The interface between research and control can be a sticking point - whereas some tools move rapidly from research into control practice, others move only slowly or not at all. Traditionally, research stops with the ‘proof of principle’ – when the scientist has found evidence to support the theory – and the publication. But it has to reach beyond the bench for the results of research (the tools) to be put into policy and practice. Drawing on the lessons of 25 years of experience, TDR is now putting emphasis on the transfer of results into action through ‘implementation research’.

Implementation research is a question of both implementation of research (i.e. moving results into practice e.g. their incorporation into policy for disease control), and of research on implementation (i.e. research on tools according to the needs of control programmes). It is a question of joint agenda-setting, and of defining the characteristics of desired tools before they are developed. In the new TDR strategy, implementation research will become a major focus.

For a tool to have an impact, the research and public health sectors must work closely together. As an example, we can take multidrug therapy (MDT) for leprosy, which TDR helped to develop. There is little doubt that the transition of this tool from the research bench to implementation was facilitated by involving both the control (WHO leprosy control programme) and research (TDR) sectors in the Scientific Working Group on Chemotherapy of Leprosy. Furthermore, research on Chagas disease and onchocerciasis has always been conducted in close collaboration with control programmes. Today, these three diseases are approaching elimination.

A tool that TDR developed and that entered use only slowly is the insecticide-treated bednet. Although developed some years ago and shown to be very effective in malaria, this tool is only now being taken up by the control sector. This illustrates the importance of having effective working relationships between the research and control sectors. The tool is presumably also of use for other infections, e.g. in leishmaniasis, but is not promoted in this way.

Thus, a main lesson in putting tools into action that TDR has learned, is the need for research and disease control sectors to work closely together, despite their specializations. These sectors each have their own, very different, issues to consider, but implementation research should be the domain of both, and the research mentality must extend to the public health community.

The problem of unused tools – a ‘tool’ being the results produced from research, whether it be a tangible instrument such as...
TDR at the interface of research and control

a drug or vaccine, or more nebulous instruments such as knowledge or skills - was noted by TDR’s Third External Review Committee in 1998. Since then, TDR has placed emphasis on working closely with control. In filariasis, for instance, research is now carried out in close collaboration with the department of Control, Prevention and Eradication (CPE) in WHO, through a Filariasis Coordinating Group; recently a poll was carried out to seek the views of experts in filariasis control and research around the world to ensure that the needs of control are being met by research (see page 12).

The recently developed diagnostics initiatives in TDR are also organized in close collaboration with disease control programmes, around the principle of responding to their needs and through joint formulation of performance characteristics of desired tests. A recent meeting on malaria diagnostics, co-sponsored with Roll Back Malaria (see TDRnews No. 61), highlighted opportunities for close links between laboratory and operational research and disease control. Field assessments of the utility and impact of diagnostics are necessarily conducted jointly with disease control programmes.

In tuberculosis, the recent Scientific Working Group recommended that TDR develop a conceptual framework for the research-control link and priority setting in health systems and services research to ensure that the research agenda is driven by expressed control needs (see page 3).

In malaria, TDR works closely with WHO’s Roll Back Malaria (RBM) movement. RBM also places much emphasis on the research/control link; one of the principal components of the RBM strategy is to encourage evidence-based actions against malaria at country level. As the control sector is not always able to provide the necessary evidence on which to base its interventions, RBM is encouraging the formation of technical support groups at national level, comprised of researchers, technical experts and malaria control programme staff, to identify priority operational problems and implement evidence-based interventions. Already in Asia, a joint meeting of research and control staff has been held in Chiang Mai (Box 1). Annexed to this meeting was a TDR task force meeting on drug resistance and policy for both control and research workers. TDR will work together with RBM in calling for, reviewing, selecting and funding proposals on control-oriented research, and in monitoring progress and impact (Box 2).

Thus, TDR has begun to bridge the gap and strengthen the links between research and control, and will be investing in a new type of expertise - to work at the interface of research and control. The Research Capability Strengthening team, for example, will be strengthened in public health expertise to better respond to the new TDR vision and ensure that the needs of control programmes are efficiently addressed. A revised call for RCS grant applications will be issued by July 2000 to reflect the new strategic orientation of TDR.

