Strategic emphases for tropical diseases research: a TDR perspective


Setting priorities for health research is a difficult task, especially for the neglected diseases of the poor. A new approach to priority setting for tropical diseases research has been adopted by the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (known as the TDR). Priorities are defined on the basis of a comprehensive analysis of research needs and research opportunities for each of the ten major tropical diseases in the TDR portfolio. The resulting strategic emphases matrix reflects the priorities for tropical diseases research from the perspective of the TDR. Its purpose is not to impose global research priorities, but we believe the results could be useful to other organizations.

There is growing recognition that research is critical in the fight against disease [1–3]. However, the limited resources available can fund only a fraction of the promising research opportunities. Hence, prioritization is essential for health research and considerable effort has gone into developing effective prioritization mechanisms [1,4,5].

Factors affecting prioritization

Resources are particularly limited for research into neglected diseases of the poor. Less than 10% of global spending on health research is spent on these diseases, which account for 90% of the global disease burden [6]. Prioritizing research into neglected diseases is therefore even more necessary but also inherently more difficult than prioritizing research into high-profile diseases.

In 1990, the Commission for Health Research for Development highlighted the need for better prioritization of health research, at both national and global levels [1]. In 1996, the Ad Hoc Committee on Health Research Relating to Future Intervention Options proposed a basic framework to set priorities for the allocation of resources to research and development, involving five steps to assess: (1) the size of the disease burden; (2) the reasons for its persistence; (3) the state of current knowledge; (4) possible interventions and their predicted cost-effectiveness; and (5) ongoing research into the health problem [4]. This initial framework was elaborated by the Global Forum for Health Research into the Global Forum Combined Approach Matrix for priority setting [6].

TDR, the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases, was created in 1975 to address the need for research into neglected tropical diseases that represent major public health problems in developing countries [7] (http://www.who.int/tdr). Since then, four of these diseases – Chagas disease, leprosy, lymphatic filariasis and onchocerciasis – have been targeted for elimination as public health problems. Despite the recognition of the key role played by TDR [8,9], resources remained limited and, following the 1999 addition of tuberculosis (TB) and dengue to TDR's disease portfolio, prioritization became more important than ever.

TDR, most prioritization used to be based on recommendations from committees of independent scientists. TDR's Scientific and Technical Advisory Committee (STAC) provided guidelines on budget allocations between programme areas, and steering committees within each area recommended funding for specific research activities and projects. This system allowed for effective allocation of funds in response to research opportunities within each programme area. Over time, however, this system resulted in an imbalance between diseases (e.g. there was a significant decline in funding for African trypanosomiasis), a disconnection between research activities in different programme areas and a decline in the interaction between research and disease control [9]. It became increasingly clear that a more strategic approach to planning and priority setting was needed. TDR's new strategy for 2000–2005 thus called for more evidence-based strategic planning and the necessary analytical work [10]. The first step was to conduct a detailed analysis of research needs and opportunities for each disease in the TDR portfolio, and to define the strategic priorities, or strategic emphases, for research. This analysis, now completed, is presented here, with an outline of the methodology used, the outcomes and the resulting strategic emphases for TDR research on each of the ten diseases in its portfolio.

Strategic analysis methodology

As the results of the analysis were to be used for prioritization within and between diseases, a standardized approach was adopted to ensure the results could be compared. After experimenting with different approaches, TDR decided on an analytical method that is based on the prioritization framework of the Global Forum of Health Research but modified to suit the TDR's requirements (Box 1). For each disease, the analysis was undertaken by TDR's Disease Research Coordinator for that disease, in consultation with a reference group of experts from research and disease control.

A push and a pull

Table 1 shows a summary of the data on disease burden and epidemiological trends for the ten diseases in the TDR portfolio. The burden of disease varies considerably...
Three main patterns have been identified: countries by more than 50% [15]. The level of GNP per capita in malaria-endemic areas affects the impact of malaria, which has reduced the production [14]; and the dramatic economic impact of African trypanosomiasis, the devastating impact of onchocerciasis [13].

The principal output needed from research on these diseases is new and improved control tools and implementation strategies, with the emphasis depending on the disease.

In addition to research needs, which reflect the 'pull' from disease control for new tools and strategies, TDR strategy takes into account the 'push' from new research opportunities. These include opportunities of a generic nature as well as specific research opportunities, such as the discovery of a specific drug candidate that provides the opportunity for drug development or a radically new intervention tool that provides the opportunity to test alternative control strategies. Box 2 lists generic research opportunities that are of particular importance to TDR.

