Severe anaemia in highly malarious areas is invariably a consequence of malaria and a major cause of infant death in malaria endemic Africa. In recent years, TDR and partners have funded studies to answer the policy question of whether iron supplementation or intermittent chemoprophylaxis during infancy is the better strategy for preventing severe anaemia and which should be recommended, by the United Nations Children’s Fund (UNICEF) and World Health Organization (WHO), on a large scale in high transmission areas.

Iron supplementation has been shown to be safe and effective when given orally and daily during the infant’s first year of life.

A recent follow up study shows that treatment with a single-dose antimalarial drug, sulphadoxine-pyrimethamine (SP), given to infants in an area of intense malaria transmission in Tanzania, reduced severe malarial anaemia by 50% and clinical malaria attacks by 59%. In the study, SP was delivered at 2, 3 and 9 months of age as a component of the Expanded Programme on Immunization (EPI) vaccination schedule – incurring additional costs to the EPI programme of about 25 US cents per child. The intervention appeared to be safe.

Intermittent treatment of infants with an antimalarial drug significantly reduces severe malarial anaemia and clinical malaria attacks.
...severe anaemia in infancy

(continued) The study was conducted in an area of Tanzania in which the uptake of insecticide-treated bednets and iron supplementation was good. It is hoped that the efficacy and safety findings from this single study will be confirmed by two other studies being funded by WHO/TDR and already under way in Ghana and Kenya.

While the further studies are ongoing, adequate safety information on the use of SP is being sought from Hoffmann-La Roche (the manufacturer of the drug) and other sources, and production of an infant-dose tablet of SP is being pursued. Assessment of the full impact of the intervention on infant mortality, through its larger-scale operational use in Africa, is also under discussion by EPI, TDR, UNICEF and Roll Back Malaria. This will provide further information on safety and efficacy to support policy formulation and routine use of the intervention in malaria endemic countries in Africa. Studies are also being planned to assess the full impact of the strategy in different malaria epidemiological situations and to evaluate alternative therapies to single-dose treatment with SP.

The addition of this intervention to national EPI programmes could enhance their value; it could also be combined with other EPI deliverable interventions such as insecticide-treated bednets, rectal artesunate or micronutrient supplementation. And there is also the possibility that the intervention could be delivered through national immunization days for polio in unstable situations such as prevail in the eastern part of the Democratic Republic of Congo.

The findings of this recent study, therefore, open up the possibilities for an important new strategy for reducing childhood deaths in malaria endemic regions of the world – offering an inexpensive, high impact intervention against malaria in the context of the EPI programme. The results of the ongoing studies are awaited with interest.


Dear Reader,

Please send us your comments and views (in writing or by e-mail) to:

Communications Unit, TDR, World Health Organization,
1211 Geneva 27, Switzerland
or to
tdr@who.int

We look forward to hearing from you, and encourage and welcome the participation of all our readers in the effort to ensure a 2-way flow of information. Ed.

TDR reserves the right to edit any correspondence published in the newsletter. Please note that we can neither guarantee publication nor are we able to return any materials submitted.

Corrigendum

To our article on ARTEMOTIL, in TDRnews No. 63, October 2000:

Artemotil is the ethyl ether of dihydroartemisinin and not artemisinin. The majority of the drug is metabolized by an oxidative dealkylation, and not an oxidative alkylation. We thank Dr Arnold Brossi for alerting us to these errors.
Imagine the scene: a young child with severe malaria, who cannot take drugs by mouth, and no alternative (injectable) treatment is available; the patient’s condition worsens rapidly, and death ensues. This scenario is all too common in some areas that are highly endemic for malaria, and is the situation for which artesunate suppositories are being developed. A vast body of data on this drug – including quality, preclinical, clinical and safety information – has been submitted for regulatory approval. If approved, the medication is expected to have a profound effect on mortality from malaria, and to soon be in use where most needed, having been actively promoted through WHO’s Roll Back Malaria campaign and included on the WHO list of essential drugs.

Artesunate is one of a number of artemisinin derivatives discovered and developed by Chinese scientists and registered in China in the 1980s. During the 1990s, TDR supported studies to assess the properties of the drug. Results from these and other studies have shown artesunate to have an immediate, potent, sustained and predictable clinical and parasitological effect, superior to that of any other non-artemisinin antimalarial to date. This led TDR, in the late 1990s, to begin assessing the drug’s potential for early emergency treatment of severe malaria. There were already indications that artesunate, given rectally, was effective in severe malaria. Significant work with artemisinin suppositories in severe malaria had been conducted in Vietnam in the early 1990s, and clinical trials of rectal artesunate followed by mefloquine treatment in moderately severe malaria had been conducted in Thailand. Other studies had shown that, in children with severe malaria, treatment with intrarectal artemisinin results in reduction of mortality comparable to that achieved with intravenous quinine or intramuscular artesunate. These studies led WHO to assess the potential of artesunate given through the rectal route for treatment of patients unable to take drugs by mouth and who live at a distance from facilities for parenteral treatment. WHO’s artesunate task force commissioned a series of studies to examine the clinical, parasitological and pharmacokinetic response to the drug when given as a single dose over 24 hours. In severe disease, it is critical that treatment is rapidly available and quick-acting – pooled data from these studies showed that a single dose of artesunate can result in a significant decline in parasitaemia within 24 hours. Although the artemisinin compounds have been in use for some time and have proved remarkably non-toxic, WHO has taken great care to explore the safety of this class of drugs, especially with regard to neurotoxicity and reproductive toxicity, and a post-marketing surveillance programme has been developed to monitor their safety in use. International experts have reviewed the extensive primary data made available to WHO from different institutions, and these data and their review have now been submitted for assessment to regulatory authorities in the US and Europe under the orphan drug designation and accelerated approval process.

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5 Looareesuwan, Ann Trop Med Parasitol, 1997, 57(3): 348-353
Decoding a major malaria vector: international network established

A network linking researchers and other public and private partners in the field of Anopheles gambiae genomics research (see list) has been launched. A. gambiae is the major vector of malaria in Africa, where 85-90% of the world’s malaria cases and deaths occur. The ultimate goal is to fill a public database with complete details of all the genes in the genome of A. gambiae, providing a springboard for better understanding of malaria and development of new malaria control tools.