Already the new approach is making some headway – TDR’s Scientific and Technical Advisory Committee, in February 2000, noted ‘seamless lines of cooperation between TDR on the one side, and RBM and other control activities, such as filariasis, onchocerciasis and Chagas, on the other side’.

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Box 1  RBM control/research meeting in Chiang Mai

All countries participating in this meeting (Bangladesh, India, Indonesia, Myanmar, Nepal, Papua New Guinea, Philippines, Sri Lanka, Thailand) were represented by national technical expertise including researchers as well as malaria control staff. Three important technical challenges were taken up by Roll Back Malaria (RBM) during the meeting:

- reduction of risk in transmission
- drug resistance and policy
- surveillance, information management and epidemics.

In each of these areas, each country will constitute a technical support group comprising malaria control and ministry of health staff as well as researchers, thus bringing together all malaria expertise in the country without distinction as to research or control, where all are equal. Regional networks will be formed from the national groups - an action which is strongly supported by the WHO regional offices.

The meeting was attended by development partners of RBM who subscribe to the idea of research/control interaction, including USAID (US Agency for International Development), JICA (Japan International Cooperation Agency), and the EC (European Community).

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Box 2  RBM control/research partnership grants

The first call for control/research partnership applications will be to South America, but the initiative will soon be extended to other regions.

This first call (to be issued shortly) will be for monitoring of chloroquine resistance in vivax and falciparum malaria for the purpose of improving antimalarial drug policy. The call will be issued jointly by RBM, TDR and the WHO Regional Office for the Americas/Pan American Health Organization (AMRO/PAHO).

Applications are expected from ministries of health, jointly with a research partner, and possibly with a research training component for the ministry partner (i.e. the application is to be initiated by the ministry partner, in contrast to the normal TDR grant, where the application is initiated by the research partner).
TDR research on dengue: Recommendations of a scientific working group

Research needs in dengue prevention and control, and the directions that TDR research should take, were the subject of a scientific working group meeting in April 2000. Dengue was included in the TDR disease portfolio in June 1999, on recommendation of the TDR Joint Coordinating Board.

Dengue is a major public health challenge that will increase in magnitude as a result of demographic change including increasing, and frequently unplanned, urbanization. Today, the infection is found in over 100 countries and territories, and causes an estimated 50-100 million cases a year. A first infection sensitizes a person so that approximately 2% of second infections with a different serotype (there are four serotypes) go on to develop vascular permeability – i.e. dengue haemorrhagic fever (DHF), which can be fatal.

Research needs pertinent to DHF control that can be achieved with TDR’s comparative advantage, were considered with reference to TDR functional areas. In Basic and Strategic Research, research on pathogenesis of DHF is expected to be conducted largely in dengue-endemic countries on clinical cases, and to include studies of humoral and cell-mediated immune responses, factors that predict onset of DHF, and viral virulence. In entomology, there is need for research on molecular/ genetic methods to reduce Aedes aegypti (the dengue vector) populations and/or vectorial capacity (e.g. anti-sense RNA), as well as on the longevity and density of A. aegypti, and transmission of the four dengue viruses. In Social, Economic and Behavioural Research and Intervention Development and Evaluation research, TDR is expected to promote multicentre studies for developing and evaluating community-based mosquito control strategies that would lead to effective and sustainable community participation in vector control, identification of appropriate entomological indicators, and appropriate behaviour change with regard to mosquito control.

In Product Research and Development, a high priority is to develop tests to detect primary or secondary dengue infections early in the course of infection. Also, new treatment approaches need to be considered, e.g. new antivirals and anti-mediators directed at the causes of increased vascular permeability or altered homeostasis. Vaccine development remains a high priority within WHO. Much work is already ongoing on live attenuated vaccines, and it was recommended that TDR accelerate development of the current candidates, in collaboration with the current research groups, by appointing a task force with responsibilities for the design and conduct of phase I-III trials. Complementary to this is the need to appoint a working committee to establish guidelines for the safety of dengue vaccines.

