Public/private partnership: developing an oral treatment for visceral leishmaniasis

Nina Mattock

A boy whimpers as the doctor searches for the vein in his skinny arm, in which to insert the catheter. He knows what he’s in for: six hours on a drip with shivering and fever. But it’s worth it and he will tolerate it. Otherwise he will die.

Twelve beds, each with a clean green sheet, are neatly arranged along the length of a ward, each with a plastic bottle of golden-coloured fluid suspended above, attached through a length of tube to the vein in a patient’s arm. Twelve patients lie, stoically bidding the month of treatment. There are children, men and women, old and young.

A mass of patients crams a waiting room. Inside, more people. The doctor is well known and patients, from the poorest sectors of society, are referred to him from far away. A young child has received pentostam, first-line treatment for kala-azar. His buttocks, the site for injection of the drug, are sorely ulcerated. Is he one of the 40% who don’t respond to this treatment any more?

A boy’s eyes are earnestly fixed on the doctor’s face. The doctor pronounces him cured after six months of follow-up, and signs him off. The boy looks eager. Now he knows he will live, he is full of hope.

A man with a walrus moustache listens intently to the doctor’s careful explanation about the trial. He looks at the informed consent papers, now translated into Hindi on advice from the local ethics committee, and answers the doctor’s questions. He knows he must receive treatment else he will die. Finally he decides to refer to his family members before consenting to enter the trial.

In the laboratory where samples from the kala-azar patients are analysed, the equipment is arranged systematically around the room. There is a row of little tubes, each labelled clearly, the analyst methodically testing each in turn. He codes, and carefully wraps, each microscope slide made from samples taken from the patients’ spleens. The up-to-date reference books lining the walls already wear an aged look.

This is the setting for imminent Phase III clinical trials of a new oral treatment - miltefosine - for visceral leishmaniasis. The trial is being run by TDR and ASTA Medica, a pharmaceutical company based in Frankfurt, Germany.

The place is Bihar, most poverty-stricken of Indian states and the home of kala-azar. Traveling north from Patna, the capital, to Muzaffapur where there are two kala-azar clinics, one is struck by the fertility of the land, the lush crops of all descriptions, and wonders why the poverty. Hand-in-hand with the poverty goes kala-azar, and north of Muzaffapur, where poverty is perhaps even greater, kala-azar becomes hyperendemic.

The current drugs for kala-azar all have drawbacks. They are administered by injection or infusion and require the patient to be hospitalized - miltefosine will be the first oral treatment. Nearly 40% of cases in Bihar, where the disease is anthropopic, are resistant to treatment with pentostam. The drug causes serious side-effects - mortality in 2.5% of patients and toxicity in 10-15%. The second-line treatment, pentamidine, also has serious side-effects, causing 7-9% mortality and 60% toxicity with irreversible damage such as diabetes.
Amphotericin B is most effective, but is also toxic, causing severe rigor and fever and sometimes anaphylaxis. It requires infusion every other day for 15-20 days, and besides is so expensive as to be unaffordable by 95% of patients. In fact, cost is a problem with all the treatments available; miltefosine will certainly be cheaper, should it reach the market, although the exact price is yet to be determined. Affordable cost for target populations is a key feature of all TDR product profiles.

In preparation for the trial, a workshop was held in Bihar in early July. This was a follow-up to earlier workshops, mentioned in TDR news Nos. 58 and 59, where clinical monitors were trained. Four teams from three kala-azar clinics and a laboratory in Bihar, who constitute the investigators in the trial, and an international team of three from India, Thailand and Viet Nam, who constitute the monitoring team, discussed the finer details of the protocol with representatives of ASTA Medica. The role of the monitors is to oversee the trial at the three centres to ensure that the rights of the patients are protected and that details of all treatments of all patients, including all adverse events, etc., are recorded accurately, and that each and every miltefosine capsule is accounted for. Between them, a monitor will be on site for almost the entire duration of the trial; it is hoped their work will hasten the drug’s passage through regulatory affairs.

How do the doctors view the new oral treatment? “Compliance is good, and earlier trials have shown it to have an overall cure rate greater than 90%.” It is specific, and on the whole not too toxic. “On a toxicity:benefit ratio it scores well and on all parameters should be an ideal first-line drug” said one investigator. “The major drawback is its effect on the foetus, and for this reason it cannot be used as mass outpatient treatment - it will need to be monitored all the time. However, women constitute only 25% of cases (more men are infected owing to their habit of sleeping outside), and among female patients, only 30% are of child-bearing age. Thus a relatively small number of patients will be excluded from treatment on these grounds.”

What do TDR and ASTA gain by working together? TDR provides scientific and organizational input, and tropical diseases know-how, while ASTA provides the full backing and experience of industry. Costs are shared 50:50 between the two partners, and when finally the drug is ready to proceed to the regulatory authorities, the application will be more powerful for being backed by both partners. ASTA feels that WHO, through its relationship with governments, will help bring the drug to the market more quickly, and views its relationship with WHO as an asset and mark of high quality. “It is an example of a relationship that’s really working” said an ASTA representative.

Anopheles gambiae: new targets for genetic analysis for researchers and donors.

There could be all sorts of long-term spin-offs in terms of controlling Plasmodium falciparum, the most virulent form of the malaria parasite, if complete genome information of Anopheles gambiae - the major vector in Africa - becomes available.