The network was established on 3 March 2001 at a meeting in Paris, co-organized by TDR and the Institut Pasteur; it followed an earlier informal meeting in July 1999. The project will build on the initial genomics research carried out at some of the participating institutions, and draw on the strengths of the different partners. Research capacity strengthening of developing country laboratories in contemporary genomics techniques is a priority. The network is open to all players in the field of genomics, and hopes are that other centres will join in.

To collect data for the database, a number of lines of research need to be followed sequentially or in parallel. A full shotgun approach will be used to completely sequence the laboratory strain of A. gambiae, which should be achieved by the end of 2001. Once sequencing data are available, several other types of investigation must be carried out before the information is ready to use for design of control tools. These investigations include working out how all the separately sequenced sections of genome fit together in the whole genome ('assembling' the genome), identifying where individual genes lie among the full extent of sequence data ('annotation'), fathoming the function of each gene ('functional genomics'), and investigating which proteins are expressed by which genes in a cell ('proteomics'). Although this is a logical order of events, it is not necessary to wait for the whole genome to be sequenced before beginning to understand the role and functions of individual genes - the different lines of work can take place in parallel. All data issuing from the project will be made freely available in public domain databases, and also distributed worldwide through CD-ROM or DVD discs.

No other sequencing project has been of use to such a large number of people in developing countries as this project promises to be. The project will help bridge the gap between completion of the annotated sequence and its use in Africa – the network is already looking ahead to the interface with malaria programme control.

TDR will play a coordinating role in the network, bringing all partners together, mediating, and facilitating the participation of developing country scientists by opening possibilities for them, e.g. bioinformatics training, which will begin soon. The human genome sequence has recently been released; the malaria parasite sequence will soon be completed. Thus the completion of the Anopheles project will provide information on the final link in the life cycle of the malaria parasite. Together the information from these three organisms should lead to new understanding of the epidemiology of malaria, and of the ecology of vectors and parasites, and to new tools and methods for malaria control.
New Research Capacity Strengthening strategy

Under the TDR strategy for 2000-2005, research capacity strengthening activities will be, to a greater extent than before, driven by the TDR research and development (R&D) agenda. While part of the resources will continue to be directed to open investigator initiated projects to strengthen institutions in least developed, low-income, high disease-burden countries with limited capacity for research, around 60% of the capacity building budget will be invested in targeted R&D initiatives in disease endemic countries.

Two major funding approaches have been established in response to the new strategy:

• the Programme Grant, an approach restricted to least developed countries.
• RCS-Plus, the coordinated R&D-driven initiative approach, open to all disease endemic developing countries.

The Programme Grant

The Programme Grant will support long-term institutional plans designed as multidisciplinary research development programmes rather than as isolated individual research projects. The grant is expected to develop research leadership, infrastructure, and a research environment, and to improve training opportunities, scientific expertise in the biomedical and social science areas, and information and communication systems. Research projects are expected to address areas at the interface between laboratory-oriented research and applied field research, with the aim of extending, where possible, research findings into policy and practice. A first call for applications was issued in May 2001.

RCS-Plus

R&D-driven initiatives will be established year-round, based on priorities identified by TDR Steering Committees in collaboration with the Research Strengthening Group (RSG). The initiatives will be jointly implemented and funded by the RCS unit and the corresponding R&D functional unit/committee. Individual initiative teams, formed by external experts and managed by TDR, will be responsible for preparing a development plan, implementing and monitoring each initiative.

Four new RCS-Plus initiatives began in 2001:

• Trials of fixed-dose combinations of four anti-TB drugs, and health systems research for TB.
• A bioinformatics training programme.
• Capacity building in social sciences for scaling-up field interventions.
• Socioeconomic factors associated with TB multidrug resistance.

The new RCS strategy was designed to attune TDR activities to developing countries’ research capabilities. TDR operations and investment have been reshaped to enhance the participation of developing countries in the TDR research and development agenda, maintaining support to countries with lesser developed research capacity.
Putting TDR implementation research into action

A main new element in the TDR strategy for 2000-2005 is research to facilitate the implementation of control tools. As, for example, research to scale up the management of malaria close to the home in an attempt to reduce malaria morbidity and mortality in under-5-year-olds in sub-Saharan Africa; research to expand the use of insecticide-treated materials in communities; or research on the most appropriate indicators for monitoring the impact of antimalarial interventions. Or, to take an example from another TDR disease, research to address why, despite the more clearly expressed common (rather than local) need for the research, enunciated by disease control; and an expected ultimate impact on health of the poor. IR will test and improve new tools, procedures and strategies under conditions of routine disease control, and identify the best way to introduce these tools into use. IR will help to market, in disease endemic countries, new tools, procedures and strategies resulting from research. In operation, IR will be linked actively to disease control, and be rapidly responsive to the priority needs of disease control.

Roll Back Malaria sets the standard

Examples of IR were presented at the 4th Meeting of the Global Partnership to Roll Back Malaria (RBM), held in Washington, USA, in April 2001. On the agenda, amongst other things, was discussion on malaria research and development (R&D) in the context of its role in strengthening the scale and scope of national malaria control programmes. Key presentations were from:

- Tanzania, illustrating how malaria researchers are working to inform the Ministry of Health on evidence for policy.
- Sri Lanka, illustrating how a group of malaria researchers assists and advises the national malaria control programme.
- Cambodia, illustrating how solutions provided by research, including the pre-packaging of drugs and their distribution through public and private channels, are being used to counteract the problem of counterfeit drugs.

