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]. 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.

In 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 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...

†The list of diseases in the TDR portfolio is likely to change in the future following the adoption by TDR’s Joint Coordinating Board in June 2002 of the principle of a dynamic disease portfolio for TDR and of corresponding criteria for entry or exit of diseases.
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 information 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

Between diseases, ranging from 141,000 disability-adjusted life years (DALYs) lost annually for leprosy to >40 million DALYs for malaria. The relative health impact of the different diseases in terms of DALYs has been taken into account in TDR’s research budget allocation by disease, and the relationship between research budget and disease burden is shown in Fig. 1. The degree to which research funding should reflect the burden of disease has been the subject of extensive debate [11, 12]. For TDR, the approved budget for each disease was adjusted in proportion to its respective burden. A strictly linear relationship, however, was not the final aim, as additional factors had to be taken into account including the social and economic consequences of tropical diseases, such as the impact on food production in West Africa, where fertile agricultural land was abandoned because of onchocerciasis [13]; the devastating impact of African trypanosomiasis on agricultural production [14]; and the dramatic economic impact of malaria, which has reduced the level of GNP per caput in malaria-endemic countries by more than 50% [15].

With regard to epidemiological trends, three main patterns have been identified: (1) the epidemiological situation is getting worse and the incidence of infection and disease is increasing (e.g. for African trypanosomiasis and dengue); (2) the epidemiological situation has greatly improved in some regions of the world but is stagnant or getting worse in others (e.g. for schistosomiasis and malaria); and (3) the global burden of disease is declining as a result of effective control (e.g. leprosy, Chagas disease and onchocerciasis).

Table 2 shows, for each disease, the principal control strategy, main problems and challenges for control, and the corresponding research needs. Case-finding and treatment, often in combination with active surveillance, is the core intervention for five diseases; for another three diseases, the main intervention is based on mass treatment of the total population at risk in defined endemic areas. Malaria is a special case, with a more complex control strategy involving treatment and vector control and demanding requirements such as early diagnosis and prompt treatment of individuals in high-risk groups within 24 h of the onset of symptoms. Treatment is a key element of the intervention strategy for all diseases in the TDR portfolio except Chagas disease and dengue, the intervention strategies for which are mainly based on vector control.

For several diseases, the predominant problem is the lack of effective and affordable control tools; the available drugs are toxic, expensive, not very effective or losing their effectiveness because of increasing drug resistance; diagnostics perform poorly or have practical limitations; and there are no effective vaccines. For others, effective tools do exist, even if they are far from perfect, and the main problems relate to poor implementation, poor access and the challenge of sustaining control. 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
Epidemiological trends

For example, on identifying new basic knowledge, the TDR portfolio, addressing the specific needs of the least developed, high-burden, low-income countries, development of drugs, diagnostics and new prevention and control tools at the clinical and community levels.

The table highlights the strategic needs for each disease and the corresponding research needs.

The matrix highlights the strategic differences between the disease categories. Under A (New basic knowledge), all but one of the diseases in the TDR portfolio has some strategic emphasis on new basic knowledge but these are focused on specific needs, for example on identifying new targets for drugs, diagnostics, and development of bioinformatics and applied genomics to identify new targets for drugs, diagnostics, and development of bioinformatics and applied genomics to deliver improved intervention methods.

Under B (New and improved tools), for category 1, the main emphasis is on delivering improved intervention methods, whereas for category 3, new and improved tools are required. New and improved tools are required in category 3 also to ensure that the research needs cover a wide spectrum from new knowledge to better methods of implementation, but with emphasis on new tools and methods.

For category 2, the main emphasis is on better implementation strategies.

In national control settings, methods and guidelines for application and new prevention and control need to be developed in accordance with the disease categories. For category 1, the main emphasis is on the large-scale implementation of existing tools at the clinical and community levels.

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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} + 2 211 000). This relationship and additional information on the TDR budget can be found at 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</td>
<td>Better tools: vaccine</td>
</tr>
<tr>
<td></td>
<td>Leishmaniasis</td>
<td>Case finding and treatment, selective vector/animal reservoir control</td>
<td>Toxic drugs</td>
<td>Better methods for mosquito control</td>
</tr>
<tr>
<td></td>
<td>Malaria</td>
<td>Early diagnosis and prompt treatment: ITMs, other vector control, intermittent treatment in pregnancy</td>
<td>Poor treatment coverage/DOTS expansion</td>
<td>Better tools: diagnostics, vector control</td>
</tr>
<tr>
<td></td>
<td>Schistosomiasis</td>
<td>Morbidity control through periodic treatment in high-risk populations</td>
<td>Low priority/limited resources</td>
<td>Better case-finding and treatment strategies</td>
</tr>
<tr>
<td></td>
<td>Tuberculosis</td>
<td>Case finding and directly observed multi-drug treatment (DOTS).</td>
<td>HIV and multi-drug resistance</td>
<td>Better tools: drugs, vaccine</td>
</tr>
<tr>
<td></td>
<td>Lymphatic filariasis</td>
<td>Interruption of transmission through periodic mass treatment</td>
<td>Drug that kills/sterilizes adult worms</td>
<td>Strategies for control of non-domiciliated vectors</td>
</tr>
<tr>
<td></td>
<td>Onchocerciasis</td>
<td>Periodic mass treatment to eliminate the disease as a public health problem</td>
<td>Drug that kills/sterilizes adult worms</td>
<td>Better drugs and diagnostics</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
- Full genome sequence of tropical disease pathogens available or being finalized (http://www.ncbi.nlm.nih.gov/genome/genome60)
- Systems biology
- Bioinformatics
- Genetic control strategies for insect vectors
- Evidence of impact of political, economic and social change, including health sector reform
- Recognition of the role of health in stimulating economic development
- New methods for analysis of complex social and health systems phenomena

B. New and improved tools
- Functional genomics directed to drug and vaccine discovery
- Pharmacogenomics
- Medicinal chemistry and drug discovery advances
- Combinatorial chemistry
- Robotics and chemistry for high-throughput screening
- Chemistry related to oral bioavailability
- Improved non-clinical development methodologies for optimizing compounds
- Advances in molecular diagnostic technologies
- Advances in vaccine technologies, including novel adjuvants
- Good practices (GLP, GCP, ethics)

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

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

References

Macrolarical drug targets for lymphatic filariasis and onchoceriasis, 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...
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 committees, 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].

Acknowledgements

We are grateful to all partners who contributed to the analysis, especially the members of the disease reference groups. We would like to thank Andres de Fransisco from the Global Forum for Health Research for fruitful discussions on the prioritization framework, Melba Gomes and Kamini Mendis for their contribution to the strategic analysis of malaria, Andrew Crump and Lisa Schwartb for the design of the Strategic Emphases Matrix poster, Catherine Needham for design of the web version of the matrix, and Ahmed Bellah for the development of the product database. TDR will continue to improve its strategic analysis and welcomes comments at http://www.who.int/tdr/grants/strategic-emphases

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