In July, TDR hosted an informal meeting of leading genome researchers and representatives of funding organizations, to look at the benefits of sequencing the A. gambiae genome, and at the way in which a coordinated sequencing project might proceed. An informal network, based on the group at the meeting and extended to include other interested parties, will coordinate efforts to initiate and maintain the funding - TDR will take a central, coordinating role in this (initial contact Dr R. Ridley). A small scientific group will coordinate initial applications to appropriate funding agencies. It is hoped to establish a true consortium of funding agencies in the coming year, similar to the P. falciparum genome project.

Work on sequencing and discovery of genes of A. gambiae has already begun in a few laboratories. Priority is being given to work on genes which, in other (resistant) species of Anopheles, are involved in preventing development of the malaria parasite, and to genes associated with insecticide resistance.

Wherever possible and appropriate, it was agreed that research capability strengthening of developing country laboratories in the techniques associated with the genome project will be encouraged. Most likely this will be through training of developing country scientists as participants in the project. The A. gambiae genome is 260Mb (about the same as one large human chromosome), and, depending on the economies achieved in sequencing technology in the coming years, it may cost anything from US$50 - US$90 million to sequence. If the project takes 5 years to complete, then US$10 - US$20 million will need to be raised each year. A limited amount of funding has already been secured, and the US National Institutes of Health has made A. gambiae a top priority organism for future sequencing projects. A number of funding agencies have indicated interest.
Health policy research is essential, ...but difficult  

Erik Blas

Even the best public health drugs, vaccines and health promotion tools will be unsuccessful if health policies and systems are not responsive to the epidemiological realities and the social needs of the population

The research teams who were given grants under a Comparative Studies on Health Sector Reform initiative have fully realized the difficulties of doing health policy research. They have all struggled with problems of defining research questions and what to measure, selecting appropriate methods, inadequate national databases, lack of good tools for holistic analysis of qualitative and quantitative data, and wanting skills and knowledge for analysis and communication of study results.

Since 1996, TDR and the International Clearinghouse for Health Sector Reform Initiatives in Mexico, with funding from Norway, have managed a competitive small grants programme called Comparative Studies on Health Sector Reform. The programme came into being after the Ad Hoc Committee on Health Research found that very little was known about the impact of the many ongoing health sector reform initiatives around the world, in particular, about their impact on poor and disadvantaged population groups. Fifty-four research teams received grants during the three rounds of the programme in 1996, 1997, and 1998.

In 1999, three workshops were held. Two - in Indonesia and Mexico - focused on analysing results, developing writing skills, and writing articles for publication in international scientific peer-reviewed journals. These workshops were for researchers who had started their studies in 1996 and 1997. The third workshop took place in the Philippines and involved research teams who had only recently received their grants. This workshop focused on refining the research questions, and selecting and developing appropriate research methods and tools. A number of lessons can be learned from the workshops:

• Health policy research requires teams of multidisciplinary researchers. In most countries it is difficult to assemble and develop such teams, the main difficulties being related to lack of sustained local resources for policy research. When international resources are available, local researchers are often involved only as junior partners, as, for example, in multicountry projects.
• Health reform initiatives are often ideologically and politically determined and their objectives opaque or ill-defined. They are rarely based on an assessment of the current situation and a precise description of a desired future situation. This frequently makes it difficult for researchers to specify research questions and select appropriate indicators when attempting to evaluate the effect of a particular reform element.
• National information systems are often so weak and scanty that they are of little use in studying the trends and magnitude of a phenomenon. This is often the case for health and economic/financial information systems, as well as for other social information systems, and is a result of general weakness and/or an effect of the reforms themselves. Many teams have found that they have to rely entirely on their own survey results or on secondary analysis of other survey data.
• The holistic nature of most policy research requires application of a diverse range of quantitative and qualitative methods taken from epidemiology and the economic, social, and political sciences. Very few researchers are conversant with all the methods and tools required for a single study, the field of policy research is still new and the literature sparse in this respect. Attempting to draw on tools from different disciplines, the research teams have often found confusing and contradicting terminology, incompatible approaches, and lack of guidance on how to integrate and benefit from the use of multiple tools.

Although the programme on Comparative Studies on Health Sector Reform has been an appropriate and timely response to a research need, much more support, tools development and capacity strengthening are required in the years to come. With the reorganization of WHO and the creation of the Global Alliance on Health Policy Research, much of this work will be supported through the Evidence and Information for Policy cluster (EIP) of WHO, where the Secretariat of the Alliance is also housed.

However, TDR will continue to support all ongoing studies until they are completed, and, in future, will initiate and support basic health policy and systems research projects under the new Steering Committee on Social, Economic and Behavioural Research within the Basic and Strategic Research area of TDR. Efforts will concentrate on health policy and systems research in relation to TDR target diseases, which now include tuberculosis and dengue.
Meetings on *Plasmodium vivax* and *Schistosoma japonicum* in Asia

Two meetings on malaria and schistosomiasis for Asian scientists were held in Manila in June of this year. One of the outcomes of the meetings was a proposal to form a network of workers in *Plasmodium vivax* malaria. The second meeting was designed to stimulate interest among Asian researchers in developing a vaccine for schistosomiasis japonicum.

**Forming a network for *P. vivax* in Asia**

*P. vivax* remains a significant public health problem in parts of Latin America and Asia, where it can account for 40-50% of malaria cases. In addressing the path to a vaccine for *P. vivax* malaria, a number of issues were highlighted:

- The need for greater understanding of the epidemiology of vivax malaria, antigenic polymorphism and sequence diversity of antigens in *P. vivax*, the development of immunity, and interactions between the two main species of *Plasmodium*.