The activity portfolio of the Multilateral Initiative on Malaria illustrated how current global R&D strengthening efforts are responding effectively to the capacity development needs, especially of Africa. In some countries, R&D has already become an integral part of RBM, and functional linkages have been developed between research and disease control.
Molecular targets for anti-parasite drug screens

For several years, the Drug Discovery Research (DDR) unit of TDR has supported a network of laboratories that test substances for their activities against several parasites (Plasmodium, Leishmania, Trypanosoma, nematode species). Over 15,000 compounds (or, in some cases, natural product extracts) have been evaluated and the results reported back to their suppliers. This approach has been successful in identifying a number of compounds that have been further developed, or are still being developed, as anti-parasite drugs, for example, ivermectin for treatment of onchocerciasis, eflornithine against African trypanosomes (see TDRnews No. 64), and miltefosine and moxidectin, two new drug candidates still in development for treatment of visceral leishmaniasis and onchocerciasis, respectively (see TDRnews Nos. 60, 62).

The general testing procedure was reorganized about two years ago, and presently incorporates initial screening against all relevant parasites at a single primary testing centre (Tibotec NV, Belgium), followed by more detailed analysis of activities on individual parasite species. This takes place in specialized testing centres including the London School of Tropical Medicine and Hygiene, UK, The Swiss Tropical Institute in Basel, and the Northwick Park Institute of Medical Research, UK. In addition, the Kitasato Institute in Japan is screening several thousand compounds a year for antimalarial activity under an agreement made in 1999 between the Japanese Ministry of Health and Welfare, representatives of the Japanese pharmaceutical industry, and WHO (see TDRnews No. 61). Additional information on DDR-supported compound screening, and on how to submit compounds for screening, can be found in TDRnews No. 60 or obtained from the TDR contact.

To date, the screening activities supported by DDR have focused mainly on testing of compounds against whole organisms. However, the availability of parasite genome sequences, together with high-throughput screening technologies, is increasing the potential for discovering new drugs for parasitic diseases by conducting screens based on purified enzymes or other molecular targets from parasites.

DDR is seeking suggestions of molecular targets, particularly from kinetoplastids and filariae, that would be suitable candidates for high-throughput screening.

Call for molecular targets as candidates for high-throughput screening

If you can suggest molecular targets for drugs against parasitic diseases, particularly kinetoplastid or filarial diseases:

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The Oswaldo Cruz Foundation: 100 years

Paulo Buss, President of the Oswaldo Cruz Foundation
Nísia Trindade Lima, Director of the House of Oswaldo Cruz

The history of the Oswaldo Cruz Foundation began in 1900, at a time when the need for producing serum against bubonic plague was becoming imperative. The disease had reached the city of Santos, in the State of São Paulo, and was beginning to threaten Rio de Janeiro, capital of the Republic itself. At this time, the Institution was called Instituto Soroterápico Federal (Federal Serum-Therapeutic Institute).

In 1902, Oswaldo Cruz became head of the Institute. He inaugurated a process for consolidating scientific research and organized campaigns against epidemic diseases such as bubonic plague, yellow fever and smallpox, which were regarded as detrimental to the settling of European immigrants in Brazil and a hindrance to the transformation of Rio de Janeiro into a 'civilized' a city as a European one. Oswaldo Cruz directed, simultaneously, the Diretoria Geral de Saúde Pública (Public Health General Board) and the institute that would be named after him in 1908, at that time often referred to as ‘Instituto de Manguinhos’. The activities of the Oswaldo Cruz Institute were not restricted to Rio de Janeiro. Throughout the country there were sanitation and hygiene-related initiatives and, after 1909, scientific expeditions accompanied the construction of railroads, sanitation of ports and the Amazon rubber boom. The impact of these excursions was summarized by the statement that ‘Brazil is an immense hospital’ (Dr Miguel Pereira, 1916) which stemmed from reports by scientists of the Oswaldo Cruz Foundation that people from the Brazilian hinterland were completely weakened by diseases such as malaria and Chagas disease.

It was in the course of these excursions to the interior that the complete life cycle of American trypanosomiasis was discovered – a discovery that would confirm Carlos Chagas as successor to Oswaldo Cruz as Director-General of the Instituto de Manguinhos. Chagas held this position from 1917 to 1934, the year of his death, in conjunction with that of Director of the Departamento Nacional de Saúde Pública (National Department of Public Health). The three major lines of work – research, teaching and immunobiological production – and careful articulation of public health policy guidelines in Brazil, have been distinguishing features of the Oswaldo Cruz Foundation throughout its 100-year history. These progressed in spite of the serious problems faced during periods of military government, among which the most dramatic was the episode in 1970 referred to as ‘Massacre de Manguinhos’ by the scientist Herman Lent, when ten scientific staff members had their political rights suspended and were put into retirement. After 1974, under the powerful impact of a crisis in public healthcare provoked by a meningitis epidemic, and also as an outcome of the scientific and technological development programme promoted by the Federal Government, the Institution experienced another period of resurgence of investment, accompanied by the entry of new scientists who played an important role in further development of the Foundation.

Since 1985, with the process of re-democratization of Brazilian society, the Oswaldo Cruz Foundation has undergone intense redefinition of its policies on topics such as the complexity of health and disease. Now the focus is on improving public healthcare, increasing democratic and internal participatory mechanisms, and harmonizing established traditions with the research demands of contemporary society. Intensified research on infectious diseases, chronic-degenerative diseases, violence and other problems of collective healthcare takes place alongside the traditional activities of public health.

With the courtesy of Fiocruz

SEE ALSO
www.fiocruz.br
health research and keeping abreast of international debates on the epidemic profiles of populations. Awareness of the importance of the multi-disciplinary approach and recognition of the need to creatively integrate scientific research work with technological development has been growing. In addition to meeting the Government’s demands for producing goods and services and to affirming itself as a reference centre in biomedical research and public healthcare, the Institution also contributes to the formulation of public policy, as in 1988, when the unified national healthcare system was created in Brazil. Currently, the Oswaldo Cruz Foundation comprises 15 technical-scientific units situated in various Brazilian cities, including regional research centres in Belo Horizonte, Salvador, Recife and Manaus. Biological and biomedical research, at various levels and in many disciplines, and clinical research, particularly in the areas of infectious-parasitic diseases, women’s health and child care, is ongoing. In the field of public health, research is ongoing in the areas of epidemiology, environment, social sanitation, historical topics, healthcare systems and services. The Foundation is the largest non-academic institution in the country providing human resources training and education in healthcare. About 700 students are enrolled in 10 Masters and Doctoral degree programmes, and more than 1500 students in other types of postgraduate courses. The staff comprises more than 800 personnel with PhD and Master’s level qualifications.

