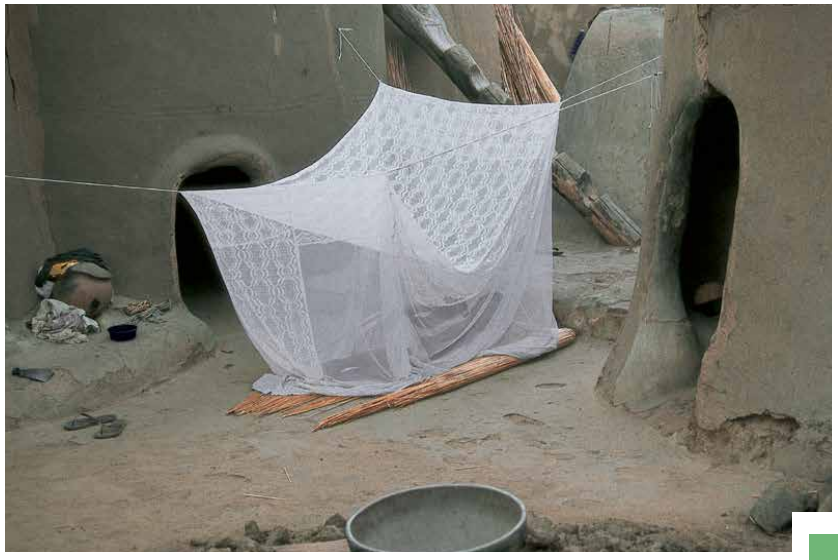
> *The development of miltefosine was, in my view, one of the major successes of TDR in this period. It was the first oral drug for VL, it involved an excellent partnership between TDR, the Indian authorities and the private sector. And the initiative involved capacity building with the Indian hospitals involved in the drug trials.*
>
> Dr Carlos Morel, former TDR Director

Establishing the effectiveness of bednets to control malaria

Today the use of insecticide-treated bednets is a mainstay of malaria control. The evidence of effectiveness for this innovation came from TDR support in the 1990s. Following the success of small-scale trials in The Gambia, TDR funded far larger-scale trials across Africa, in what was to prove one of the programme's most ambitious investments.

The Ghana trials had shown a highly significant 63% reduction in childhood deaths from malaria due to bednets. This was sufficient for TDR Director Dr Tore Godal to recommend the funding of large-scale trials necessary to prove whether this could work on a broad scale. A unique blend of highly controlled scientific trial and operational research was set up in sites across Ghana, Burkina Faso, Kenya and The Gambia that covered 400 000 children.

The final results that insecticide-treated bednets could reduce overall childhood mortality by an average of around 20% led to the WHO recommendation that they be a standard preventive treatment in malaria-endemic areas, and their extensive distribution across the African continent.



Woman sleeping under bednet in Korania village, Ghana, 1991. (WHO/TDR/Crump)

- Research publications provide new methodologies and priorities:
  - Community participation
  - Mapping of diagnostics for sexually transmitted diseases
  - Manual of social mobilization on dengue
  - Training manual for non-clinical testing
- Dr Robert G. Ridley becomes TDR's 5th Director
- International Glossina Genomics Initiative launched to sequence the tsetse fly genome

2003

- Evaluation of rapid syphilis diagnostic tests leads to placement on WHO procurement list at negotiated pricing for Member States, leading to elimination programmes for congenital syphilis in several countries
- UNICEF joins as co-sponsor

unicef

2004

- Definitive evidence of the effectiveness of insecticide-treated bednets to reduce overall childhood mortality by 20% provided by large field trials involving more than 400 000 people in Africa
- Regulatory label extension obtained for Coartem© oral treatment in infants and young children

Rapid diagnostic test for syphilis being tested in Haiti, 2006. (WHO/TDR/Craggs)

2005 - 2014

ACCESS FOR THE MOST VULNERABLE

What are the most important lessons from the early history of TDR? To have the courage to experiment.