- The role of primate models of vivax malaria. Two models have been developed in Old World monkeys, both using *P. cynomolgi*, a close relative of *P. vivax*, which produces a pattern of disease similar to *P. vivax* in humans. The Toque monkey model has already been used to test candidate vaccines in Asia and the Rhesus monkey model will be used to test different adjuvant formulations and study immune responses in an attempt to identify correlates of protection.

- The unique biological questions posed by *P. vivax*, such as the nature of the characteristic hypnozoite stage, and the total dependence of the species on the presence of the Duffy blood group antigen for invasion of human erythrocytes (to the extent that individuals lacking this antigen - around 95% of people in West Africa - are completely resistant to infection).

- The leading vivax candidate vaccines - including a number of blood-stage candidates, a transmission-blocking candidate and a liver-stage candidate - which could reach clinical trial in 3-5 years. Good manufacturing practice (GMP) methods to produce these candidates on a large enough scale for clinical trials must be developed, as must field sites where the vaccines can be tested.

Funding will have to be found, perhaps from the national governments of the many countries in Asia where *P. vivax* remains a significant public health problem, before research efforts can be expanded. The next meeting of the network will take place at the International Centre for Genetic Engineering and Biotechnology (ICGEB), New Delhi, India in February/March 2000.

**Developing a vaccine for *Schistosoma japonicum***

*Schistosoma japonicum* continues to pose a public health problem in Asia - particularly in parts of China and The Philippines - despite extensive control efforts and the availability of praziquantel. The epidemiological situations in these two countries are quite distinct: in The Philippines, humans appear to be responsible for most of the transmission, although infections are common also in dogs and pigs; whereas in China, water buffalo are the main reservoir host. Even though a wide range of potential vaccine candidate antigens (at least 11) is available, other candidates need to be identified. Of those currently available, the majority have undergone only limited testing, and in general, they have given low to moderate levels of efficacy. Of the available antigens, Sj97 (Paramyosin) is the most advanced in development, but no consensus was reached on which of the other candidates should be progressed towards clinical trials. Six major *S. japonicum* research groups have been identified in China and at least ten others throughout the world.

It was agreed that preliminary screening of antigens should take place in mice, although there was no consensus on the extent of testing in this model. If promising results are obtained in a mouse model, follow-up experiments could be made in larger natural host animal systems (pigs, buffalos). There is a need to develop a standardized protocol and standard operating procedures (SOPs) to allow more direct comparisons of trial results.

The profile of a candidate *S. japonicum* antigen was discussed but there was diversity of opinion over what is expected from the vaccine. In China, the situation seems to call for a vaccine for animal use that would reduce transmission of infection to humans; but in The Philippines, a vaccine is required for human use with the aim of reducing morbidity. Key indicators for any potential vaccine would be impact on acquisition of infection, worm burden, fecundity, and egg output or transmission in the target species and groups for vaccination.

Technical expertise in the production of vaccines has improved in Asia but links between researchers and vaccine manufacturers need to be improved.
Roll Back Malaria update

Taking off in Asia

Activities under WHO’s Roll Back Malaria (RBM) initiative are taking shape in Asia. In Nepal, Indonesia, India, Bangladesh, Sri Lanka and The Philippines, situation analyses are currently being carried out and plans are being made to roll back malaria in 2000. In some of the countries, a few areas have been selected to start with, to try out the new ways of working - i.e. in partnerships, using evidence as the basis for planning, and moving health care closer to the community - before implementing RBM widely in all endemic areas.

In India, RBM will begin in five districts which have a major malaria problem. A national committee to support national Roll Back Malaria activities has been formed between researchers (Indian Council of Medical Research) and people in the National Anti-Malaria Programme. This committee, based in a country which is a seat of malaria expertise, will be able to provide much in the way of operational and strategic support and research know-how to RBM.

In Bangladesh, RBM is beginning in sparsely populated hill tract areas of Banderban and Chittagong where access to health care is very poor. The government is taking the opportunity posed by the malaria situation in these regions, which is exacerbated by drug resistance, and using it as an entry point to improving peoples’ access to health care. About half the populations in these areas are indigenous. At the district level, effective partnerships with private practitioners, politicians, community leaders, school teachers, the press and district Ministry of Health officials are operating to plan for rolling back malaria. Discussions on trials of combinations of drugs and provision of other operational support to the Ministry of Health have begun with a research group (also supported by TDR) based at the medical school in Chittagong. Thus, as in India, the research end of the disease control process is coming closer to the operations end. Since health planning and implementation in Bangladesh occurs through the Health and Population Sector Programme (HPSP), this body will support and channel funding to RBM.

In Myanmar and five other countries of the Mekong sub-region - Cambodia, Lao People’s Democratic Republic, Yunnan province of China, Viet Nam, Thailand - malaria will be tackled in the shared border regions. Here, where the populations are isolated and have little access to health care, malaria is a huge problem and constitutes a major world focus of multidrug resistance. In this region, the emphasis is on moving health care as close to the communities as possible. A consolidated sub-regional Mekong Roll Back Malaria plan is now being prepared, based on the individual country plans. Mekong RBM is being supported by a partnership led by a WHO/UNICEF alliance - an alliance which builds on the comparative advantages of each partner: the technical advantage of WHO and the community-based monitoring, surveillance and advocacy strengths of UNICEF. Other partners such as the US Agency for International Development, Japan International Cooperation Agency and UNDP are also involved.