TB transplant to TDR: rapid take, minimal rejection

Tuberculosis is slotting rapidly into the TDR portfolio and ‘culture’. In February 2000, a scientific working group on TB met to make recommendations for research and capability strengthening activities in TDR. It clarified TDR’s role and niche among the ongoing alliances and initiatives in TB. Later in the month, the recommendations were presented to the TDR Scientific and Technical Advisory Committee (STAC). Altogether, TDR input to TB research is now looking quite distinct, with significant funds already identified to support some of the proposed work. Further interest in TB will definitely have been stimulated by the Ministerial Conference on TB and Sustainable Development held in Amsterdam, 22-24 March 2000, from where the final declaration called for acceleration of both basic and operational research. The scientific working group (SWG) recommended that TDR adopt a two-pronged policy on TB research:

- health systems and services research (HSSR) – being the most neglected area in TB research.
- research and development (R&D) of new diagnostics, drugs and vaccines – being an area where TDR has considerable comparative advantage.

The HSSR agenda should be driven by the needs arising from TB control programmes, and the SWG recommended that TDR develop a conceptual framework for the necessary research/control link. TB-HSSR also needs to be established in high burden countries (especially the 22 countries that account for 80% of the world’s TB burden) e.g. through building up national TB research institutions, expanding assistance for protocol development, and linking with other TDR diseases. In R&D of new tools for TB, the first priority is diagnostics. Particularly needed are a replacement for the sputum smear test, a rapid test for rifampicin sensitivity, and evaluations of marketed products, as well as expansion of the specimen bank established by the TB diagnostics initiative and already transferred to TDR. Second, equal priority is to both drugs and vaccines. In drugs, the particular need is to evaluate available antibiotics and ‘off the shelf’ drugs, and to encourage production by small pharmaceutical companies in the South. TDR will work with other actors in this area – the IFPMA/WHO Roundtable, Stop TB, and the Global Alliance for TB Drug Development. As a partner in the Global Alliance, TDR is delighted to announce the award (on March 24) of US$25 million to the Alliance by the Bill and Melinda Gates Foundation. With respect to vaccines, product profiles, animal models and correlates of protection are specifically needed, and the SWG encouraged TDR to look for ways to speed up vaccine development.

Continued on page 15
Natural products for the treatment of parasitic diseases

Traditional medicines, often herbal in origin, are widely used the world over, yet it has often been difficult to establish how effective they really are. Considering parasitic diseases alone, the examples of quinine and artemisinin suggest that herbal medicines can be medically very effective, and underline that plants have been important sources of new pharmaceuticals. To develop a strategy for more effective, evidence-based use of traditional medicines against malaria, TDR and the Global Initiative on Traditional Systems of Health (Oxford, UK) have coordinated a Research Initiative on Traditional Anti-malarials (RITAM), and co-sponsored a meeting in Moshi, Tanzania, in November 1999. Funding for the meeting was provided by TDR, the Multilateral Initiative on Malaria (MIM), the Rockefeller and Nuffield Foundations and others. A review of the meeting can be found in the Lancet (2000, 355: 761), and a full report can be found on the MIM and TDR web sites: http://mim.nih.gov/, http://www.who.int/tdr or is available on request from TDR (see page 20).

TDR is planning to organize a follow-up meeting to the Moshi conference, with the title: Natural Products in the Treatment of Parasitic Diseases: Traditional Medicine and Pharmaceutical Medicine Perspectives. The aims of this meeting will be to build on the Moshi results – for example by updating a database of traditional treatments for malaria established by RITAM. Specific topics will include regulatory guidelines for traditional medicines and natural products, case studies of their use, clinical efficacy and safety, screening methods and preclinical evaluation. There will also be sessions on the costs and benefits of fractionating mixtures and optimizing activity, and on development, production and commercialization of traditional medicines. Participants will consider how the clinical efficacy and safety of traditional treatments for anti-parasitic diseases can best be investigated, and how the benefits of an active traditional treatment, or its purified active ingredients, can best be disseminated to larger numbers of patients while keeping cost and quality acceptable.