Dr Adetokunbo Lucas, TDR Director, 1976–1986

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. 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 the JCB

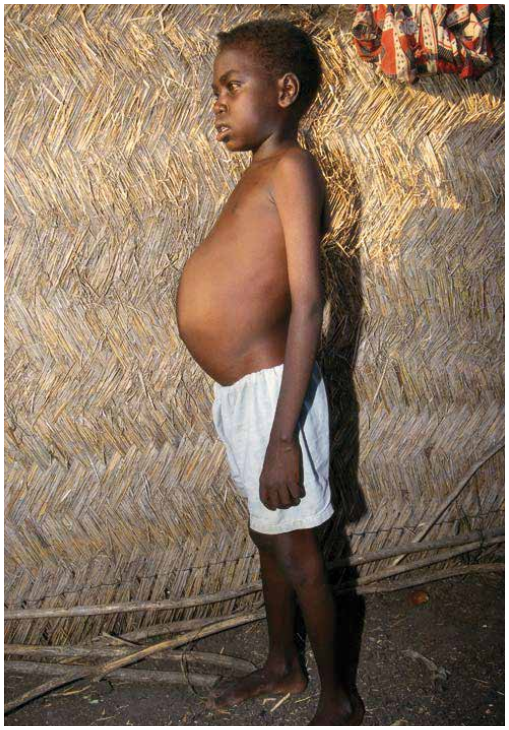
TDR Directors

Dr Robert G. Ridley (2004–2011)
Dr John Reeder (2012–present)

Scientific highlights

- WHO recommendation to stop using single-drug treatments for malaria and move to only artemisinin-combination therapy (ACT), supported by TDR studies
- Visceral leishmaniasis elimination progresses with new diagnostics, treatments and delivery strategies
- WHO calls for stopping TB serological tests and issues new recommendations based on TDR-supported evidence
- Rapid malaria diagnostic test evaluations improve quality of marketed tests
- Effectiveness of rectal artesunate to treat severe malaria established
- Ivermectin shown capable of eliminating onchocerciasis
- Trapping methods for 6 vectors of sleeping sickness standardized across 9 African countries
- Antifilarial drugs shown to reverse lymphatic pathology in children with Brugia malayi infection (lymphatic filariasis)
- Trypanosomatid genome sequences published
- Community-based approaches reduce dengue mosquito breeding.

2005 - 2014



Eliminating visceral leishmaniasis in Bangladesh, India and Nepal

In 2005, a Memorandum of Understanding signed by the health ministers of Bangladesh, India and Nepal signalled a major joint effort to eradicate the deadly disease of visceral leishmaniasis (VL) over a ten-year period.

TDR research helped adopt diagnostic tools, test drug treatments, and develop measures to control the parasite-carrying sandflies with bednets and insecticide sprays.

TDR has shown that a single dose of liposomal amphotericin B (manufactured as AmBisome®) can be provided at primary health care centres instead of just at hospitals which are often far from where patients live. The single intravenous drip takes about 2 hours instead of the standard dose of miltefosine pills taken over a 28 day course.

Although the best available treatments may be present at the primary health care centres only several kilometres away, this is of limited value if VL cases remain undiagnosed in the villages.

TDR worked with multiple partners to study new ways to reach into the community to find potential cases.

Early diagnosis and treatment are essential for not only individuals, but also for the community because it reduces VL transmission. If a community's overall level of infection is reduced, fewer cases can be transmitted by the sandflies that carry the parasite.

Together with the national control programmes, WHO, and drug development partnerships like Drugs for Neglected Diseases initiative, visceral leishmaniasis is well on its way out of this region.

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)

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.

2005

- Trypanosomatid genome sequences published
- RK-39 diagnostic tool validated in use in India and incorporated into VL elimination programme
- Guidelines published for clinical trials and data and safety monitoring boards
  - Operational guidance: Information needed to support clinical trials of herbal products
  - Operational Guidelines for the Establishment and Functioning of Data and Safety Monitoring Boards
- Gatifloxacin for TB Phase III clinical trial announced

Helping communities manage dengue and Chagas disease

Dengue has long plagued urban regions of Latin America, while Chagas disease presents a persistent threat to the continent's rural areas.