Fellows appointed

Recently WHO established a Global Health Leadership Fellowship Programme, designed to enable professionals who are potential leaders in health to experience the work of UN agencies and to contribute to the work of these organizations for up to two years. This programme is supported by the UN Foundation, the Rockefeller Foundation and WHO. Four fellows have been appointed to RBM - they are among the first to receive these prestigious awards. Three of the fellows have already taken up their duties:

- Dr Paola Marchesini, from Brazil, who is liaising with the malaria adviser in the WHO Regional Office for the Americas to coordinate RBM activities in Latin America. Paola’s experience is in defining the malaria risk profile of a poor community in north-west Brazil, using qualitative and quantitative methods. She will focus very much on the link between malaria and poverty. RBM activities in Latin America will initially focus on indigenous populations of the Amazonas where morbidity is high, mostly from vivax malaria but, in some countries, from falciparum malaria; countries will develop their plans of action at a meeting in early October.

- Dr Tieman Diarra, from Mali, will focus very much on the community, on getting RBM as close to the home as possible. His expertise is in community level health care and he worked previously on community directed treatment of onchocerciasis with ivermectin, under funding from TDR. Now Tieman is applying his skills in community approaches to malaria control and expanding the use of the community to include distribution. His work is focused at country level - on situation analysis, community responsibility and involvement in control of malaria, development of monitoring tools for community use, and developing partnerships at country level in Africa.

- Dr Bob Taylor, from UK, is working on drug resistance and policies. He is based in TDR and is coordinating all clinical trials of combination chemotherapy of acute, uncomplicated falciparum malaria in Africa. He has a background of general medicine and infectious diseases; most recently he was conducting clinical trials of malaria treatment and prophylaxis in Indonesia.
MMV comes of age

The Medicines for Malaria Venture (MMV), a partnership established between a number of public sector agencies and the pharmaceutical industry and which has been incubated within TDR over the past two years, will soon be established as an independent not-for-profit foundation. It will however still operate from Geneva in close proximity to WHO and TDR. This course of action has been agreed by MMV’s major donors and was given an endorsement and final seal of approval at a meeting of the WHO Cabinet under Dr Brundtland in August. WHO will remain fully engaged as a partner in the venture through membership of MMV’s Governing Board. The process of establishing MMV is a clear example of how the new WHO and TDR can act as catalysts to initiate substantive new activities in partnership with other organizations.

MMV will operate under the paradigm of a not-for-profit business. Its goal is to develop and manage a portfolio of malaria drug discovery and development projects that will yield one new product every five years. These products will be targeted for appropriate and affordable use in disease endemic countries. It is estimated this R&D effort will require $30 million per year in cash, combined with gifts in kind and other resources and expertise from industrial partners. Funding will be focused on a limited number of projects, but at a level (up to several million dollars per project per year) adequate to get the job done. The projects will involve pharmaceutical companies operating in partnership with academic groups and public sector agencies. Products generated through these collaborations will be licensed out to companies for production and commercialization.

MMV currently has funding of $5 million per year over the next few years and has completed its first round of project selection. Several drug discovery projects have been identified for full funding, each with a major pharmaceutical company as a partner. At one stroke this massively increases the level of pharmaceutical industry R&D in malaria. It is anticipated that, with the establishment of MMV as an independent operation in its own right and the demonstrated commitment of the pharmaceutical industry to this process, further funding can be obtained. With this achieved, MMV will have every opportunity of achieving its ultimate goal of registering and commercializing one new antimalarial product every five years and assisting in the global efforts of sustainably reducing the malaria disease burden.

Blister packages of antimalarials for babies produced in partnership with local pharma

Improving management of malaria in the home has been the topic of TDR-sponsored studies in recent years because in Africa, where many children die from malaria, there is often lack of access to formal health services and facilities, lack of drugs in what facilities there are, and provision of poor quality care by drug vendors, shop-keepers and traditional healers. One strategy to improve the management of malaria in the home is to use prepackaged doses of antimalarials.

Earlier TDR studies, reported in TDRnews in 1997 and 1998, showed that prepackaging significantly improves, among other things, compliance with the full course of treatment (also improves drug management and case management, leading to reduced costs and reduced waiting times in dispensaries, etc.), particularly when coupled with provision of better information to prescribers and dispensers of antimalarials.

Now, a package of interventions including prepackaged antimalarials and appropriate information is under pilot study in populations of about 10,000 each in three districts in Ghana, Nigeria and Uganda. Results are expected to indicate whether it is feasible to scale up use of the package, whether it is possible to sustain the interventions, and which methods of providing appropriate information are best. Results of these extensive studies are expected by mid-2000.

For use in the study, the first commercial blister packages of antimalarials for treatment of babies and children have been produced in Nigeria. For children of under one year, the unit dose is 75 mg base chloroquine, used at one tablet per day for 3 days; for children up to 5-6 years, the unit dose is 150 mg base chloroquine, given at one tablet per day for 3 days. The shelf life of the packages is 3-5 years; and the cost of a course of treatment is 50 Naira, equivalent to US$0.5.

Blister packs: Prepackaging of antimalarials improves compliance and helps stop resistance developing.
Vaccine research: WHO takes stock

All WHO-supported efforts in vaccine research will in future be coordinated under one umbrella, together with UNAIDS activities in this field. Currently there are a number of strands of vaccine research throughout both organizations, for instance:

• TDR (from within the WHO cluster on Communicable Diseases) supports research on vaccines for malaria, schistosomiasis and leishmaniasis.
• The WHO cluster on Health Technology and Pharmaceuticals promotes the development and field evaluation of vaccines for major bacterial diseases (such as pneumococcal diseases, diarrhoea caused by e.g. *Shigella* spp. and cholera, TB, meningococcal meningitis) and major viral diseases (such as rotavirus, dengue, measles, Japanese encephalitis). Generic issues such as mucosal and early life immunization, use of DNA/live vectors, and needle-less vaccination procedures are also addressed, as is vaccination-related epidemiological research (in preparation for the introduction of new vaccines in immunization programmes).
• UNAIDS promotes the discovery, development and field evaluation of vaccines for HIV infection.