The Oswaldo Cruz Institute (Fiocruz) building in Rio de Janeiro.

The Oswaldo Cruz Foundation is a member of the National Network of Laboratories for Health Quality Control. It produces more than 60% of the vaccines used in the national immunization programme (about 100 million doses/year) and, each year, almost 3 million kits – many of which are achievements of the Institute’s own technological development programme – for diagnosis of various infectious parasitic diseases. The Foundation develops and improves pharmaceuticals and medications. It also produces drugs essential for public healthcare, and 8 of the 12 drugs comprising the ‘cocktail’ used in treatment of HIV sufferers.

In a country marked by discontinuity in policies towards science and public healthcare, it is important to honour the resilience of this institutional model. It invites us to reflect on the importance of attention to life and scientific education as fundamental aspects of citizenship.
**UPDATE**

**Support for the development of two antimalarial combinations**

The Medicines for Malaria Venture (MMV) has awarded funding to twoWHO/TDR co-sponsored antimalarial combination development projects, subject to contract:

**The pyronaridine-artesunate project for treatment of uncomplicated malaria.**

Partners:

- Shin Poong
- TDR

**The chlorproguanil-dapsone-artesunate (CDA) project for treatment of uncomplicated malaria.**

Partners:

- GlaxoSmithKline
- UK Department for International Development (DFID)
- University of Liverpool
- TDR

In both of these development programmes, it is planned to develop a cost-effective oral artemisinin derivative in a fixed-ratio combination with another antimalarial drug for the treatment of uncomplicated malaria. The theory behind the development of these products is that the combinations will be highly effective and provide the following advantages over traditional single agent therapy:

- Faster malaria treatment response as measured by fever and parasite clearance.
- Prevention of development of resistance due to the combined use of two drugs with different mechanisms of action.
- Reduction of malaria transmission based on the activity of artesunate (and other artemisinin derivatives) against gametocytes.

Both projects are currently at the preclinical stage of development. The combinations will not be used experimentally in humans before late 2001, while submission for national regulatory approval will not occur before 2004.

**UPDATE**

**Companies offer more help for the control of sleeping sickness**

In February 2001, Bristol-Myers Squibb (BMS) announced that it would donate 60 000 doses of eflornithine annually for three years, starting in June 2001, for use in treatment of sleeping sickness (see TDRnews No.64). However, this development was overtaken in May 2001 by an agreement signed between WHO and Aventis (was Hoechst Marion Roussel), by which Aventis will donate US$25 million to support WHO’s activities in the field of African trypanosomiasis for a five-year period. The donation comprises: three key drugs – pentamidine, melarsoprol and eflornithine; funds for disease management and control; and funds for research.

Out of the annual Aventis donation of US$5 million, US$750 000 will come to TDR as a designated fund for drug development, focusing on oral eflornithine, development of a new route of synthesis for eflornithine, and initial development of existing molecules for future treatment. BMS has agreed to fund production of the bulk material for 60 000 doses of eflornithine for the first year and also to provide 140kg of eflornithine for Phase III clinical trials of an oral formulation.
**UPD A T E**

**TB diagnostics development receives a boost**

The Tuberculosis Diagnostics Initiative (TBDI) in TDR has been awarded a five-year US$10 million grant by the Bill and Melinda Gates Foundation to speed the development and evaluation of new diagnostic tests for tuberculosis. The need for new diagnostics for TB was summed up by Dr Gordon Perkin, Director of the Global Health Program at the Gates Foundation. “Existing diagnostic tests are slow, cumbersome and often expensive. We need tests that are low cost, highly specific, and suitable for use in the field. We are optimistic that this programme [TDR] will help us take a major step forward”. According to Dr Mark Perkins, Manager of Diagnostics Research and Development in TDR, “We are 100 years behind in TB diagnostics. Existing technologies leave many patients undiagnosed, resulting in substantial morbidity, mortality and ongoing transmission. This focused investment in a declared priority area for TDR will allow diagnostic activities to shift into high gear. There is now the real expectation of bringing improved techniques to the field within the coming five years.”

**UPDATE**

**The Southern Cone Initiative**

Progress towards the elimination of Chagas disease in Argentina, Brazil, Bolivia and Paraguay.

The tenth meeting of the Southern Cone Initiative for the elimination of Chagas disease was held in Montevideo, Uruguay, in March 2001. The advances attained in each country of the initiative were reviewed.

In Argentina, the house infestation rate in the whole country had dropped from 6.1% at the beginning of the initiative in 1992 to 1.2% in 2000, while the infection rate in 0-4 year olds had dropped from 1.7% in 1992 to 0.9% in 2000. The data indicate that vectorial transmission has been interrupted in 13 of the 19 endemic provinces of this country.

In Brazil, infection rates were also very low in 2000: 0.24% in 7-14 year olds, and 0.12% in 0-4 year olds. Some 290 000 houses were searched for the presence of the vector Triatoma infestans in 2000, but altogether only 295 insects were found – a number far lower than that needed for transmission of the disease.

In Bolivia, beginning in 1998, it was planned to spray 600 000 houses over three years. So far, 50% of the houses have been sprayed in two cycles of spraying, and initial data indicate that the house infestation rate had dropped to 5% at the end of the second spraying cycle in 2000, from 79% in 1998. In Paraguay, 32% of the houses requiring insecticide treatment in the country have now been sprayed. Finally, both Uruguay and Chile have been declared free of transmission of Chagas disease, in 1997 and 1999 respectively.

