TDR: a Knowledge Management and Network Organization

At the dawn of the 3rd millennium, the world is quite different from 25 years ago, when TDR was created. Scientific and technological advances, as well as economic, political, social, cultural and environmental changes, have dramatically modified the global landscape. We live today in an Internet village, supported by powerful information and communication technologies. Biology has become ‘big science’, with its own Manhattan project – the sequencing of the human genome. Dolly, the sheep clone, has illustrated the power and challenges of the biotechnological revolution and the implications it will have for the future of humankind. The Berlin wall, symbol of a world split between military superpowers, has given place to a globalized economy.

The 20th century also brought about a global transformation in human health, unmatched in history, with overall improvements in health and human development. But over one billion people entered the 21st century without having benefited from the health and human development revolution, their lives scarred by a ruthless disease categorized under code Z59.5 in WHO’s International Classification of Diseases: Extreme Poverty.1

DISEASES OF THE POOR: WHAT DID TDR DO OVER 25 YEARS?

The evolution of TDR

In May 1974, Resolution WHA27.52 of the World Health Assembly created TDR to address the need for new and improved tools for disease control, and for strengthening the research capability of the disease endemic countries so that they would become active actors in this endeavour.*

Operating in the changing environment of the last 25 years, TDR had to evolve to efficiently fulfil its mandate. In this dynamic process of constant change and adaptation, TDR’s top governing body (the Joint Coordinating Board, JCB), top scientific body (the Scientific and Technical Advisory Committee, STAC) and the three External Reviews commissioned by the JCB, played a crucial role in the stewardship of the Special Programme. The External Reviews, in particular, have been the basis for every major reform of TDR, pushing the Programme into different phases of its own ‘life cycle’.

TDR’s 1st phase – ‘historic/heroic’

The Programme was initially shaped as a funding agency in the area of biomedical research and training, structured on a disease-by-disease basis. The then current idea was that the potential impact of scientific discoveries on disease control would be obvious and therefore would attract the interest of the private sector, which would assure their development into real products. This conception of what we now know to be a very complex development pipeline translated into a simple organizational structure for the Programme: four areas of work, two of them being the major functional areas (Fig 1) with activities organized by disease and operated through steering committees.**

During this ‘historic/heroic phase’, TDR struggled with the lack of interest in tropical diseases research shown by more advanced laboratories in the North, and with the scarcity of institutions and trained human resources in disease endemic countries. Notwithstanding these immense

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** The other two areas were related to management: Area I: Technical and Administrative Bodies. Area IV: Programme Management.
challenges, already during this first phase, important new tools were generated and put into use for disease control (Table I). In spite of its predominantly biomedical orientation, early on in its history, in 1974, TDR established a Social and Economic Research (SER) unit for leading the scientific agenda in social science research related to tropical infectious diseases. SER significantly contributed to a better understanding of how social, cultural and economic factors affect disease control measures and what can be done to overcome them.

| Table I – Selected products of TDR and its partners during TDR’s three historical phases* |
|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| **Phase I: Historic/Heroic**                  | **Phase II: Growth by Trial and Error**        | **Phase III: Reaching Maturity**               |
| 1987: Ivermectin for treatment of onchocerciasis | 1993: Integrated management of childhood illness | In the pipeline |
|                                                | 1995: Community directed treatment (ComDT) of onchocerciasis and lymphatic filariasis | * Chlorproguanil-dapsone oral for treatment of malaria |
|                                                | 1996: Insecticide treated bednets for prevention of malaria | * Artesunate rectal for treatment of malaria |

* A comprehensive list of products and corresponding TDR partners in their development has been published (also available at http://www.who.int/tdr/morel.pdf).