A unified inter-cluster vaccine research (IVR) initiative will allow more streamlined management of activities, avoiding duplication of effort, reducing the number of steering and advisory committees, and providing opportunities for joint projects which justify high priority and additional resources. The work will be managed functionally by the IVR Coordinator, a post jointly resourced by TDR and V&B (the WHO department of Vaccines and Other Biologicals). Vaccine research will be managed in three categories:

• Exploratory research, concerned with discovery of candidate vaccines for agreed priority diseases (including malaria and TB) and new vaccination approaches (e.g. mucosal immunization).
• Pre-regulatory research, concerned with preclinical and clinical studies of candidate vaccines to assess safety, immunogenicity and efficacy prior to regulatory approval.
• Post-regulatory research, concerned with field studies of new vaccines and development and assessment of new vaccination strategies.

A Global Vaccine Research Forum will meet annually in Montreux, Switzerland, to allow key private and public sector players to share information on the development and application of new technologies and approaches, discuss what needs to be done and make recommendations on global priorities.

TDR adds diagnostic discovery operation to product R&D

Diagnostics, a previously under-represented area at WHO, has become increasingly important for disease control, outbreak detection, and epidemiological surveys. It will now have a focus in TDR, where the portfolio of the Product Research and Development team, led by Dr Win Gutteridge, has been expanded to include a diagnostics component, complementing sister activities in drug and vaccine discovery. The diagnostics operation is managed by Dr Mark Perkins; it will focus initially on previously determined priority areas, but will grow with time to include new diseases as priorities are identified.

The current centrepiece of diagnostic activity is an initiative in tuberculosis. New diagnostics are badly needed to improve detection of both smear-positive and smear-negative cases and to rapidly and inexpensively detect antibiotic resistance. Existing technologies are usually slow, insensitive, or laborious, and delays and errors in diagnosis significantly hamper disease control efforts. The WHO TB diagnostics initiative (TBDI) was launched to accelerate the exploitation of technical advances for the development of new products appropriate for use in low-income countries. TBDI has partnered with industry, academic researchers and public health workers to identify obstacles to the development of tests, to elaborate product performance guidelines and to frame TB diagnostic priorities.

A major focus of TBDI has been the development of the WHO TB specimen bank, a collection of clinical reference materials from well-characterized patients, and the formation of a network of field sites for specimen collection and test evaluation. At present, four sites with experienced personnel in TB diagnosis, care and clinical trials, are enrolling TB patients and symptomatic controls, according to detailed standardized protocols, to collect clinical specimens for the bank. Already more than 6000 aliquots of serum, sputum and saliva (along with associated clinical information) have been collected, processed and cryopreserved. The specimen bank gives test developers access to high-quality pedigreed specimens, a service that will facilitate quality control and speed the development of tests appropriate for settings of endemic disease. A number of promising assays are under development, including simple multi-antigen serologic tests, phage-detection assays, antigen capture systems, and nucleic acid amplification or probe tests; WHO will use the specimen bank and the field site network to perform laboratory and clinical evaluation of the most promising of these in the near future.

The need for improved diagnostic tools for malaria has also been identified as critical in some geographic regions. The new diagnostics programme is co-sponsoring, with Roll Back Malaria and the US Agency for International Development, an international consultation to define the role of rapid diagnostic tests for falciparum and vivax malaria in disease control. The current commercial availability in low-income countries of sensitive qualitative blood tests for plasmodial antigens increases the urgency of defining their most appropriate use.

The TDR diagnostics operation also collaborates with the WHO Communicable Diseases cluster (CDS) on initiatives in other key areas, such as sexually transmitted infections.
Severe malaria

The Task Force on Severe Malaria invites proposals from investigators based in malaria endemic developing countries where morbidity and mortality from severe malaria is high, in the following areas:

• Development and application of a safety register for rectal artesunate, post-registration, on a pilot basis, in a malaria endemic country. The approach, to be developed jointly with WHO, is intended to maximize the collection of adverse experiences related to the drug, and to promote monitoring of drug safety and rational use of drugs in malaria endemic countries. It is intended that the safety register be developed initially for rectal artesunate but be modifiable for oral artesunate and other artemisinin derivatives.

• Development and implementation of a detailed proposal for clinical neurological investigations of patients treated with artesinin compounds and derivatives. Further information is available from TDR Communications in document TDR/TDF/99.1: WHO informal consultation on clinical neurological investigations required for patients treated with artesinin compounds and their derivatives. The studies will be dependent on the facilities available, and the distribution of artesisin drugs, in the country.

• Development and pilot testing, at least in malaria endemic countries, of the distribution system to be used by WHO for making rectal artesunate available, the health education messages to accompany use of this emergency drug once it becomes available, and the packaging and follow-up material to be used to ensure correct treatment and follow-up of emergency treatment with the drug. Development and pilot-tests will be carried out in collaboration with WHO’s Roll Back Malaria project, Drug Action Programme, and Health Promotion Programme.

• It is TDR’s intention to include an in-service training component in the various areas, so that young investigators can become proficient and be able to continue to work in the relevant field of activity after their project is completed.