Strategic emphases matrix

The results of the strategic analyses are summarized in the strategic emphases matrix, which shows TDR's strategic research emphases by disease and by expected result (see the poster in this issue of Trends in Parasitology and Trends in Microbiology) (also available at http://www.who.int/tdr/grants/strategic-emphases).

The expected results categories in the matrix correspond to the main areas of research and development for TDR:

(A) New basic knowledge about the biological, social and economic factors, health systems, behavioural determinants and other factors important for effective control of infectious diseases.

(B) New and improved tools for use in infectious disease prevention and control, for example, drugs, vaccines, diagnostics, epidemiological tools and environmental tools.

(C) New and improved intervention methods for applying existing and new

{Box 1. Seven-step analysis process

The analytical framework uses a seven-step process that addresses the following questions:

1. What is the nature and size of the disease burden and what are the epidemiological trends?
2. What is the current disease control strategy?
3. What are the major problems and challenges for disease control?
4. What research is needed to address these problems and challenges?
5. What is currently being done in research and development? What research opportunities exist?
6. What are TDR's comparative advantages?
7. Based on the above, what should be TDR's strategic research emphasis for this disease?

Several sources of information were used. Information on disease burden and epidemiological trends (Step 1) was obtained from reports and databases available to WHO, scientific publications and TDR research reports. The World Health Report 2001 [a] was the source for statistics on mortality and disability-adjusted life years (DALYs) [b] lost annually. Information on control strategy and problems in strategy implementation (Steps 2 and 3) was obtained from disease control experts in WHO and in Ministries of Health in selected countries, from scientific publications and TDR research reports, and from results of country-level situation analyses as available. Step 4 involved extensive consultations with the group of experts in research and control on the basis of the information collected in Steps 1–3. Information on ongoing research and development activities (Step 5) was based on available knowledge in TDR, as well as from the scientific literature and from websites of other organizations. Research opportunities (Box 2) were identified through TDR's extensive network of collaborating scientists and, for three of the diseases (dengue, TB and African trypanosomiasis), through recent TDR scientific working group meetings held in 2000 and 2001.

Based on the results of Steps 1–5 and an internal assessment of TDR's comparative advantage with respect to other research organizations working in the same field, a draft research strategy was developed for each disease. The draft strategies were subsequently critically reviewed by the TDR's Scientific and Technical Advisory Committee (STAC) before they were finalized in 2002. Detailed results are available on TDR's website (http://www.who.int/tdr/grants/strategic-emphases).

References

Table 1. Burden of disease and epidemiological trends for the ten diseases in the TDR portfolio

<table>
<thead>
<tr>
<th>Category</th>
<th>Disease</th>
<th>Death (thousands)</th>
<th>DALYs (thousands)</th>
<th>Other major aspects of disease burden</th>
<th>Epidemiological trends</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>African trypanosomiasis</td>
<td>50</td>
<td>1585</td>
<td>Economic impact of epidemics Physical and intellectual impairment in children Depopulation of fertile lands</td>
<td>Fourfold increase in reported number of new cases since 1990 (48 000 in 1999), actual incidence is much higher Epidemics especially in conflict zones Fourfold increase in incidence since 1970 Regular epidemics: 1.3 million cases of DF/DHF in 1998 Increase in number of cases in many parts of the world Emerging Leishmania/HIV co-infections</td>
</tr>
<tr>
<td></td>
<td>Dengue</td>
<td>12</td>
<td>433</td>
<td>Cost of DF/DHF epidemic outbreaks Burden of DF (DALYs only reflect DHF)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Leishmaniasis</td>
<td>41</td>
<td>1810</td>
<td>Psycho-social impact of disability Impact of epidemics on development projects</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Malaria</td>
<td>1080</td>
<td>40 213</td>
<td>1.3% reduction in annual economic growth rate in Africa Disability owing to severe disease Significant indirect morbidity and mortality Growth stunting, nutritional and cognitive impairment</td>
<td>Increase in mortality and drug-resistant malaria Increase in epidemic malaria and P. vivax Decline in Asia, Middle East and Americas. 85% of DALYs now in Africa</td>
</tr>
<tr>
<td></td>
<td>Schistosomiasis</td>
<td>11</td>
<td>1713</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tuberculosis</td>
<td>1660</td>
<td>35 792</td>
<td>$12 billion reduction in income in the poorest countries</td>
<td>Increasing HIV-related trend in Africa and Eastern Europe Increase in multi-drug resistance</td>
</tr>
<tr>
<td>3</td>
<td>Chagas disease</td>
<td>21</td>
<td>680</td>
<td>Forced retirement of seropositive employees High cost of palliative treatment in chronic disease</td>
<td>Towards elimination in Southern Cone countries No change in Andean and Central American countries Major decline in registered cases Impact of MDT on transmission not clear</td>
</tr>
<tr>
<td></td>
<td>Leprosy</td>
<td>2</td>
<td>141</td>
<td>Psycho-social impact of disability</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lymphatic filariasis</td>
<td>0</td>
<td>5549</td>
<td>Psycho-social impact of disability Economic impact: loss of $1 billion annually in India alone</td>
<td>Major decline in past decades in Pacific and China Impact of global elimination campaign not yet known Eliminated as public health problem in OCP area Declining disease burden in treated populations elsewhere</td>
</tr>
<tr>
<td></td>
<td>Onchocerciasis</td>
<td>0</td>
<td>951</td>
<td>Psycho-social impact of skin lesions Fertile land abandoned for fear of onchocercal blindness</td>
<td></td>
</tr>
</tbody>
</table>