Surveillance programmes are in action in both countries in case of possible reinfestation.
Operational research in TB control programmes: Challenges in the WHO Eastern Mediterranean region

Dr A. Seita, WHO Regional Office for the Eastern Mediterranean Region (EMRO)

Control programme managers sometimes have to differentiate between two approaches in public health: the programme approach and the research approach. The former is dogmatic - pursuing strict implementation of the principles. The latter is flexible - asking and verifying questions even on the principles. The approaches are not mutually exclusive. However, programme managers should be careful. If, for instance, a national TB manager questioned the validity of DOTS (the WHO strategy for TB control) principles in a meeting with peripheral health workers, the workers might become totally confused.

At EMRO, we took the dogmatic rather than the research approach when we started DOTS promotion in 1995. At that time, only one out of 23 countries in the region was using DOTS. Our priority was 'first things first': introduce DOTS and achieve DOTS All Over (or 100% DOTS coverage) by 2000. We trained TB managers and requested, actually pushed them, for strict DOTS implementation. This approach worked well. DOTS All Over was achieved in 18 countries by the end of 2000 and in 2 more countries in 2001.

Interestingly, the more progress we made in the dogmatic approach, the more we realized the importance of the research approach. In 1998, health ministers in Egypt and Syria asked us about the cost-effectiveness of their DOTS activities - an extremely valid research question in the middle of their DOTS expansion. We conducted research on this question with the Royal Tropical Institute (KIT), the Netherlands. The research concluded that DOTS in primary health care is most cost-effective. We reported these results to the ministers, and the countries subsequently achieved DOTS All Over.

The importance of the research approach became obvious in 1999 when, through rapid expansion of DOTS, our constraints in DOTS activities became clearer: e.g. uncontrolled private sector activities, poor defaulter management, lack of community involvement. Operational Research (OR) is necessary to address these issues appropriately. Fortunately, TDR included TB in its targeted diseases in 1999, and the WHO/EMRO/TDR/RCS/CDSS Small Grant Scheme (SGS) also included TB in 2000. SGS is a joint project funded by EMRO, TDR/RCS and CDSSHQ, which aims to provide funds for OR in TDR-targeted diseases. We had to prepare good OR protocols to obtain funds from SGS.

In June 2000, we conducted a ten-day training workshop on research methods for TB, in collaboration with TDR/RCS and the International Union Against TB and Lung Diseases (IUATLD). We invited two participants (a programme manager and a researcher) from each of 11 high-burden countries in the region: Afghanistan, Djibouti, Egypt, Iran, Iraq, Morocco, Pakistan, Somalia, Sudan, Syria and Yemen. The workshop aimed to introduce participants to research methods and develop research protocols on priority topics in TB control. The workshop had four elements: didactic presentations of epidemiological principles; practical exercises in evaluation and critical review; hands-on experience of data entry and checking; group work on development of the research protocol. The workshop was successful, and five OR protocols were produced. These protocols were submitted to the SGS committee. In September 2000, the SGS selection committee met and awarded grants to three of the protocols developed in the workshop: private sector activities in Iran, Pakistan and Somalia; community involvement in Djibouti and Iraq; treatment failure in Egypt. This is clearly a good start in OR for our TB control programmes, and we learned a lot.

It was indeed good that national TB managers raised OR questions. All questions were relevant.
to daily control programme management, and the outcome of OR activities are expected to facilitate DOTS activities. It was also good that we ‘educated’ programme managers about the research approach. They highly appreciated the workshop, which expanded their scope in programme management. The availability of SGS was also critical. The ‘small’ grant, maximum US$10,000 for each project, is sufficient to carry out this kind of OR in TB control. However, we noticed limitations. The bridge between control programme managers and national academic societies is weak: despite our invitations, participants in the workshop were mainly from the programme side. Programme managers could not always develop good protocols, even after the intensive input in the workshop, which is probably because of their different discipline. This reminded us that, without close monitoring, the OR protocol in receipt of a grant might not be carried out at the highest standard.

The steps that we think important are as follows:
- OR should be initiated from programme managers based on their OR questions;
- A link between programme managers and national academic societies is a must for the implementation of OR;
- A link between these national groups and international research facilities such as the Royal Tropical Institute, The Netherlands (KIT) and IUATLD is critical to ensure the high quality of OR.

This triangle - programme manager/national academic society/international research facility – is the key for successful OR. We have started to develop this triangle for protocols granted in SGS 2000, and have succeeded in some countries. We have also begun preparations for SGS 2001 in the same direction. Our challenge continues to be to bring tuberculosis under real control in the region.

PRODUCT RESEARCH AND DEVELOPMENT

Leishmaniasis: Second generation vaccines

Several recombinant antigens offer promise as candidate leishmaniasis vaccines, but there is need for stricter quality control.

Second generation Leishmania vaccines were the subject of a meeting held in Merida, Mexico, in May 2001. Results from recent testing of recombinant Leishmania antigens were reviewed, and individual presentations on second generation vaccine candidates were given.

The meeting was hosted by the Universidad Autonoma de Yucatan in Merida, organized jointly by this University and TDR, and co-sponsored by TDR and the Infectious Disease Research Institute (IDRI), USA.

The work on recombinant Leishmania antigens was carried out in two independent laboratories as part of an effort to systematically test candidate antigens as potential vaccine candidates. Ten different recombinant antigens (recombinant proteins expressed in E. coli) had been prepared and sent to the two laboratories, one at the Universidad Federale de Bahia, Brazil (laboratory of Manoel Barral-Neto), and the other at the University of Copenhagen, Denmark (laboratory of Thor Theander). The ten antigens were tested as vaccine candidates in murine models for leishmaniasis. Adjuvants used were MPL (donated by Corixa corporation) and IL-12 (donated by Genetics Institute).

The data showed that none of the antigens produced significant protection (two of the antigens gave positive results in one laboratory, but not in the other). However, it was hard to draw solid conclusions from the results because of several technical problems, including inadequate information about the stability and potency of the antigens. Because of this issue, TDR has recommended stricter guidelines for the characterization and quality control testing of recombinant antigens before they are used for pivotal animal studies.

As to the individual presentations on second generation Leishmania vaccine candidates, there were suggestions of several promising candidates, including anti-virulence vaccines and vaccines comprised of fusion proteins of two antigens. The presentations have been summarized and will be published on the TDR website.