Working with the Ecosystem and Human Health Program of Canada's International Development Research Centre (IDRC), TDR's research combines an environmental and community approach to develop healthy solutions that can reduce the use of insecticides and improve overall housing conditions.

In Uruguay – a dengue-free country but still at risk from its proximity to disease-prevalent Brazil and Argentina – residents have learned the importance of emptying receptacles containing stagnant water and treating water tanks with environmentally safe larvicides.

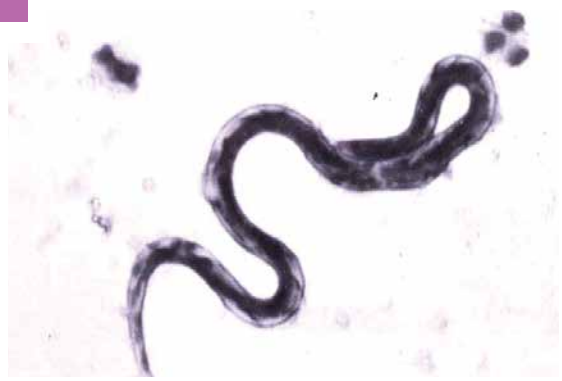
In Brazil, early studies looked at replacing insecticides to kill the mosquito larvae with covers for outside family water store containers.

On the banks of Colombia's Magdalene River, a similar approach went hand-in-hand with a new social enterprise to produce window curtains to keep mosquitos out of households.

In Bolivia, this approach is also helping fight Chagas disease in the farming communities. Villagers have been taught the value of checking mattresses for nests of the triatomine bug, and reducing breeding grounds by keeping dirt floors clear of leaves and debris and moving farm animals further away from the house.

The work has been conducted in 13 different countries in Latin America and Southeast Asia, and is now being investigated in some countries for full national scale-up.

The number of mosquitoes that transmit dengue are reduced by identifying and managing the water containers where larvae breed in Thailand, 2006. (WHO/TDR/Craggs)



Photomicrograph of the filarial worm Loa loa, 1990. (WHO/TDR/Pasteur Institute)

- RAPLOA (rapid assessment procedure for determining areas of Loa loa endemicity) developed, validated and incorporated into disease control use
- Review of gender in tropical disease control published

- Strategic review of traps and targets for tsetse and African trypanosomiasis control

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/Baldry)

EVIPNet
EVIDENCE-INFORMED POLICY NETWORK
World Health Organization

- Evidence-Informed Policy Networks (EVIPNet) launched in 2005, using TDR research evidence for pilot
- Effective project planning and evaluation for biomedical and health research publication and training launched

2005 - 2014

A new treatment approach by the community, for the community

Most low- and middle-income countries struggle with not having enough healthcare providers to deliver vital services. One approach to address this has been the use of community health workers, called CHWs, where people are trained to diagnose and treat common ailments in the villages in which they live.

TDR supported critical research into the effectiveness of this model, and showed that CHWs can reduce childhood mortality due to malaria, and effectively and safely distribute annual treatments for onchocerciasis.

In 2000, TDR published a report that pointed to the "absence of capacity and understanding in how to engage with communities and ensure their participation, and of the ability to adapt research methods and health technologies to local contexts."

Support went to both training scientists from low- and middle-income countries on this research methodology, as well as to conduct the research.

A broader strategy has come out of this called community case management that is used to address the symptom of fever, which can be caused by any of the three major childhood killers – malaria, pneumonia or diarrhoea. The CHWs have shown that they can correctly diagnose and provide the appropriate treatment, so that children are getting the treatment they need, when they need it.

Both the World Health Organization and UNICEF have since called for scaling up this approach, and TDR has expanded its support and training in implementation and operational research, working closely with national control programmes and research organizations to help communities help themselves.