*Based on the epidemiological trend, the main challenges of control and the corresponding research needs, we grouped the TDR diseases into three categories. Category 1 contains diseases that are re-emerging or uncontrolled, and for which the most important research needs are new basic knowledge and better intervention tools. Category 2 contains diseases for which a control strategy exists but which has not yet proven effective in achieving a sustained reduction in the disease burden. The priority research needs cover a wide spectrum from new knowledge to better methods of implementation, but with emphasis on new tools and implementation strategies. Category 3 contains diseases with a control strategy of proven cost-effectiveness, declining burden, and a target for elimination. The most important research need is for better implementation strategies.

*Abbreviations: DALY, disability-adjusted life years; DF, dengue fever; DHF, dengue haemorrhagic fever; MDT, multi-drug therapy; OCP, Onchocerciasis Control Programme in West Africa.

tools at the clinical and community levels. (D) New and improved strategies for large-scale implementation of existing and new prevention and control methods, and guidance for application in national control settings.

With respect to TDR’s investments in building research capacity, strategic emphases have been adopted that are uniformly applicable to all diseases in the TDR portfolio, addressing the specific needs of the least developed, high-burden, low-income countries, as well as the needs for other research and development-driven capacity building (http://www.who.int/tdr/grants/workplans/rcs4.htm).

Under A (New basic knowledge), all but one of the diseases in the TDR portfolio have as a strategic emphasis the application of bioinformatics and applied genomics to identify new targets for drugs, diagnostics, vaccines or vector control, capitalizing on recent scientific breakthroughs in this area. Under B (New and improved tools), a common strategic emphasis is discovery and development of drugs (eight diseases), diagnostics (eight diseases) and vaccines (five diseases). In the matrix, C (New and improved intervention methods) covers a wide range of strategic emphases dealing with improvement and field evaluation of existing tools and methods. Under D (New and improved strategies), the emphasis is predominantly on strategies for improved delivery of available interventions.

The matrix highlights the strategic differences between the disease categories. For category 1, the main emphasis is on new basic knowledge whereas for category 3 it is on new and improved strategies. These patterns are not exclusive: category 3 also has some strategic emphases on new basic knowledge but these are focused on specific needs, for example on identifying...
**Fig. 1.** Relationship between the research budget for diseases in the TDR portfolio and disease burden. In the TDR strategy, the higher the burden of a disease, the higher the investment in research and development related to that disease. The graph displays the relationship between the TDR investment (operations) for each of the ten target diseases in the 2002–2003 approved budget and the disease burden in disability-adjusted life years (DALYs) [17] according to the 2000 estimates [18] (regression line: budget = DALYs^{0.964} + 2.21 1 000). This relationship and additional information on the TDR budget can be found at [http://www.who.int/tdr/publications/publications/pdf/budget.pdf](http://www.who.int/tdr/publications/publications/pdf/budget.pdf).