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1 The reports on Cost-effectiveness of Directly Observed Treatment, Short-course (DOTS) for tuberculosis in Egypt and Cost-effectiveness of Directly Observed Treatment, Short-course (DOTS) for tuberculosis in Syria are both available from the WHO Regional Office for the Eastern Mediterranean, WHO Post Office, Abdul Razzak Al Sanhouri Street, Naser City, Cairo 11371, Egypt.

2 Report available from the WHO Regional Office for the Eastern Mediterranean, WHO Post Office, Abdul Razzak Al Sanhouri Street, Naser City, Cairo 11371, Egypt.

* Second generation vaccines are comprised of recombinant antigens, in contrast to first generation vaccines, which consist of killed whole Leishmania parasites, as have been tested in clinical trials in Iran, Sudan, and Latin America.1, 2

1 Sharifi I et al, Randomised vaccine trial of single dose of killed Leishmania major plus BCG against anthropomorphic cutaneous leishmaniasis in Bam, Iran. Lancet, 1998, 351(9115):1540-3

RESEARCH CAPACITY STRENGTHENING

MIM symposium on insecticide resistance in African malaria vectors

Dr Barbara Sina, MIM Scientific Advisor

Malaria control programmes in Africa face increasingly complex issues when crafting strategies to effectively deploy their efforts. Just as the alarming spread of malaria drug resistance throughout the continent presents challenges for effective treatment strategies, the spread of insecticide resistance in vector mosquito populations threatens to undermine the increased deployment of pyrethroid-treated bednets to reduce malaria transmission. With the assistance of the WHO Regional Office for Africa (AFRO) and WHO/TDR, the Multilateral Initiative on Malaria (MIM) convened a symposium on insecticide resistance in mosquitos that transmit malaria in Africa, in March 2001, in Harare, Zimbabwe (prior to the MIM/TDR Task Force meeting, see opposite). The meeting was initially planned as a networking opportunity for African vector biologists and their collaborators supported by MIM/TDR grants. However, interest grew, and 60 scientists from 14 African countries, Europe, the USA, and representatives from donor agencies and agrochemical companies, participated to discuss their research on insecticide resistance and its implications for vector control.

Reports of insecticide resistance in various parts of Africa have appeared in scientific journals since the 1960s. Recent surveys conducted by MIM/TDR-supported laboratories from each region, although limited in scale, indicate that the highest levels of resistance are found in mosquito populations in western and southern Africa. Scientists found up to 80-90% pyrethroid resistance in Anopheles gambiae, the primary malaria vector, in some parts of Côte d’Ivoire, Benin and Burkina Faso, due to mutations in the gene that encodes the pyrethroid target protein in the mosquito nervous system. Evidence was presented that these high levels of resistance evolved in response to mosquito larval exposure to insecticide contaminated agricultural runoff from cotton and vegetable fields near mosquito breeding sites. In South Africa, a dramatic increase in malaria in recent years coincided with the reappearance of pyrethroid-resistant Anopheles funestus mosquitos, presumed to have migrated from Mozambique. Data collected by vector biologists formed the basis of the decision by the South African malaria control authorities working with an environmental NGO to return to the use of residual DDT house spraying. Less insecticide resistance was reported in East Africa. No resistance was detected in the three primary malaria vector species in Tanzanian villages that have been using pyrethroid-treated bednets since 1988, or in mosquitos collected from cotton estates with a long history of pyrethroid and other insecticide use. Studies on pyrethroid-resistant mosquitos collected during a previous bednet trial in western Kenya indicated that they express a combination of several different resistance mechanisms. It appears that insecticide
WHO Regional Office for Africa hosts MIM/TDR Task Force

The Multilateral Initiative on Malaria (MIM) activities developed under the coordination of TDR have focused on developing research partnerships and promoting African research leadership in targeted scientific areas relevant to disease control. A portfolio of research projects has been established, opening up opportunities for training and international collaboration.

The MIM/TDR Task Force is now supporting 23 collaborative programmes based on North-South collaboration and involving 24 African countries, 8 European countries and the USA. Annual meetings of the principal investigators and task force members have optimized the outcomes and assured smooth implementation of projects. The 4th meeting of principal investigators (PIs) and task force members was held in March in Harare, Zimbabwe. The PIs and their collaborators (around 60 participants) reviewed the progress of their activities. The technical presentations reflected a high level of commitment, scientific maturity and collaboration that pleased all members of the task force, the W HO Regional Office for Africa (AFRO) and local authorities.

The projects have focused on issues at the interface between laboratory-based research and potential applications for malaria control. The full engagement of W HO / AFRO and Roll Back Malaria has established an important interaction between research and control groups favouring the application of research results into policy and practice. The task force model has been recommended by the TDR governing bodies, the Scientific and Technical Advisory Council (STAC) and the Joint Coordinating Board (JCB), as the approach to be used in promoting capacity building in developing countries. The plan of activities for the coming years will concentrate on developing networks around ongoing projects to foster standardization of methods and exchange of experiences to allow inter-country comparison of data. The National Institute of Allergy and Infectious Diseases (NIAID)/NIatonal Institutes of Health (NIH), the W orld Bank, W HO / AFRO, Roll Back Malaria and international development agencies from TDR partner countries have already confirmed continued support to the Task Force.