TDR’s 2nd phase – ‘growth by trial and error’

It soon became clear that the paradigm that had shaped the initial Programme’s structure and *modus operandi* – academic research leading to products – was an oversimplification. The 1st External Review called attention to the fact that:

- Industry did not show interest in shifting its priorities and activities towards the area of tropical diseases (a phenomenon now well known and denominated ‘market failure’).
- In most cases the new knowledge generated remained ‘on the shelves’ – i.e. in scientific and academic publications – and did not have *per se* the power to drive or catalyse the remaining steps of the development pipeline.
- The new products needed to be evaluated in the field in disease endemic countries, and TDR was not giving sufficient priority to field research.

In a first attempt to address these concerns, the steering committees broadened their scope in order to cover all aspects of research within each disease, from basic to operational. However, the 2nd External Review recognized that the needs of product development were still not being met. In 1990, a product development unit was introduced to oversee product development by the steering committees, and to manage a special product development initiative.

It soon became apparent that these incremental changes would not suffice. Steering committees, although a proven mechanism for the peer review of academic research proposals, were not a substitute for the private sector and could not manage the development pipeline alone. The exhaustion of the historic paradigm led TDR into the second phase of its history, which was described as ‘growth by trial and error’. In 1994, the Programme had its structure radically changed from a disease basis to a functional area basis. The initial two areas of work gave origin to four areas: Strategic Research (STR), Product Research and Development (PRD), Applied Field Research (AFR) and Research Capability Strengthening (RCS). The relationships among the first three areas were pictured as shown in Fig 2.

This structure proved to be a real improvement, driving the Programme towards a more active role in product development. During this second phase, TDR delivered new and improved tools...
for disease control (Table I). It is worth noting, however, that RCS does not appear in figure 2 (drawn in 1992) in spite of the fact that TDR’s policy on capability strengthening passed through broad phases and major policy changes.5

**Figure 2. The structure of TDR during Phase II – ‘growth by trial and error’**

### TDR’s 3rd phase – ‘reaching maturity’

Although the Special Programme maintained its leadership and productivity, the shift from ‘disease orientation’ towards ‘functional area orientation’ brought unforeseen consequences, identified by the 3rd External Review.5 The following comments and recommendations from this review played a crucial role in shaping TDR’s 3rd phase:

- The disease components of the Programme were losing visibility and their role in priority setting was decreasing.
- The interaction between TDR and disease control activities needed fundamental restructuring and strengthening.
- TDR’s organizational structure should address both components – diseases and functions. TDR should become a matrix organization.
- TDR should adopt a differentiated approach for capability strengthening, focusing on the least developed countries, particularly those facing a high disease burden.

In the same year that the 3rd External Review issued its report and recommendations, WHO’s new Director-General, Dr Gro Harlem Brundtland, started a reform process that profoundly changed the Organization. Of particular importance to TDR were:

a) Adoption by WHO of a new corporate strategy,6 which emphasizes the role of knowledge, evidence-base and research in improving health.

b) Location of TDR in the cluster of communicable diseases (CDS), facilitating a closer interaction among the Special Programme, the regular departments involved in disease surveillance and control, Roll Back Malaria and Stop TB.

WHO’s new corporate strategy and reform process were recognized by TDR as a golden opportunity. To enable the Special Programme to operate in this new environment and efficiently address the health challenges at the start of a new millennium, the issues raised by the 3rd External Review were used to shape the Strategy 2000-2005,7 formally approved by the JCB in June 2000.

The new strategy recognizes TDR as a ‘knowledge management network organization’ in health research and capacity building.8 The Programme’s major driving force was seen to reside in its operational capability – the ability to bring together a large number of partners and catalyse processes to solve public health problems, and to build research capacity in the disease endemic countries. The new strategy introduced several major changes to the Programme:

- TDR became a real matrix-management organization. In addition to the team coordinators of the four functional areas, management also became the responsibility of disease research coordinators.
- TDR became more involved in research directly related to disease control. Its mandate was

* For our purposes we define a knowledge management organization as an organization with the infrastructure to serve as both a repository of knowledge and a facilitator for the creation of new knowledge, in forms that are easily usable, customized or suited to varying individual, institutional and national needs, and which allow the distribution of that knowledge to members of the organization and all external audiences, as and when needed and when the recipients are ready to accept, adapt and employ that information to help protect and improve global health.
expanded to go beyond obtaining ‘proof of principle’ that a new tool works. * Under this new paradigm, TDR will work in a seamless linkage with control programmes and national governments in the area of ‘implementation research’ – the research needed to answer specific questions arising when an intervention is introduced by health systems.