The meeting will be held in Geneva, 28-30 August, 2000, and convene about 20 invited participants. The hope is that issues of common interest to both traditional medicine and pharmaceutical medicine disciplines will be identified and discussed so that the two disciplines can better interact to develop safe, effective treatments for tropical parasitic diseases including (but not limited to) malaria.

MMV: US$25 million of Gates funding leads to further opportunities

The Medicines for Malaria Venture (MMV) - the public/private partnership for discovery and development of new antimalarial drugs, which was incubated within TDR for several years until established as an independent foundation in November 1999 - received a major boost in March 2000 when it was awarded US$25 million over five years from the Bill and Melinda Gates Foundation.

Last year, MMV selected three drug discovery projects for funding at a total cost of around US$4 million a year. A new round of project selection has been initiated this year (see: www.malariamedicines.org for details) and applications have been requested for both malaria drug discovery and malaria drug development projects. The goal of MMV is to develop a portfolio of drug discovery and development projects that will enable the registration and commercialization of one new antimalarial drug every five years. This requires funding to rise to a level of US$30 million per year over the next four years.


New drug for severe malaria

Artemotil (previously β-arteether), a new type of antimalarial, has been registered for use in severe malaria. The drug, developed by TDR with designated finance from the Government of the Netherlands and in collaboration with a Dutch pharmaceutical company, was approved for use by the Dutch regulatory authorities. News of the approval came through during TDR’s Scientific and Technical Advisory Committee meeting in February 2000.
MIM participants meet in Ouagadougou

In early March 2000, 20 principal investigators supported by the Multilateral Initiative on Malaria (MIM)/TDR Task Force on Malaria Research Capability Strengthening met with task force members in Ouagadougou. Each principal investigator (PI) gave a brief presentation of his/her project and progress to date. This was the first gathering of task force members and PIs to review progress of the projects. A formal review and deliberation by the task force was held during the following week.

Speeches delivered at the meeting, by the Minister of Health of Burkina Faso, the WHO Representative in Burkina Faso, and Ogobara Doumbia, Minister of Health of Burkina Faso, the WHO

In conjunction with this meeting was a workshop on handling and managing biological materials, arranged by the Malaria Research and Reference Reagent Resource Centre (MR4) – a National Institute for Allergies and Infectious Diseases/National Institutes of Health (NIAID/NIH) contract hold by the American Type Culture Collection (ATCC), of which the overall objective is to provide standard reagents for the global malaria research community. The workshop was designed for investigators who were new to malaria research or were preparing for collaborative projects on malaria, with priority given to MIM/TDR project participants; it was attended by African researchers and health workers involved in handling and managing laboratory reagents and clinical specimens.

On the first day of the MIM/TDR meeting, MR4 organized a symposium on creating new research opportunities in malaria, which included discussion of the role of biological resource centres in Africa, where they might be situated, and the problems that might be encountered in their operation. The symposium served to introduce MR4 to PIs and the malaria research community in Africa – there were 45 participants from 21 countries. Topics of specialist lectures and discussions included intellectual property issues and research involving human subjects.

Additional information can be obtained from Dr Fabio Zicker, Coordinator RCS: zicker@who.int

INTERVENTION OF THE WHO REPRESENTATIVE
Opening of the MIM meeting on capacity building in malaria research
OUAGADOUGOU, 6-8 MARCH 2000

Minister of Health
Director of TDR at WHO
Manager of MIM in TDR

Ladies and gentlemen,

On behalf of the Regional Director of WHO for Africa I welcome you.

After the meeting in Dakar in 1997 when the world’s malaria experts met to launch the Multilateral Initiative on Malaria (MIM), and the Durban meeting in 1999 which enabled African research workers to explain their work and exchange views with colleagues from elsewhere, it is now the turn of Ouagadougou to host the meeting of the main researchers in MIM. This meeting will show what progress has been made in projects financed under the Multilateral Initiative on Malaria; it will review the financing strategy of the Task Force and foster exchanges among research groups.