MIM/TDR success in bridging the gap between research and control

The crucial question for current malaria control strategists is whether insecticide resistance in malaria vector mosquito populations affects malaria transmission to people using treated bednets. Surprisingly, studies in Côte d’Ivoire in areas with a very high proportion of pyrethroid-resistant An. gambiae showed that pyrethroid treated bednets still reduced entomological malaria inoculation rates and the incidence of malaria episodes in children. Further studies have indicated that the repellency of the insecticide used appears to maintain the efficacy of the bednets. Similar critical research studies are needed to examine the epidemiological impact on malaria of insecticide resistance as it occurs in vector populations in other parts of Africa. Researchers urged that new focal vector control strategies designed to manage insecticide resistance be based on scientific evidence. The lessons learned from the successful management of blackfly insecticide resistance were reviewed. The results of an ongoing large-scale longitudinal study of different residual insecticide house spraying methods and An. albimanus resistance in Mexico were highlighted and may offer applications for African control programmes - so far, after three years, rotation or mosaic spraying of two insecticides has resulted in lower levels of resistance than continuous spraying of a single insecticide. Scientists from the International Centre of Insect Physiology and Ecology in Nairobi, Kenya, reported successful isolation of a number of novel insecticides or mosquito repellents from plant extracts that have chemical properties less likely to induce resistance. At the end of the symposium, scientists were confident that additional collaborative research using geographical information systems (GIS) based data collection could provide predictive computer models of the impact of insecticide resistance useful for designing malaria control strategies in the near future.

WHO/AFRO, Roll Back Malaria and international collaboration.

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www.who.int/tdr/publications

TDR LIMITED DISTRIBUTION

• Good laboratory practice (GLP) training manual (TRAINEE)
  A tool for promoting good laboratory practice (GLP) concepts in disease endemic countries through training.
  TDR/PRD/GLP/01.1B

• Good laboratory practice (GLP) training manual (TRAINER)
  TDR/PRD/GLP/01.1A
  Companion manual to the above, distribution of this trainer’s manual is strictly limited to those who have undertaken the TDR-GLP training of trainers workshop, or who are already GLP experts.

• TDR website CD-ROM (June 2001)
  TDR/GEN/CD/01.1

• TDR Image Library CD-ROM (June 2001)
  TDR/GEN/CD/01.2/Rev.2

TDR VARIOUS

• Reaching maturity - 25 years of TDR
  Dr C. M. Morel

• Snippets of achievement .... examples from the past illuminating the future...
  TDR/GEN/01.1
  Selected from the past 25 years of TDR, these examples demonstrate the way forward under the new TDR strategy.

• TDR - Final Report Series 2000/2001, Portfolio II (No. 21-35)
  TDR/GEN/01.2
  A collection of final reports from projects selected by independent scientific experts.

Also available:
• TDR - Final Report Series 1998/99, Portfolio I (No. 1-20)
  TDR/GEN/00.1

HOW TO OBTAIN PUBLICATIONS

All TDR publications are available to download from the TDR website: www.who.int/tdr/publications/publications or on request from TDR Communications

This manual provides resource material for GLP training. It is based on the Organisation for Economic Cooperation and Development (OECD) principles of good laboratory practice (GLP), which are recognized as the international standard for GLP. The manual is designed to be used at TDR-GLP training workshops (in conjunction with the trainer’s guide - see below). The manual contains an introduction which highlights the history of the OECD principles of GLP, and the fundamental points. Included is training on the resources required (personnel and facilities); preparation of the protocol and standard operating procedures (SOPs); characterization of the test item (its storage, use, quality control, test system); documentation (reporting, deviations from the protocol, indexing, archiving, retrieval); and quality assurance (validity of results must be ensured through all phases of a study). The material is presented in a clear, lively and informative way. Also included are several practical and interesting workshops on how to prepare, review and improve protocols and SOPs, based on actual case studies. Finally there is a self-assessment questionnaire – so the trainee can recognize how much he/she has learned and what issues need clarification, if any. This trainee’s manual will be distributed only through organized GLP training programmes.
Never in recent times has African trypanosomiasis – or sleeping sickness – received so much attention. In February of this year, Bristol-Myers Squibb, along with others, agreed to make and donate 60 000 doses of eflornithine for the treatment of gambiense sleeping sickness. This was followed in May by news that Aventis Pharma AG had signed an agreement worth US$25 million with WHO, to donate drugs and support WHO’s control and research activities (see on page 10).

On the web, three websites stand out as providing quality information on sleeping sickness. The PAAT (Programme Against African Trypanosomiasis) Information System is an international alliance that aims to promote integrated trypanosomiasis control. The website, at www.fao.org/paat/html/home.htm, provides access to country fact sheets, maps, data, position papers, training manuals, the journal ‘Tsetse and Trypanosomiasis Information Quarterly’ and the PAAT newsletter. Another website – www.trypanosome.com – is being developed as a ‘centralized source of information on all kinetoplastid diseases’. Currently hosting the Third Internet Conference on Salivarian Trypanosomes and other Tryanosomatids, plans are under way to use the site for a 4th conference before the end of 2001, and a 5th in 2002. Finally, the Trypanosoma brucei genome project website, at parsun1.path.cam.ac.uk, lists laboratories and researchers, and gives access to information on genome libraries, mapping, sequencing, biological resources, network activities, and links to genome data.

At WHO, African trypanosomiasis appears high on the A-Z Health Topics list of the newly redesigned website, with a disease index page www.who.int/health-topics/aftrypths.htm linking to control, surveillance and basic disease information, and to TDR’s very own web pages on sleeping sickness.

Net News/African trypanosomiasis

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Recent TDR graduates

Awarded a TDR Research Training Grant in 1998, Enock Matovu of Uganda received his PhD in Molecular Parasitology in April 2001. Dr Matovu initiated his studies with Dr Ronald Kaminsky at the Swiss Tropical Institute, Basel, Switzerland, and subsequently completed his studies at the University of Bern under the supervision of Professor Thomas Seebeck. Dr John Enyaru, Livestock Health Research Institute (LRHI), Tororo, Uganda, served as local supervisor for the PhD programme. The topic of Dr Matovu's thesis was 'Investigation of the role of the P2 adenosine transporter in drug refractoriness of Trypanosoma brucei gambiense field isolates'. Dr Matovu's research has made an important contribution to the understanding of drug resistance, and generated a significant number (six or more) of publications in peer reviewed journals. He has now resumed his research duties at LRHI, a major research centre in Africa.

Other recent PhD graduates include:
- Irene Akua Agyepong, Ghana
- Margaret Gyapong, Ghana
- Carlos Alberto Rojas-Arbalaez, Colombia
- Prasanta Mahapatra, India
- Abdisuley Djimde, Mali
- Djibril Sangare, Mali
- Luo Dapeng, China
- Cho Min Naing, Myanmar
- Ousmane Koita, Mali.