- Research capability strengthening will invest 60% of its resources on integrated, high-priority R&D projects/programmes (‘RCS-plus packages’), shaped, managed and evaluated in close collaboration with the other three TDR functional areas. The remaining 40% of RCS resources will be used to strategically fund work in the least developed, high burden countries.

- TDR’s workplan, budget and management will be implemented adopting an output rather than input approach to planning, centred around ‘results/expected products’, instead of the current functional area, organigram-based approach.

This new phase of TDR (‘reaching maturity’ – Fig. 3), although relatively recent, has also seen important developments taking place (Table 1).

**Has TDR been cost-effective?**

From 1974 to 2000, TDR received US$600 million (exactly US$ 607 312 922) from its contributors. A widely quoted 1993 study by the Boston Consulting Group estimated that each new drug that reaches the market needs US$500 million dollars of investment in R&D, a figure which includes the costs of failures – products that do not make it; others estimate a lower cost, of around US$300 million.8**

An independent analysis of TDR’s action in product development noted that:

“...TDR helped develop 24 tropical disease drug products from 1974 to 1995; 14 were still in trials in 1995, and 10 were in clinical use ... TDR worked with private industry to develop most of these agents…”

[Michael R. Reich9]

In order to be able to accomplish these results, TDR established strong collaborations with the private sector,10,11 becoming a lead organization in promoting ‘PPPs’ – public-private partnerships.10,12-14 ***

A more careful economic analysis of the cost-effectiveness of TDR will be conducted in the future. However, the above-mentioned evaluation, in just one functional area (product R&D) of TDR activities, indicates that the Special Programme can indeed be regarded as an efficient, cost-effective investment – even had all the funds been used exclusively for product development and not for any other activities (capacity strengthening, strategic R&D, field research).

### DISEASES OF THE POOR: WHAT CAN TDR DO IN THE FUTURE?

#### The challenges ahead

TDR has a formidable challenge ahead. Progress has been considerable in a number of TDR diseases such as leprosy, Chagas disease, onchocerciasis and filariasis,15 and the overall contribution of TDR has been extensively documented in the External Reviews and other publications.11,16

The health situation, however, has deteriorated in other areas due to the emergence of new diseases (e.g. HIV/AIDS), spread of drug resistance (e.g. in malaria), socioeconomic deterioration,1 and resurgence of old scourges such as tuberculosis and dengue, which were added to the TDR disease portfolio in 1999. To keep up with the challenges, the mandate of TDR has evolved from being very simple and focused exclusively on biomedical research, to its present format, which addresses all stages of the development pipeline – strategic research, product development, product registration, ‘proof-of-principle’ trials, and participation in the implementation of new tools by health systems.
The new opportunities

From all viewpoints, there are new opportunities on the horizon underlying the development of new interventions:

- From the ‘offer’ or ‘push’ viewpoint, there are new scientific and technological advances resulting from the ‘biotechnological revolution’ (e.g. genomics, proteomics), and new information and communication technologies.17,18

- From the ‘demand’ or ‘pull’ viewpoint, there is a growing consciousness that health is not only a consequence of development and prosperity, but also actually plays a role in the promotion of these issues;19 and there is growing awareness of the crucial role that social, behavioural, political, economic and health system factors play in the persistence and re-emergence of infectious tropical diseases.