Community healthcare worker providing malaria treatment for sick child, Nigeria, 2006. (WHO/TDR/Craggs)

2007

- Evaluation methodology on VL diagnostics published
- MIM evaluation finds malaria research capacity strengthened in 17 African countries

2008

- Publications:
  - Implementation and operational research frameworks
  - Ethical guidelines for social science
  - Evaluation of TB diagnostics methodologies and research priorities
  - Social context of schistosomiasis and control
  - Report on moxidectin development
  - Health economics research capacity report
  - Implementation and operational research frameworks published
- Marketed TB serologic diagnostic tests evaluation identifies none that are effective

2009

- ESSENCE on health research initiative launched to increase collaboration among international funders to strengthen African research capacity
- African Network for Drugs and Diagnostics Innovation launched

ANDi

Genome sequencing to fight sleeping sickness and build African research capacity

In 2004, with funding from TDR, WHO and the Wellcome Trust Sanger Institute – and overseen by the International Glossina Genome Initiative (IGGI) – a project took shape to map the genetic blueprint of Glossina morsitans, one of 32 species of tsetse fly that transmits the deadly trypanosomiasis parasite and causes sleeping sickness.

With TDR support, IGGI was able to meet annually, growing steadily larger and planning peripheral projects to incorporate African scientists.

Ten years after the project began – a decade of work involving 150 scientists (half from African institutions) – the genetic code of a highly unusual insect, whose capacity as a vector had long puzzled scientists, was sequenced and annotated. This led to improved trapping systems and other control methods.

Importantly for TDR, the project also marked the first time that African countries were closely and collaboratively involved in an initiative from the very start. The sequencing project helped strengthen capacity in African institutions, and the side projects that developed as its momentum grew encouraged more and more interest and involvement from the Sanger Institute, whose financial contribution is estimated to be around $4 million.

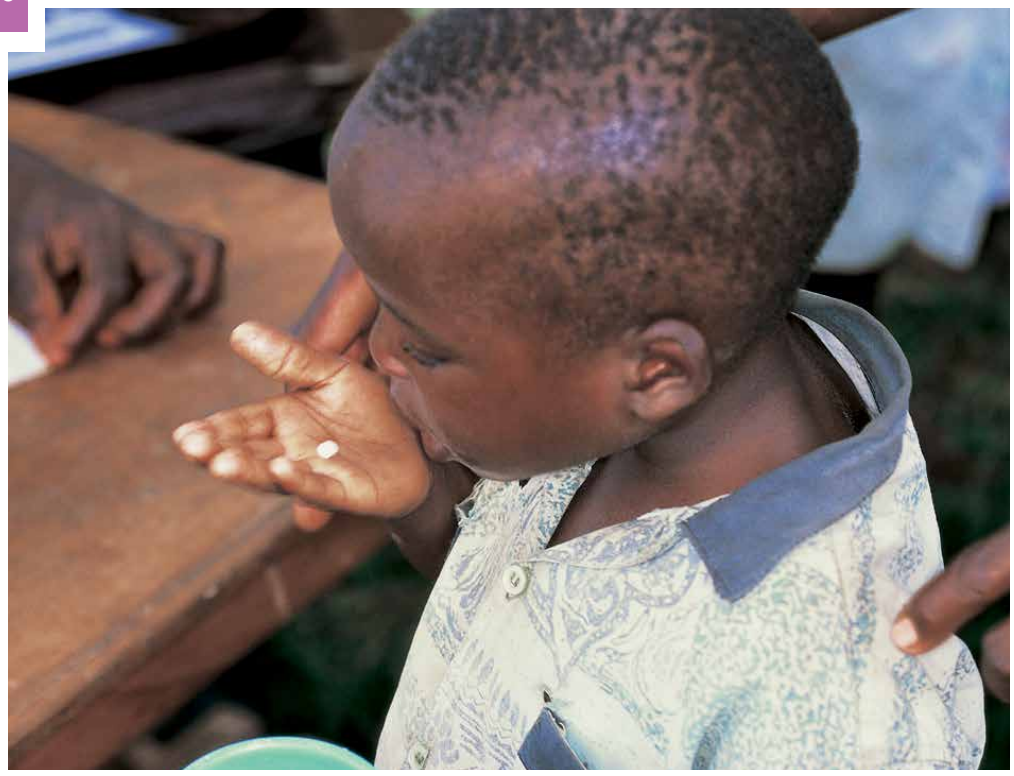
The success of the initiative inspired further sequencing work, with US National Institutes of Health awarding funding to IGGI to sequence and annotate four other species in the Glossina genus as well as the common housefly.