Researchers interested in collaborating in the above activities should write to:

Dr Melba Gomes, Task Force on Severe Malaria, WHO/TDR, 1211 Geneva 27 - Tel. (41) 22 791 3813/3775 - Fax: (41) 22 791 4774 - E-mail: gomesm@who.int

Paludisme grave

Le Groupe spécial sur le paludisme grave invite les chercheurs amis dans des pays à développement où le paludisme est endémique et où la morbidité et la mortalité dues au paludisme grave sont élevées à soumettre des propositions dans les domaines suivants:

• Mise au point et utilisation, à titre d’essai pilote, d’un registre d’innocuité post-hospitalisation des suppositoires d’artésunate dans un pays d’endémie palustre. Le but de ce projet, qui sera exécuté conjointement avec l’OMS, est d’optimiser la collecte d’informations sur les effets indésirables du médicament et de promouvoir la surveillance de l’inocuité ainsi que l’utilisation rationnelle des médicaments dans les pays d’endémie palustre. En principe, le registre d’inocuité sera d’abord mis au point pour les suppositoires d’artésunate mais il pourra ensuite être adapté pour les préparations orales d’artésunate et d’autres dérivés de l’artésunate.

• Préparation et mise en oeuvre d’un projet détaillé pour des examens neurologiques cliniques de malades traités au moyen de composés d’artésunate et de leurs dérivés. On trouvera de plus amples renseignements à ce sujet dans le document TDR/TDF/99.1: WHO informal consultation on clinical neurologist investigations required for patients treated with artesinin compounds and their derivatives. Les études faites seront fonction des installations disponibles et de la distribution des médicaments à base d’artésunate dans le pays.

• Préparation et mise à l’essai, du moins dans les pays d’endémite palustre, du système qui sera utilisé par l’OMS pour la distribution des suppositoires d’artésunate, des messages d’éducation sanitaire qui seront donnés sur l’utilisation de ce médicament réservé aux situations d’urgence, ainsi que des dispositifs d’emballage et des matériels qui seront utilisés pour veiller à l’administration correcte du médicament et au suivi des traitements administrés en urgence. Les travaux de préparation et les essais pilotes seront exécutés en collaboration avec le projet Faire reculer le paludisme, le Programme d’Action pour les Médicaments essentiels et le Programme de Promotion de la Santé de l’OMS.

Le TDR prévoit des activités de formation en cours d’emploi dans ces différents domaines de sorte que de jeunes chercheurs acquièrent les compétences nécessaires pour pouvoir poursuivre des travaux dans ces domaines une fois le projet achevé. Les chercheurs qui souhaiteraient collaborer aux activités ci-dessus sont priés d’écrire à l’adresse suivante: Dr M. Gomes, Paludisme grave, OMS/TDR, 1211 Genève 27 Tel.: (41) 22 791 3813/3775 - Fax: (41) 22 791 4774 - E-mail: gomesm@who.int

Chagas disease

The Task Force on Chagas Disease will focus its activities on the study of population dynamics of non-domiciliated triatomite vectors of Chagas disease present in the northern part of South America and Central America. It is expected that the entomological data generated will assist national control programmes in adapting the vector control strategies that have been successful in interrupting the vectorial transmission of Chagas disease in the countries of the Southern Cone Initiative.

Research needed:

• Studies on triatomite distribution and house/peridomical infestation by non-domiciliated species.

• Studies on the genetic structure of populations of non-domiciliated triatomites.

• Studies on the sylvatic/domestic mobility of vector populations.

• Studies on the cost-effectiveness of different methods used to ascertain house infestation.

• Studies on the sensitivity of methods used to detect infestation by non-domiciliated species.

• Studies on monitoring insecticide efficacy.

• Effect of bioclimatic changes on domiciliated and non-domiciliated vector populations.

Researchers interested in collaborating in the above activities should write to:

Dr Alvaro Moncayo, Task Force on Operational Research on Chagas Disease, WHO/TDR, 1211 Geneva 27 - Tel. (41) 22 791 3865/3903 - Fax: (41) 22 791 4774 - E-mail: moncayo@who.int

Peaceful Use of Outer Space

While the objectives of tropical diseases research may seem far removed from those of the peaceful uses of outer space, they are closer that one might imagine.

The Third United Nations Conference on the Exploration and Peaceful Uses of Outer Space (UNISPACE III) was held 19-30 July, in Vienna, Austria. This is an occasional meeting (UNISPACE II was held in 1982). At the invitation of Byron Wood, Head of NASA’s Centre for Health Applications of Aerospace Related Technologies (CHARART), TDR participated in the technical discussions on
Peaceful Use of Outer Space

interagency activities, including outreach and training in the use of remote sensing (RS) and geographic information systems (GIS) technologies for research and control of infectious diseases.

Through a series of NASA sponsored workshops, the user community has identified lack of disease-focused training as one of the major obstacles to implementing the use of RS and GIS technologies in health research and disease surveillance and control on a global scale. The UNISPACE Technical discussions gave five past participants in CHAART’s training (including two former and one current TDR trainee) the chance to discuss the opportunities and obstacles they face in developing local RS and GIS capabilities. The five speakers were Ali Hassan (Egypt), Gustavo Bretas (Brazil), Roberto Barrera (Venezuela), Magaran Bagayoko (Mali), and Lou Dapeng (China). Other participants were Louisa Beck, CHAART, and Steven Wayling, TDR. CHAART and TDR collaboration goes back a number of years -- a recent collaborative GIS workshop in China was documented in TDRnews (February 1999).

The presentations at the meeting were excellent, and details will be published in the proceedings of the meeting (to be announced in TDRnews when available). In future, increased collaboration between CHAART and WHO is foreseen in the area of GIS and remote sensing technology.