These new opportunities have spearheaded renewed political commitment at the highest level (G8, European Union), while powerful new players in health research have emerged (e.g. the Bill and Melinda Gates Foundation), allowing increased support for an ever-growing number of health initiatives (e.g. International AIDS Vaccine Initiative, IAVI; Medicines for Malaria Venture, MMV; Global Alliance for TB Drug Development, GATB; Malaria Vaccine Initiative, MVI; Global Alliance for Vaccines and Immunization, GAVI).

In response to these new opportunities, as well as to WHO’s new corporate strategy, TDR reemphasized its commitment to social science research, including research on the impact of health sector reforms on equity, gender-sensitive interventions, and recently, research on the impact of social and economic inequalities and globalization on the persistence and re-emergence of tropical diseases.

TDR’s comparative advantages

As pointed out in the Strategy 2000-2005, the Special Programme is well prepared to seize these new opportunities and remain a key player in coping with the health challenges, particularly those affecting poor and marginalized populations, because:

- TDR has unmatched experience, know-how and operational capability in its area of work as a consequence of constant evolution through ‘experimentation and adaptation’ during its 25 years of existence.

- As a network organization, TDR can tap into the expertise of a very large number of partners in the North and South, in the public and private sectors – governments, academia, industry, NGOs, communities.

- The Programme’s scientific independence, global perspective, quality and leadership in a number of areas play an important role in setting the global health research agenda.

- TDR is considered a trusted broker, able to organize, initiate and monitor large-scale field trials, being at the forefront in training scientists and strengthening institutions in the fields of ethics20* and good laboratory practice.21-23

- Addressing all aspects of the development pipeline, the Programme is able to collaborate and partner a range of initiatives in specific, different areas of the R&D process. This allows TDR to play, and be asked to play, the unique role of ‘transmission belt’ between partners.” TDR’s actions span basic research – including in the social, economic and behavioural sciences – product development, field trials, implementation research, and capacity building.

THE 15th PROGRAMME REPORT

How it is organized

This 15th Programme Report addresses the 1999-2000 biennium, which, as described above, was an unusual one. WHO reform, addition of tuberculosis and dengue to the TDR portfolio, adoption of WHO corporate strategy, adoption of the TDR Strategy 2000-2005, proliferation of public-private partnerships – were among the key issues that were addressed in this period.

Far from slowing down TDR’s productivity, this new environment became a strong stimulus for change, reform and growth:

- The synergy between the WHO and TDR strategies – both of which underscore the importance of the role of research and knowledge in improving health – created an enabling environment for the Special Programme.

* The 5th Amendment of the Declaration of Helsinki has considerable implications for medical research in developing countries.

** As an example, TDR was requested to play a leading role in establishing the international network to sequence the genome of Anopheles gambiae.33
• The broadening of the TDR disease portfolio to include TB and dengue, and of the TDR research areas to include social, economic and behavioural sciences, on the one hand, and the location of TDR in the Communicable Diseases cluster of WHO, on the other hand, provided the grounds for the ‘fundamental restructuring’ as requested by the 3rd External Review. The result is a much closer, growing and constructive collaboration between R&D and disease control components.

• TDR was able to keep up the momentum in stimulating PPPs,10,12,13,24 as per its historical role, and played a key role in the shaping and implementation of two important new initiatives – MMV and GATB.

As an outcome of the new strategy, this report is structured according to the expected results in the seven areas of work of TDR:

A. New basic knowledge: New basic knowledge about biomedical, social, economic, health system and behavioural determinants, and other factors of importance for effective prevention and control of infectious diseases, generated and accessible at national and international levels.

B. New and improved tools: New and improved tools devised for prevention and control of infectious diseases, e.g. drugs, vaccines, diagnostics, epidemiological tools, environmental tools.

C. New and improved methods: New and improved intervention methods developed and validated for applying existing and new tools at clinical and community levels.