2009

Oncherciosis treatments:

- First evidence that onchocerciasis elimination is feasible with ivermectin treatment published
- Moxidectin begins Phase 3 clinical trial

First rapid malaria diagnostic test evaluation finds uneven quality (starts series of regular evaluations that improves quality and appropriateness of tests)



A young boy swallows his ivermectin tablets during a central point distribution in his village, Masindi district, Uganda, 2001. (WHO/TDR /Crump)

Antifilarial drugs, in the doses employed in mass drug administrations by the Global Programme to Eliminate Lymphatic Filariasis, reverse lymphatic pathology in children with Brugia malayi infection. Before this, the only other option was chemotherapy.

2005 - 2014

Improving policy and practice by evaluating rapid diagnostic tests

An early focus of TDR was on increasing standards for conducting quality drug trials in low- and middle-income countries. But it became quickly apparent that there was an equal need to apply this to diagnostic tests.

Companies were free to manufacture and market tests without the oversight and quality control of an independent and authoritative regulatory body. By 2005, it was unclear how well the growing numbers of rapid diagnostic tests (RDTs) actually worked in harsh field conditions.

TDR played a crucial role in initiating evaluations of RDTs for several diseases – such as dengue, tuberculosis (TB), and sexually transmitted diseases.

Evaluations of rapid malaria tests helped incentivise manufacturers to meet international performance recommendations based on the evaluation programme.

TDR's extensive scrutiny on a variety of tuberculosis tests underpinned 12 WHO diagnostics policies. This included a WHO recommendation to end the use of serological tests to diagnose TB – the first such negative policy recommendation issued by the organisation against a widely used care measure.

This overall area of work shows how research has provided a critical foundation to ensure quality for new health tools, and has played an important role in how these tools are monitored and their use agreed by national, regional and international authorities.

Rapid malaria diagnostic test. (WHO/TDR)

2010

- Visceral leishmaniasis elimination research tools published
- Community-based approaches to reducing dengue mosquito breeding through environmental approaches developed

Visceral leishmaniasis (VL) patients receiving treatment at the Kala azar Medical Research Centre, Muzaffarpur, India, 2006. (WHO/TDR/Ghalib)

2011

- TDR wins Gates Global Health Award

Ambassador John Lange, the Bill & Melinda Gates Foundation; Dr Robert Ridley, TDR Director; Dr Margaret Chan, Director-General, World Health Organization; and Mr Jeffrey L Sturchio, President, Global Health Council; after the presentation of the 2011 Gates Award for Global Health to TDR in Geneva, Switzerland.

Tuberculosis patient in Rural Nepal, 2007. (WHO/SEARO/Orr)

WHO calls for ending use of TB serological tests based on TDR-supported evidence

Number of effective rapid malaria diagnostic tests increases due to ongoing evaluations

WHO issues new recommendations based on TDR research that improve TB diagnostic procedures

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.

Dr Richard Wilson, TDR Programme Management, 1975-1985

2012

Manual on rectal artesunate use to treat malaria published, and treatment transitioned to MMV for manufacturing solution

Conclusive proof established that ivermectin can eliminate onchocerciasis

Standardization and optimization of trapping methods for 6 HAT vectors across 9 African countries

Operational research and training (SORT IT) initiated at TDR

2013

Evidence on single-dose liposomal amphotericin B use in rural public Bangladesh hospitals contributes to VL elimination plan