**Table 2.** Control strategies, major challenges and research needs for the ten diseases in the TDR portfolio*

<table>
<thead>
<tr>
<th>Category</th>
<th>Disease</th>
<th>Principal control strategy</th>
<th>Major problems/challenges</th>
<th>Major research needs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>African trypanosomiasis</td>
<td>Active surveillance, case finding and treatment, selective vector control</td>
<td>Poor surveillance</td>
<td>Better tools: drugs and diagnostics</td>
</tr>
<tr>
<td></td>
<td>Dengue</td>
<td>Active surveillance and case management, selective vector control</td>
<td>Poor diagnostics, Toxic drugs</td>
<td>Better methods for mosquito control</td>
</tr>
<tr>
<td></td>
<td>Leishmaniasis</td>
<td>Case finding and treatment, selective vector/animal reservoir control</td>
<td>Poor mosquito control, Case management in epidemics</td>
<td>Better tools: vaccine</td>
</tr>
<tr>
<td></td>
<td>Malaria</td>
<td>Early diagnosis and prompt treatment</td>
<td>Inadequate care close to home, Low coverage of ITNs, Decreasing efficacy of current tools</td>
<td>Better implementation strategies</td>
</tr>
<tr>
<td></td>
<td>Schistosomiasis</td>
<td>Morbidity control through periodic treatment in high-risk populations</td>
<td>Poor health systems/surveillance, Low priority/limited resources</td>
<td>Better tools: drugs and diagnostics</td>
</tr>
<tr>
<td></td>
<td>Tuberculosis</td>
<td>Case finding and directly observed multi-drug treatment (DOTS).</td>
<td>Low priority/poor health systems, HIV and multi-drug resistance</td>
<td>Better case-finding and treatment strategies</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Poor diagnostics, drugs, vaccine</td>
<td>Better tools: diagnostics, rapidly acting drugs, better vaccine</td>
</tr>
<tr>
<td>2</td>
<td>Malaria</td>
<td>Prevention: ITMs, other vector control, intermittent treatment in pregnancy</td>
<td>Inadequate implementation by health system</td>
<td>Better implementation strategies</td>
</tr>
<tr>
<td></td>
<td>Schistosomiasis</td>
<td>Early detection/prevention epidemics</td>
<td>High rate of reinfection</td>
<td>Better tools: drugs, vaccine, diagnostics, vector control</td>
</tr>
<tr>
<td></td>
<td>Tuberculosis</td>
<td>Morbidity control through periodic treatment in high-risk populations</td>
<td>Inadequate implementation by health system</td>
<td>Better surveillance strategies</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Low priority/limited resources</td>
<td>More effective implementation strategies for Africa</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>High rate of reinfection</td>
<td>Improvement of available tools</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Low priority/poor health systems</td>
<td>Additional tools: drugs</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HIV and multi-drug resistance</td>
<td>Better implementation strategies</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Poor diagnostics, drugs, vaccine</td>
<td>Better tools: diagnostics, rapidly acting drugs, better vaccine</td>
</tr>
<tr>
<td>3</td>
<td>Chagas disease</td>
<td>Interruption of transmission through vector control and improved blood transfusion</td>
<td>Control of non-domiciliated vectors</td>
<td>Strategies for control of non-domiciliated vectors</td>
</tr>
<tr>
<td></td>
<td>Leprosy</td>
<td>Case finding and multi-drug treatment</td>
<td>Sustained vector control</td>
<td>Better drugs and diagnostics</td>
</tr>
<tr>
<td></td>
<td>Lymphatic filariasis</td>
<td>Interruption of transmission through periodic mass treatment</td>
<td>Millions infected at risk of disease</td>
<td>Integration of leprosy control</td>
</tr>
<tr>
<td></td>
<td>Onchocerciasis</td>
<td>Disability alleviation by local hygiene</td>
<td>Incomplete MDT coverage</td>
<td>Improved diagnosis of infection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Periodic mass treatment to eliminate the disease as a public health problem</td>
<td>Impact on transmission not known</td>
<td>Simplified MDT regimen</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Need for high treatment coverage</td>
<td>Strategies for high Rx coverage</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Unknowns in elimination strategy</td>
<td>Guidelines for elimination strategies</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Limited effect of current drugs</td>
<td>Drug that kills/sterilizes adult worms</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Need to sustain high coverage</td>
<td>Strategies for sustained high treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Risk of ivermectin resistance</td>
<td>coverage</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Eradication not possible with current tools</td>
<td>Drug that kills/sterilizes adult worms</td>
</tr>
</tbody>
</table>

*Abbreviations: DOTS, directly observed treatment short-course; ITM, insecticide-treated material; ITN, insecticide-treated mosquito nets; MDT, multi-drug therapy.
Box 2. Generic research opportunities

A. New basic knowledge
- Genomics and health [a]
- Full genome sequence of tropical disease pathogens available or being finalized (http://www.niaid.nih.gov/cgi-shl(genome/genome.cfm])
- Systems biology [b]
- Bioinformatics [c]
- Genetic control strategies for insect vectors [d]
- Evidence of impact of political, economic and social change, including health sector reform [e]
- Recognition of the role of health in stimulating economic development [f]
- New methods for analysis of complex social and health systems phenomena [g]

B. New and improved tools
- Functional genomics directed to drug and vaccine discovery [h]
- Pharmacogenomics [i]
- Medicinal chemistry and drug discovery advances
  - Combinatorial chemistry [j]
  - Robotics and chemistry for high-throughput screening [k]
  - Chemistry related to oral bioavailability [l]
  - Improved non-clinical development methodologies for optimizing compounds [m]
- Advances in molecular diagnostic technologies [n]
- Advances in vaccine technologies, including novel adjuvants [o]
- Good practices (GLP, GCP, ethics) [p–r]