As you know, malaria is one of the main causes of mortality in children, and political decision-makers in northern as well as southern countries will pay close attention to the results of your research.

In its current strategy renewing malaria control, WHO in recent years has helped strengthen the work of national malaria control programmes through its Roll Back Malaria programme, with the emphasis on building up basic health facilities. I wish you much success in your research to provide better guidance for malaria control.

Thank you.

WHO Representative in Burkina Faso

INTERVENTION DU REPRESENTANT DE L’OMS
Ouverture réunion MIM sur le renforcement de la capacité de recherche contre le paludisme
OUAGADOUGOU, 6 AU 8 MARS 2000

Monsieur le Ministre de la Santé
Monsieur le Directeur de l’OMS/TDR
Monsieur le Manager du MIM/TDR

Mesdames et Messieurs les participants,

Au nom du Directeur Régional de l’OMS pour l’Afrique, permettez-moi de vous souhaiter tout d’abord la bienvenue.

Après la rencontre de Dakar en 1997 où l’expertise mondiale sur le paludisme s’est retrouvée pour lancer l’Initiative multilatérale sur le paludisme (MIM) et la rencontre de Durban en 1999 qui a donné l’opportunité aux chercheurs africains d’exposer leurs travaux et d’avoir des échanges avec leurs collègues venus d’ailleurs, c’est au tour de Ouagadougou d’abriter la rencontre des investigateurs principaux du MIM. Cette rencontre aura pour but de faire le point sur l’état d’avancement des projets financés dans le cadre de l’Initiative Multilatérale sur le Paludisme et de revoir la stratégie de financement du Groupe spécial et de faciliter les échanges d’expériences des différents groupes de recherches.

Comme vous le savez, le paludisme est l’une des premières causes de mortalité chez les enfants. Ceci pour vous dire qu’une importance particulière sera accordée aux résultats de vos recherches par les décideurs politiques tant des pays du Nord que du Sud.

Dans sa stratégie actuelle de relance de la lutte contre le paludisme, l’OMS a contribué ces dernières années à renforcer l’action des programmes nationaux de lutte contre le paludisme, à travers son programme accéléré dénommé “Faire reculer le paludisme”, au cours duquel l’accent a été mis sur le renforcement des structures sanitaires de base.

Pour terminer, je souhaite beaucoup de succès à vos travaux de recherche afin de mieux guider la lutte contre le paludisme.

Je vous remercie.

Le Représentant de l’OMS au Burkina Faso
Monsieur le Ministre,

1) Au nom de la Communauté scientifique et des partenaires africains du MIM, nous avons l’honneur de vous adresser tout notre gratitude pour avoir accepté l’organisation de la réunion annuelle du MIM au Burkina Faso.

2) En effet, l’Initiative multilatérale sur le paludisme en Afrique a été initiée à Dakar (Sénégal) en 1997. At the dawn of the third millennium, malaria remains a major public health problem in our countries. In order to develop better control tools, the endemic countries must have local scientific capacities to deal with this major disease. Research will be one of the main areas of socio-economic development in the third millennium.

The international community has placed its trust in African researchers. We therefore have a great responsibility and although this great historic responsibility fills us with trepidation, we are ready to take up the challenge serenely.

In order to achieve this noble objective, we need the support of our political authorities and decision-makers.

Malaria knows no frontiers, which is why scientific networks have been set up under this initiative; they are operational. There are now no more physical or linguistic barriers between African scientists.

For the first time scientists are working hand in hand with national control programme officials. This new way of validating the results of research in our countries should be greatly encouraged.

Your country, Burkina Faso, has just set up a national centre for training and research in malaria, after the example of its elder brother in Mali (established in 1992). We know all the talented young researchers who work there. Most of them trained in Bamako. We ask for your support to help them gain scientific maturity so that they can make a substantial contribution to development of malaria control in their respective countries.

On behalf of all my colleagues I thank you for the hospitality and the special attention you have personally devoted to our work.