Dr John Reeder becomes TDR's 6th Director

Dengue clinical management handbook published

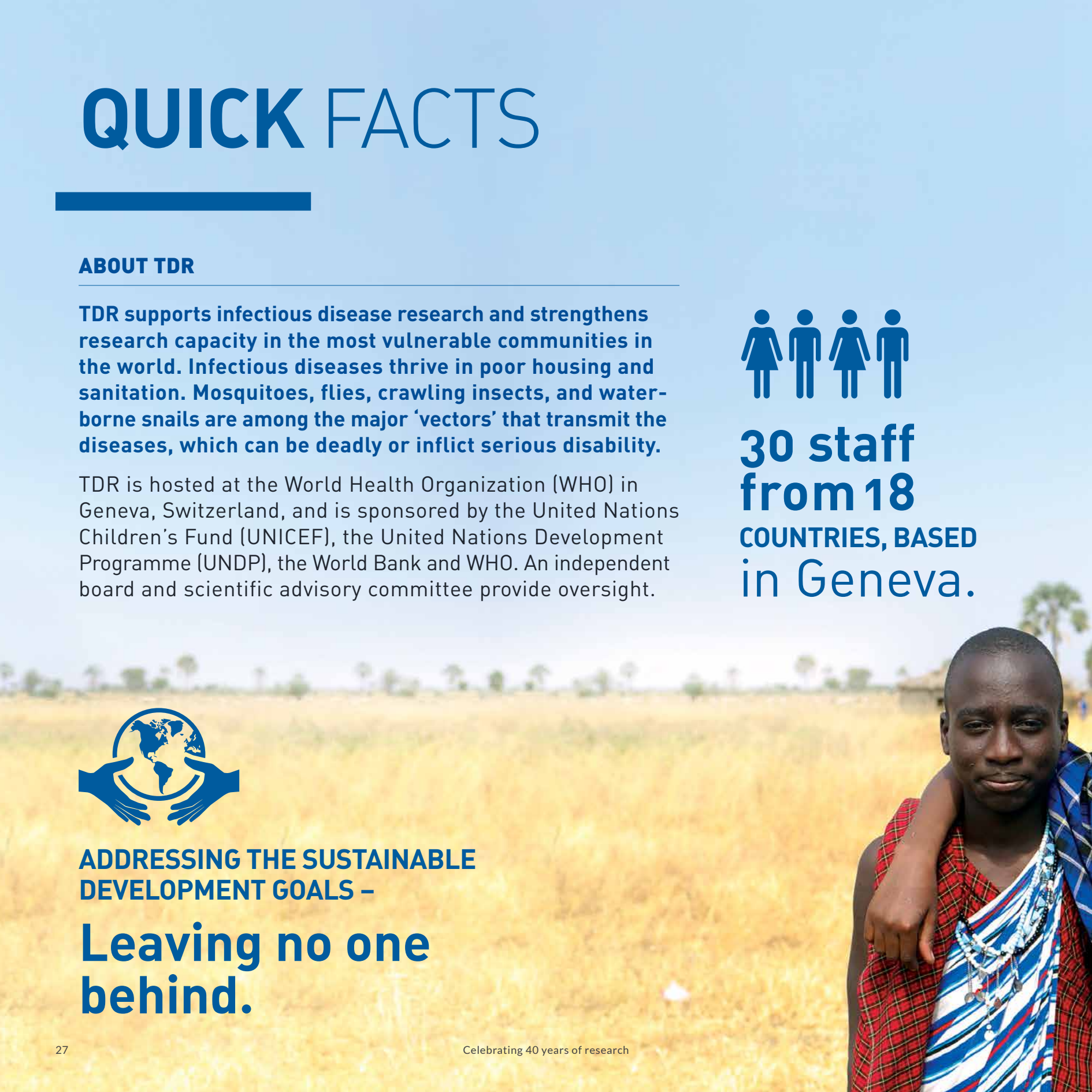
QUICK FACTS

ABOUT TDR

TDR supports infectious disease research and strengthens research capacity in the most vulnerable communities in the world. Infectious diseases thrive in poor housing and sanitation. Mosquitoes, flies, crawling insects, and water-borne snails are among the major 'vectors' that transmit the diseases, which can be deadly or inflict serious disability.

TDR is hosted at the World Health Organization (WHO) in Geneva, Switzerland, and is sponsored by the United Nations Children's Fund (UNICEF), the United Nations Development Programme (UNDP), the World Bank and WHO. An independent board and scientific advisory committee provide oversight.

30 staff from 18 COUNTRIES, BASED in Geneva.