Screening compounds for anti-parasite activity: submission of samples for testing

TDR presently puts a large amount of resources into facilities that can screen, evaluate and compare samples submitted by many different suppliers. Our specific goals in doing this are two-fold: (i) to provide a service, including data compatible with best-practice methodologies, with informed feedback and evaluation of the data, to investigators who feel they may have active anti-parasite compounds; and (ii) to enable TDR to identify classes of compound worthy of future funding for medicinal chemistry studies, and to move optimized compounds into clinical development.

To improve its efficiency in carrying out these tasks, the Drug Discovery Research (DDR) arm of TDR/PRD has recently made some changes in the organization of its screening network.

The DDR Steering Committee now funds two types of screening facility. In the first, compounds whose anti-parasite activities have not previously been studied can be tested for effects in vitro against several parasites (Plasmodium, Leishmania, Trypanosoma, nematode species), with the possibility of some initial in vivo follow-up tests if positive results are obtained. The in vitro test system has a medium-throughput capacity -- that is, tests can be made on up to several hundred compounds in a batch. About 5 mg of each compound is needed for the integrated in vitro screen on different parasites. At this stage, compounds can be tested ‘blind’, without knowledge of their chemical structures. The screens can also be adapted to testing natural product (e.g. plant) extracts.

In the second type of screening facility, more detailed follow-up tests can be carried out on compounds that have already shown interesting effects in initial tests. These laboratories are specialized in particular disease indications (e.g. malaria, leishmaniasis, African trypanosomiasis, Chagas disease, filariasis), and most have facilities for both in vitro and detailed in vivo evaluation of selected compounds. The minimum amount of material needed for these more detailed studies vary from about 50 - 200 mg, depending on the tests required. In general, structural information on compounds submitted for these follow-up tests should be made known to TDR prior to testing, so that duplication of tests on the same material submitted by different suppliers, or on already-characterized compounds, can be avoided.

The procedure for submitting samples for screening has also been simplified. Generally, what is required for initial tests is to fill out a one-page data sheet for each sample (or, in some cases, class of sample) submitted, giving information on items such as the quantity of compound submitted, its solubility and handling instructions. Further information on how to submit samples, and data sheets (in electronic version, for Mac or PC) can be obtained from Dr J.R.L. Pink (pinkr@who.int), WHO/TDR/DDR, Avenue Appia, 1211 Geneva 27, Switzerland.

Can lymphatic filariasis and onchocerciasis be eliminated together?

In Africa, programmes for elimination of lymphatic filariasis could become integrated with those already ongoing for the control of onchocerciasis. The two diseases have much in common, particularly when it comes to strategies for control. TDR recently organized a meeting of experts from nine African countries and international organizations to discuss issues relating to the integration and make recommendations to the Onchocerciasis Control Programme in West Africa (OCP) and the African Programme for Onchocerciasis Control (APOC).

What are the two diseases common? For both, the foci in Africa are in the rural areas, and there is some evidence of overlap of distribution. The main strategy for intervention is annual, single-dose chemotherapy with ivermectin (with or without albendazole for filariasis), and the community directed treatment (ComDT) approach is suitable for delivery of treatment for both diseases. Some process indicators for monitoring the two diseases are also the same (e.g. treatment coverage rates).

Recommendations included giving priority to mapping of lymphatic filariasis using RAGFIL, the method of rapid epidemiological assessment and mapping under development by TDR (see article on next page). TDR and the Control Prevention and Eradication department in CDS will coordinate the mapping, which will be carried out in three sub-regional areas (West, East and Central Africa).

Recommended also was the use of ComDT for filariasis, as was further research in filariasis on: use of the albendazole/ivermectin drug combination regimen; the effect of treatment on various stages in the course of infection; progression of the disease; strategies for treatment in Loa loa endemic areas where the risks of adverse side-reactions are higher; and the effect of use of insecticide-treated materials (e.g. bednets) on the transmission of infection. Pilot studies to test the feasibility and cost effectiveness of an integrated onchocerciasis control/lymphatic filariasis elimination programme will be necessary.
Update on rapid assessment of Bancroftian filariasis

A method to rapidly assess the geographical distribution of lymphatic filariasis is crucial to determine which communities to target with mass treatment. We first reported on a proposed method known as RAGFIL in TDRnews of June 1998. With this method, the magnitude of the filariasis problem in a small sample of endemic communities is first assessed and the results then extrapolated to the whole area or country using GIS and advanced spatial analysis techniques. In this way a map, contoured according to filariasis distribution, is obtained which can be used as the basis for planning of control activities. Such a rapid mapping method has already proved of value in onchocerciasis control and should, because of the clustered distribution of the disease, be of value also in control of lymphatic filariasis.

Selection of a random sample of communities is based on use of a grid, which is overlaid on a map of the whole country. After selecting the communities according to the intersection points of the grid, different procedures are used to rapidly assess the prevalence of filariasis in each – either clinical examination (of 50-100 adult males per community for hydrocele) or an antigen assay (using the immunochromatographic card test or ICT) by health workers. Using the prevalence data so obtained, the spatial correlation pattern is assessed using semivariance analysis (which relates the difference between prevalence in pairs of villages to the distance between them) and the technique of kriging is then used to predict prevalence at any place in the whole area/country.