D. New and improved strategies: New and improved policies for large-scale implementation of existing and new prevention and control strategies framed and validated; guidance for application in national control settings accessible.

E. Partnerships and capacity building: Partnerships established and adequate support provided for building up capacity for research and product development in disease endemic countries.

F. Technical information: Adequate technical information, research guidelines and instruments, and advice accessible to partners and users in countries.

G. Resources for research: Resources for research, product development, and capacity building efficiently mobilized and managed.

Why a new reporting format?

Areas A to D can be seen as steps in the process of product development (the so-called ‘R&D pipeline’), from the early discovery phase to the large-scale implementation of the resulting new interventions by health systems in disease endemic countries.

Areas E and F represent TDR’s knowledge management architecture25 and the needs it will address, such as:

• Building and strengthening the community and network of ‘knowledge workers’.
• Managing knowledge generation, storage and dissemination.
• Conducting analytical work relevant to priority setting.
• Assuring the flow of knowledge.

Area G aims to mobilize and manage adequate resources for both the R&D pipeline and the knowledge management requirements of the Programme.

More than just providing a different reporting format, this new framework is at the heart of TDR’s new strategy:

• Differential investments across the R&D pipeline: Infectious diseases can be considered to be at different stages of their ‘life cycle’. Some are being eliminated or eradicated due to the availability of cost-effective interventions and control strategies; others are re-emerging or continue to impose an unacceptable burden in large areas of the world and require new or better tools. R&D priorities, resources and efforts should therefore reflect: a) the burden of the disease; b) the availability of cost-effective interventions; c) the knowledge base needed for future developments. Diseases undergoing elimination or eradication need more investments in research to improve, refine and better implement control tools and policies (areas C and D), whereas, for other diseases, the acquisition of new knowledge and development of new or better tools (areas A and B) should be priorities.

• Relevance of knowledge management: evidence-based priority setting is becoming more and more important for keeping the Programme’s focus, guiding future investments, and strengthening TDR’s role in the setting of the global R&D agenda in tropical diseases. In addition, investments in TDR’s own operational capability have been defined as critical for successful implementation of the new strategy.

The ‘Expected Results’ framework is therefore a multi-purpose endeavour. On the one hand it fulfils the need to inform and report to our partners – as in the case of this 15th Programme
INTRODUCTION

Report. On the other hand, it represents a major tool for planning, managing, monitoring and evaluating the activities of the Special Programme, now being reshaped as a knowledge management and network organization under the new strategy. TDR’s operational capability, defined as its driving force in the new strategy, requires renewed efforts in conducting the analytical work needed to keep the Programme at the forefront of the complex and changing area of health R&D.

A鸟’s eye view of TDR activities in the 1999-2000 biennium

It is not an easy task to select representative results attained by TDR-funded projects in the last biennium. This section does not aim to be a summary of what was accomplished, nor to list the ‘top ten’ accomplishments. Its purpose is to illustrate the new results-oriented approach adopted by the new TDR Strategy.

A. New basic knowledge

• The long sought after breakthrough in the area of molecular entomology – stable transformation of Anopheles – was obtained by Catteruccia et al.26 and represents the first milestone in TDR’s 1991 workplan.27 This opens the way to the next goal: obtaining a laboratory strain of Anopheles gambiae unable to harbour and transmit Plasmodium parasites.

• The identification of the molecular mechanisms by which the leprosy bacillus invades peripheral nerve cells is an example of how new basic knowledge is needed to understand disease pathogenesis. TDR’s Final Report 14 (May 1999) describes the elegant work of Fischetti and collaborators,28 shedding light on the molecular basis of Mycobacterium leprae neurotropism.

B. New and improved tools

• The registration of artemotil shows that drug development is a long-term process. TDR started a partnership to develop this drug in 1991 – almost ten years elapsed between the project start-up and formal registration approval by Dutch regulatory authorities.