ADDRESSING THE SUSTAINABLE DEVELOPMENT GOALS –

Leaving no one behind.

WHAT WE DO

KEY RESEARCH AREAS:

VECTORS, ENVIRONMENT AND SOCIETY RESEARCH:

- **Reducing** the transmission of vector borne diseases like dengue, malaria and Zika virus.
- **Building** regional networks to identify insecticide resistance and prevent and manage outbreaks.
- **Reducing** health vulnerabilities due to climate change and biodiversity loss.

INTERVENTION AND IMPLEMENTATION RESEARCH:

- **Evaluating** how health interventions work in resource-constrained settings.
- **Testing** how to effectively deploy and adapt health interventions to control and eliminate infectious diseases.
- **Supporting** country infectious disease outbreak preparedness.
- **Supporting** country programmes in identifying, analysing and addressing their priority health issues.
- **Promoting** and supporting data sharing.

RESEARCH TRAINING SUPPORT:

Building national and regional research capacity is integrated into everything TDR does. Every research project has a learning component. Networks provide additional support and disseminate the information. The following are some of the core educational opportunities.

"SORT IT" OPERATIONAL RESEARCH AND TRAINING:

Training of healthcare staff and national policy-makers to identify barriers and develop solutions that improve health systems and reduce disease impact.

POSTGRADUATE TRAINING:

Support to 7 universities from low- and middle-income countries to provide PhD and Masters degrees focused on implementation research in malaria, TB and neglected tropical diseases.

- James P Grant School of Public Health, BRAC University, Bangladesh.
- Universidad de Antioquia, National School of Public Health, Colombia.
- University of Ghana, School of Public Health, Ghana.
- Faculty of Medicine, Universitas Gadjah Mada, Yogyakarta, Indonesia.
- American University of Beirut, Faculty of Health Sciences, Lebanon.
- University of the Witwatersrand, School of Public Health, South Africa.
- University of Zambia, Department of Public Health, Zambia.

6 REGIONAL TRAINING CENTRES:

Coordinated training courses across multiple countries provided within a collaborative and learning network.

- Centro Internacional de Entrenamiento e Investigaciones Médicas, Cali, Colombia.
- The University of Ghana School of Public Health, Accra, Ghana.
- Gadjah Mada University, Yogyakarta, Indonesia.
- Astana Medical University, Astana, Kazakhstan.
- Research Institute of Tropical Medicine, Manila, Philippines.
- Institut Pasteur de Tunis, Tunis, Tunisia.

RESEARCH AND CAREER DEVELOPMENT FELLOWSHIP:

One-year fellowship to low- and middle-income country candidates to learn both the product development and full registration processes by taking part at every stage, training in the some of the world's most advanced labs.

495 PARTNERSHIPS OR COLLABORATIONS IN 83 countries.

STAY CONNECTED WITH TDR:
WWW.WHO.INT/TDR

TDR e-news monthly roundup of research news and training opportunities.

TDR scientist list grant opportunities from TDR and other global health organizations.

TDR LinkedIn group.

Twitter (TDRnews).

TDR global
finding experts and building collaborations

ALL THE NUMBERS WITHIN THIS DOCUMENT COME FROM 2015/16 DATA

Cover Photo: Uganda, 1992: A local health worker (seated with cap) in a remote pygmy village delivering ivermectin tablets to the community-directed distributors. This was a key aspect of the establishment of a system that now provides annual treatments for onchocerciasis to more than 92 million people throughout Africa, bringing the disease close to elimination (WHO/TDR/Edwards).

TDR For research on diseases of poverty
UNICEF • UNDP • World Bank • WHO

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Design and layout: ACW, London, United Kingdom

The Special Programme for Research and Training in Tropical Diseases (TDR) is an independent global programme of scientific collaboration established in 1975. It has a twin mission to improve existing and develop new approaches for preventing, diagnosing, treating, and controlling neglected infectious diseases, and to strengthen the capacity of developing endemic countries to undertake this research and implement the new and improved approaches. TDR is sponsored by the following organizations:

unicef
UNDP
World Bank
World Health Organization