A multicountry study to test the proposed method has been carried out in Ghana, India, Myanmar and Tanzania. Two grids were compared – a coarser 50x50km grid and a more refined 25x25km grid, to see if the coarser grid would be adequate. In each country, the study covered an area of 200x200km. Clinical assessment and antigen assays by health workers were performed in 81 communities selected on the basis of the 25 km² grid (which includes the communities sampled with the 50 km² grid).

The results showed that RAGFIL was effective in rapidly clarifying the geographical distribution of Bancroftian filariasis, and in mapping out the approximate contours of different levels of endemcity, including areas of no or very low risk. Hence, it provides a rapid method for providing an objective basis for planning and prioritization of filariasis control.

The results from Ghana, Tanzania and Myanmar indicate that examination for hydroceles and the ICT are equally effective, but the results from India were less clear. The epidemiological maps produced with the 50 km² grid were similar to those made on the basis of data from the 25 km² grid and it was concluded that the coarse 50km² grid could be adequate for rapid mapping of Bancroftian filariasis.

The researchers recommended the use of RAGFIL in filariasis control. However, as the study sites were limited in size, some further evaluation and fine tuning of the method should be included in the first largescale applications of RAGFIL. Other recommendations include developing regional approaches to rapid mapping of Bancroftian filariasis to ensure efficient mapping of cross-border foci, because filariasis foci can be very large; further research on improved mapping methods; and exploration of the use of climate and other environmental factors to predict endemcity.

Progress towards interrupting transmission of Chagas disease in Venezuela

Progress made in interrupting transmission of Chagas disease in the Andean countries was reported at the second meeting of the Intergovernment Commission of the Andean Countries Initiative, which took place 8-9 April, in Maracay, Venezuela. The following essential data for Venezuela were presented:

- Reduction of incidence of infection in 0-4 year-olds, 1992-97, was 90%.
- Reduction in prevalence of infected blood in blood banks, 1993-98, was 78%.
- The infestation rates in ten states in the country are now less than 1.1%, although in two states (Barinas and Portuguesa) they are still more than 2.9% (the goal is to attain rates of less than 2%).
- The infection rate of the main vector (R. prolixus) by T. cruzi, is very low (0.1% - 0.6%) in all the states except Barinas (where the infection rate is 3.4%).

![ANDEAN COUNTRIES INITIATIVE](image)

**VENEZUELA: Interruption of Transmission:**
Infection rates in 0-4 year old group, 1992-1996

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<th>Year</th>
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<tr>
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<td>Molecular Entomology (BCV)</td>
<td>18-20 Sep 2000</td>
<td>18 Jul 2000</td>
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<td>Immunology of Mycobacterial Diseases (IMMYC)</td>
<td>Apr 2000 *</td>
<td>Feb 2000 *</td>
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<td><strong>Product Research and Development</strong></td>
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<td>Drugs Discovery Research (DDR)</td>
<td>Mar 2000 *</td>
<td>21 Jan 2000*</td>
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<td>Vaccines Discovery Research (VDR)</td>
<td>May 2000 *</td>
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<td><strong>Intervention Development and Evaluation (IDE) ** (formerly Applied Field Research)</strong></td>
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<td>Research on Drug Resistance and Policies (CHEMAL-R)</td>
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<td>Severe Malaria (SEVERE)</td>
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<td>Gender-Sensitive Interventions (GENDER) ***</td>
<td>Jan 2000 *</td>
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<td>Community-Directed Treatment of Filariases (COMDT)</td>
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<td>Chemotherapy of Leprosy (THEMYC)</td>
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<td>Malaria Research Capability Strengthening in Africa (MIM)</td>
<td>10-12 Mar 2000</td>
<td>6 Dec 99</td>
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* Tentative
** IDE Task Forces may call for specific research proposals at any time of the year according to their workplans
*** Renewals only
**Erratum**

In our article on *Rolling off to a quick start* in *TDRnews* No. 59, we erroneously reported that the meeting on malaria held in Alexandria was an RBM inception meeting for North African countries. In fact, the RBM inception meeting for North African countries was that held in Nairobi, in conjunction with countries of East Africa and the WHO regional offices for Africa and the Eastern Mediterranean. An RBM meeting for the Asian countries of WHO’s Eastern Mediterranean region take place in September 1999.

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**To our readers**

We are unfortunately unable to accept for publication 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.

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**TDR Information and Workplans**

*(Please tick boxes for documents you wish to receive)*

**Language:** □ English  □ French

- □ TDR news
- □ African Trypanosomiasis - Tropical Disease Research - Progress 1997-98 - 30 pages
- □ Chagas disease - Tropical Disease Research - Progress 1997-98 - 34 pages
- □ Filariases - Tropical Disease Research - Progress 1997-98 - 40 pages
- □ Leishmaniasis - Tropical Disease Research - Progress 1997-98 - 32 pages
- □ Leprosy - Tropical Disease Research - Progress 1997-98 - 24 pages
- □ Malaria - Tropical Disease Research - Progress 1997-98 - 42 pages
- □ Schistosomiasis - Tropical Disease Research - Progress 1997-98 - 28 pages

**TDR Workplans**

**Basic & Strategic Research**
- □ Functional Genomics
- □ Pathogenesis
- □ Molecular Entomology

**Product Research and Development**
- □ Drug Discovery Research
- □ Vaccine Discovery Research

**Intervention Development and Evaluation**
- □ Gender-sensitive Interventions
- □ Malaria Home Management
- □ Community-Directed Treatment of Filariases
- □ Severe Malaria
- □ Research on Drug Resistance and Policies
- □ Applied Research on Chagas Disease

**Research Capability Strengthening**
- □ Grant information and workplan

**Information for potential applicants**
- □ Schistosomiasis research grants

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