Recent TDR Master's graduates include:
- Ilkhom Gafurov, Uzbekistan
- Francisco Saute, Mozambique
- Ferdinand Villanueva Salazar, The Philippines
- Nadjitolnan Othingue, Chad
- Benjamin Vohm, Liberia
- Valentine N dikum N chafor, Cameroon
- Christopher Simoonga, Zambia.

Leprosy: notice to researchers

Remaining stocks of the leprosy laboratory reagent – synthetic PGL-1 disaccharide coupled to bovine serum albumin (BSA), and BSA alone – can now be obtained from the Bernhard Nocht Institute for Tropical Medicine in Germany (it is no longer available from WHO).

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Malaria

Appropriate treatment of children in the early stages of malaria can prevent progression to severe disease and save lives. A home management system in Burkina Faso involved the pre-packaging and selling of antimalarial drugs via trained village volunteers. In the four age groups tested, progression to severe malaria varied between 3.7-1.1% in children who received packaged drugs compared with 8.1-18.2% in the control group. In both groups, progression rates were highest in children aged 7-11 months, and lowest in children aged 4-6 years. Overall, reduction of progression in users of pre-packaged drugs was 53.6%.

A research team in Burkina Faso designed a strategy for the prompt and adequate home treatment of malaria that included retraining of health staff of the local health unit, information/sensitisation meetings and training sessions for all villages, and pre-packaged antimalarial drugs made available to homes through trained village volunteers. The drugs were provided in 4 different colour-coded packs for different age groups, (0-6, 7-11, 12-35 and 36-69 months) following the national treatment guidelines. Each pack contained a full course of treatment, and a label with pictorial instructions on how to administer the drugs. The village volunteer sold the packs at a price agreed with the local health management team, calculated to cover the purchase cost of the drugs and a 10% incentive margin for the volunteer. The aim was to increase access to treatment, improve compliance with recommended dosages and to reduce progression of malaria to complicated forms of the disease, thus reducing the incidence of severe malaria. The impact of the strategy was assessed through case-control epidemiological methods. Some 375 villages participated in the study and at least one volunteer was trained in each village. Of the children that were treated by the village volunteers, 56% complied with the treatment over the correct duration. The rate of progression from uncomplicated malaria (“memalé”) towards complicated malaria (“benoyaba”) was lower in children who were treated with pre-packaged antimalarials (5.1%) compared to those who were not treated with these drugs (11.0%) (OR 0.44, 95% CI 0.33-0.58, P < 0.001). The overall reduction of progression towards severe disease among users of pre-packaged treatment was 53.6%. In the four age groups, the progression rate to severe malaria varied between 3.7-1.1% in children who received pre-packaged drugs, and from 8.1-18.2% in the control group. In both groups, the highest progression rate was noted in children aged 7-11 months, and the lowest in children aged 4-6 years. These results show the feasibility and some degree of effectiveness in the study site. The challenge now is to demonstrate the feasibility, sustainability, cost and effectiveness over time of this home treatment strategy on a much larger scale.

Home treatment of suspected malaria leads to a marked reduction in malaria morbidity and mortality. WHO has recommended the strategy as the most effective single measure for reducing malaria mortality, especially in children.

Reference:
Meeting report: A focused research agenda to influence policy and practice in home management for malaria (8-11 May 2000). Kigali, Kenya. TDR/I/DE/MHW/00/1
TO OUR READERS
We are unfortunately unable to accept for publication in TDRnews announcements (for meetings, new programmes, institutions, publications, etc.) which readers send us. Announcements which relate to research on tropical diseases would clearly be of interest to our readers. However, because of limited space in the newsletter, we regret that we can publish only those concerning events in which TDR is directly involved.

DEADLINES

Steering Committee meetings

Research proposals and reports submitted to TDR are reviewed by the relevant committees. To guarantee review at a given meeting, your proposal should, in general, be received in Geneva two calendar months before the date of the meeting, or earlier in the case of Research Capacity Strengthening. Proposals received later than this may be reviewed at the following meeting of the relevant committee. When preparing your research proposal, it is important to bear in mind that TDR supports goal-oriented research and that your proposal should be consistent with the plans of the relevant committee. Therefore, please study the priorities of the relevant steering committee before submitting your proposal and, if you are applying for the first time, please contact the relevant research manager in TDR with an outline of your proposed research before developing a full proposal.

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<tr>
<th>Meeting date</th>
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<tr>
<td><strong>BASIC AND STRATEGIC RESEARCH</strong></td>
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<tr>
<td>• Molecular Entomology</td>
<td>24-27 Sept 2001</td>
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<tr>
<td>• Pathogenesis and Applied Genomics</td>
<td>Sept 2001</td>
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<tr>
<td>• Social, Economic and Behavioural Research</td>
<td>3-7 June 2002*</td>
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<td><strong>PRODUCT RESEARCH AND DEVELOPMENT</strong></td>
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<td>• Drug Discovery Research</td>
<td>Mar 2002*</td>
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<td>• Vaccine Discovery Research</td>
<td>May 2002</td>
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<tr>
<td>• Diagnostics Research</td>
<td>15 Nov 2001*</td>
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<td><strong>INTERVENTION DEVELOPMENT AND IMPLEMENTATION RESEARCH</strong></td>
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| The current IDE task forces (Malaria Home Management; Severe Malaria; Research on Drug Resistance and Policies; Filariasis Intervention Research; Intervention Research on Chagas Disease; Intervention Research on African Trypanosomiasis; Chemotherapy of Leprosy) are being closed and work will continue under two steering committees, which will meet for the first time in October 2001. Applications and ongoing activities will become incorporated into the new committees as appropriate. Further information will be available in the next issue of TDRnews.

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<tr>
<td>• Research Strengthening Group</td>
<td>11-15 Feb 2002</td>
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<tr>
<td>• Malaria Research Capacity Strengthening in Africa</td>
<td>11-15 Mar 2002</td>
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