C. New and improved methods
- Meta-analysis [s]
- Need for evidence for health-policy making [t]
- Improved methods for design and analysis of randomized trials [u]
- Advanced methods for analysis of qualitative data [v]
- New guidelines for ethical review of research involving human subjects [q]
- Rapid assessment procedures [w]

D. New and improved strategies
- Social marketing and communication methods [x]
- New approaches to community-based intervention [y]
- Multi-disciplinary implementation research, integrating social sciences and epidemiology [z]
- Mathematical modelling of disease control strategies [aa]
- Improved tools for cost-effectiveness analysis [bb]
- New tools for disease mapping: geographical information systems, spatial statistics and remote sensing [cc]
- Global proposals to improve health of the poor [dd]

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- y Homeida, M. et al. (2002) APOC's strategy of community-directed treatment with ivermectin (CDTI) and its potential for providing additional health services to the poorest populations. Ann. Trop. Med. Parasitol. 96 (Suppl. 1), 593–104

macrofilaricidal drug targets for lymphatic filariasis and onchocercasis, and diagnostic targets for use in leprosy elimination.

The strategic emphases matrix will be regularly reviewed and updated with new research needs or new research opportunities. Modifications will be made if they are evidence-based and endorsed by peer review of the strategic analysis for the disease in question.

The research product portfolio

The strategic emphasis matrix defines the strategic direction of the TDR over a time frame of five years. However, translating these strategic emphases into actual research outcomes requires further planning and prioritization at much shorter intervals. To facilitate this process and the monitoring of ongoing research activities, TDR operates on the basis of
research products, which are deliverables that correspond to specific strategic emphases in the matrix. For each product, the research activities needed are identified, milestones defined, success criteria and dates established and the costs estimated.

The allocation of funds to the various products in TDR’s product portfolio is revised at regular intervals and decisions can be taken to add new products to the portfolio, interrupt the development of products shown to be non-viable (e.g. a candidate for drug development showing unacceptable toxicity) or delay the development of certain products because of a shortage of funds. This continuous process of product portfolio management is carried out within the boundaries of strategic emphases and available resources. The product portfolio provides the basis for TDR’s resource mobilization efforts to attract resources to finance the portfolio as a whole (‘undesignated’ funds in TDR terminology) or resources to fund the development of specific products (designated funds). It should be stressed that the product portfolio is more dynamic and subject to change than the strategic emphases matrix. An up-to-date version of the TDR product portfolio database can be accessed online at http://www.who.int/tdr.

Considering all the options
The mechanisms used to set priorities vary considerably between different funding institutions for health research. One of the main differences lies in the extent to which strategic planning is used to guide research directions as opposed to having the strategic directions largely driven by proposals from the scientific and/or technological communities. TDR’s strategy for 2000–2005 put a clear emphasis on strategic research planning based on a comprehensive analysis of research needs and opportunities.

The first experiences with this new approach have been positive and the strategic analysis has already proven important for TDR in several ways: (1) it has provided a transparent and objective prioritization process that is fully documented and open to scrutiny; (2) it is based on a collaborative effort with active participation by partners from research and disease control, improving their interaction (as recommended by the 3rd external review of TDR [9]); (3) the direct link between strategic emphases and the research needs of disease control facilitates the translation of research products into practical interventions; and (4) the classification of diseases into three categories with different types of research needs has helped TDR clarify its strategic choices to its partners.

The push and pull – new research opportunities and disease control needs – driving the prioritization process must be seen in a broad, dynamic context. On the one hand, the latest scientific and technological advances need to be continuously monitored to ensure that relevant breakthroughs or new technological approaches are incorporated into the strategic planning process in a timely fashion. TDR’s network of scientific collaborators, and especially the steering committee, plays an important role in this regard. On the other hand, changes in the needs of disease control must be identified and new priority needs responded to, also in a timely manner. The disease reference groups and disease research coordinators are the driving force in this area. The response should go beyond the usual short- or medium-term goals, and also seriously consider interventions and objectives that, today, might be seen as too far away or impossible to achieve – history showed how important it was to keep alive the dream of a safe polio vaccine at a time when control efforts focused on developing better and cheaper iron lungs, the artificial breathing machines that were able to sustain polio patients whose diaphragm muscles had been paralysed by the virus [16].

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UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR), 20 Avenue Appia, Geneva 27, CH1211, Switzerland.

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