Ouagadougou, 8 March 2000

Ogobara Doumbo, MD, PhD
Professor and principal MIM researcher in Mali

Message from participants at the TDR/MIM Symposium, Ouagadougou, 6-8 March 2000:
Closing ceremony, under the aegis of the Minister of Health of Burkina Faso

For the first time scientists are working hand in hand with national control programme officials. This new way of validating the results of research in our countries should be greatly encouraged.

Your Excellency,

(1) On behalf of the scientific community and the African partners of MIM, we have the honour of expressing our gratitude to you for allowing the annual meeting of the MIM to be held in Burkina Faso.

(2) The Multilateral Initiative on Malaria in Africa was initiated in Dakar, Senegal, in 1997. At the dawn of the third millennium, malaria remains a major public health problem in our countries. In order to develop better control tools, the endemic countries must have local scientific capacities to deal with this major disease. Research will be one of the main areas of socio-economic development in the third millennium.

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Message des participants du Symposium TDR/MIM, Ouagadougou, 6-8 mars 2000 :
Cérémonie de clôture, sous la haute-présidence de Monsieur le Ministre de la Santé de la République du Burkina Faso

Un Centre National de Formation et de Recherche sur le Paludisme, à l’image de son grand frère malien (créé en 1992). Nous connaissons tous les jeunes chercheurs talentueux qui y travaillent. Ils sont pour la plupart d’entre eux passés par l’école de Bamako. Nous sollicitons votre soutien pour leur permettre d’avoir une maturité scientifique afin qu’ils puissent largement contribuer aux développements de la lutte antipaludique dans leurs pays.

Je vous remercie au nom de tous mes collègues pour l’hospitalité et l’attention particulière que vous avez personnellement porté à nos travaux.

Ouagadougou, le 8 mars 2000

Ogobara Doumbo, Md, PhD
Professeur et chercheur principal MIM au Mali
MINISTRY OF HEALTH
GENERAL SECRETARIAT
DIRECTORATE GENERAL OF PUBLIC HEALTH
NATIONAL CENTRE FOR RESEARCH AND TRAINING IN MALARIA

Closing speech for the meeting of MIM principal investigators by the Minister of Health, Burkina Faso

Director of TDR/WHO
Manager of MIM/TDR
WHO Representative
Representatives of the National Institutes of Health of the United States of America
Ladies and gentlemen,

It is a great pleasure for me to chair this closing session of your meeting, in which you have reviewed progress made in the projects financed under the Multilateral Initiative on Malaria, and the financing strategy of the Task Force. Over these two days you have also been able to exchange information on the aspects of research in which you specialize.

Your projects cover all the issues that could give rise to effective methods for controlling malaria, from drug resistance in parasites to study of the vector, via exploration of immune response in the host. You have used new techniques to improve the quality of your results. Your projects afford many training opportunities for personnel, thus increasing the critical mass of African researchers in malaria. It is my heartfelt wish that African researchers take the opportunity of this forum of scientific expression and research capacity building for their institutions, that is offered to them by the international community through MIM. I wish to congratulate all the principal researchers who represent African science on malaria. I wish also to thank Dr Carlos Morel for the constant support of TDR to research activities in Burkina Faso. I am grateful to the manager of MIM/TDR for choosing our country to host this meeting. It is an honour to our country and to our research facilities, especially the National Centre for Research and Training in Malaria (CNRFP).

This centre, which in spite of its youth is our reference centre, strives to solve all the malaria problems in our country; on this subject, may I pay tribute to Professor Mario Coluzzi for his invaluable support to the centre.

Finally, I wish to express my deep gratitude to the outgoing president of the Task Force, Professor Ayoade Oduola.

I wish every success to the incoming president, Dr Fred Binka, and his associates.

I wish you a safe return to your countries and I declare the Ouagadougou meeting of principal MIM researchers closed.