• In TDR, the term ‘tools’ does not apply only to physical products such as drugs and vaccines. The second example under this heading is of a quite different nature – it is an epidemiological tool called ‘RAGFIL’, or Rapid Assessment of the Geographic Distribution of Filariasis.29 The main elements of RAGFIL – the subject of Final Report 25 – will be used for mapping filariasis in Africa.

C. New and improved methods

• Simple and imaginative interventions can be very effective: iron supplementation and intermittent chemoprophylaxis, administered as components of the EPI vaccination schedule, can effectively prevent severe malaria in young children.30,31

• Reaching the home and the community more effectively with antimalarial treatment can make a difference: more than 50% reduction in progression towards severe disease, and 40% reduction in under-five mortality, are some achievements of improving home management of children with severe malaria (Final Report 29).

D. New and improved strategies

• A multicountry study completed during the biennium showed that a combined community/health services system of community directed treatment of lymphatic filariasis in Africa resulted in improved treatment coverage. Community directed treatment (ComDT) was therefore recommended as the drug delivery strategy for lymphatic filariasis elimination in Africa.34

• Molecular biology is being applied in the characterization of wild and domiciliated populations of insect vectors of Chagas disease. From the control programme’s perspective, it is necessary to know the origin of the vectors present in rural houses. Final Report 21 shows how this approach is being used to fine-tune the control strategy under implementation in Andean countries.

E. Partnerships and capacity building

• PPPs to foster new drug development against neglected diseases made the headlines a number of times during the biennium. TDR was a major player in the planning and implementation of MMV and GATB, both now operating as independent, not-for-profit organi-
zations. Another strategy was adopted by TDR to stimulate the participation of major Japanese pharmaceutical companies in the discovery of new drugs; instead of creating a new organization, a partnership was formed among 12 Japanese companies, the Kitasako Institute and the Japanese Ministry of Health and Welfare to screen the companies’ chemical libraries for antimalarials.

• The Multilateral Initiative on Malaria in Africa (MIM) is an international partnership to foster scientific research against malaria. Under this initiative, TDR set up the MIM/TDR Research Capacity Strengthening Task Force at the end of 1997. MIM/TDR became a major driving force in malaria research and capacity building in Africa during the biennium.

F. Technical information

• TDR launched its 3rd generation website in 1999, and the results have been most rewarding. In December 2000, the last month of the biennium, the website received approximately 70,000 pageviews – almost twice as many as in 1999. As TDR now positions itself as a knowledge management and network organization, further development of the website into a fully interactive tool is a high priority.

• But information and knowledge do not flow only through cyberspace: ‘old style’, hard copy paper publications are also absolutely required – and our production in the biennium has been remarkable. Books, meeting and project reports, guidelines, conference proceedings, laboratory and field manuals (including those describing ‘good practices’ – GLP, GCP – standard operating procedures), as well as formal publications in peer-reviewed journals are, and will continue to be, crucial components of ‘knowledge repositories’ and knowledge flow.

G. Resources for research

• All this work would not be possible without our core partners, who assure that TDR receives resources compatible with its mandate and responsibilities. As shown in the list of our contributors (pages 88-89), TDR continues to be supported by a broad base of donors – particularly by a faithful core group, who share with us the vision that health research is essential to cope with the burden that neglected diseases impose on poor and marginalized populations.

• The addition of two new diseases to our portfolio in 1999 was a ‘high risk’ manoeuvre. We knew that finding the corresponding additional resources in the extremely competitive environment of today would be an immense challenge. However, there are both sound evidence and good signs that we are navigating in the right direction. For one thing, new partners have already joined forces with us, supporting our new strategy and mandate; and for another, the growing recognition of the role of health in development brings new hope and sets an optimistic scenario for the future.

I hope you will enjoy reading this report and agree that the 1999-2000 biennium represented a very good ‘vintage’ for TDR.

Carlos M. Morel – Director, TDR
Geneva, May 2001

References

INTRODUCTION

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