Thank you.
The Minister of Health

MINISTERE DE LA SANTE
SECRETARIAT GENERAL
DIRECTION GÉNÉRALE DE SANTE PUBLIQUE
CENTRE NATIONAL DE RECHERCHE ET DE FORMATION SUR LE PALUDISME

Discours de clôture de la rencontre des principaux investigateurs du MIM de Monsieur le Ministre de la Santé du Burkina Faso

Monsieur le Directeur de l’OMS/TDR,
Monsieur le Manager du MIM/TDR,
Monsieur le Représentant de l’OMS,
Monsieur le Représentant des Instituts Nationaux de Santé (NIH) - États Unis d’Amérique,
Monsieurs et Messieurs les participants,

C’est un grand plaisir pour moi de pouvoir présider la clôture de votre rencontre, une rencontre au cours de laquelle vous avez fait le bilan sur l’état d’avancement des projets financés dans le cadre de l’Initiative multilatérale sur le paludisme, sur la stratégie de financement du Groupe spécial. Vous avez également pu, au cours de ces deux jours, échanger vos expériences respectives dans les différents volets de recherche dont vous êtes les spécialistes.

De la résistance du parasite aux médicaments en passant par l’exploration des mécanismes immunitaires de l’hôte et l’étude du vecteur, toutes les questions dont les réponses permettront la mise au point de méthodes de luttes efficaces contre le paludisme ont été abordées dans vos différents projets. Aussi, vous avez fait usage de techniques nouvelles pour améliorer la qualité de vos résultats. Je ne saurais passer sous silence les multiples occasions de formations des cadres qui offrent vos projets dans le but d’accroître la masse critique de chercheurs africains dans le domaine du paludisme. Je souhaite vivement que les chercheurs africains saisissent cette opportunité de tribune d’expression scientifique et de renforcement des capacités de recherche de leurs institutions que leur offre la communauté internationale à travers le MIM. Je voudrais ici congratuler tous les investigateurs principaux qui représentent la science africaine du paludisme. Je voudrais à cette occasion remercier Monsieur Carlos Morel pour l’appui constant de sa structure, le TDR, aux activités de recherche au Burkina Faso. J’exprime ma gratitude à Monsieur le Manager du MIM/TDR pour le choix de notre pays pour abriter cette rencontre. C’est un honneur que vous faites à notre pays et à ses structures de recherche, en particulier le Centre National de Recherche et de Formation sur le Paludisme (CNRFP). Ce Centre, qui est notre structure de référence malgré sa jeunesse, oeuvre à la résolution des problèmes de paludisme dans notre pays. Parlant du Centre National...
## Chagas disease

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

The research needed in this respect is as follows:

- Studies on triatomine distribution and house/peridomicile infestation by non-domiciliated species.
- Studies on the genetic structure of populations of non-domiciliated triatomines.
- Studies on the sylvatic/domestic mobility of vector populations.
- Studies on the cost-effectiveness of different methods to ascertain house infestation.
- Studies on the sensitivity of methods to detect infestation by non-domiciliated species.
- Studies on the monitoring of insecticide efficacy.
- The 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
Manager
Task Force on Intervention Research on Chagas Disease
TDR, World Health Organization
1211 Geneva 27
Tel: (41-22) 791-3865/3903 Fax: (41-22) 791-4774
E-mail: moncayoa@who.ch

## African trypanosomiasis

1. Assessment of the cost effectiveness of integration of the current passive and active surveillance strategies into primary and multipurpose health care in order to bring about improvement of surveillance coverage.
3. Assessment of the efficacy and cost-effectiveness of using the CATT and CIATT for serodiagnosis at community level and comparative evaluation, as follows:
   - CATT in whole blood test standardization
   - Comparison between CATT PBS and CATT EDTA
   - Comparison of CATT whole blood and CATT latex.
4. Prospective cohort studies of seropositive, parasitologically non-confirmed cases to evaluate the epidemiological impact of treatment.
5. Development of new protocols for drug treatment (for both old and new formulations), taking into account efficacy, and safety and socio-economic considerations.

7. Determination of the impact of decentralization on the control of sleeping sickness and development of strategies to control the disease in urban areas.
8. Standardization of new parameters to predict the evolution towards late-stage disease, and development of simple diagnostic tests based on urine and saliva.
9. Standardization of parameters of urine for patient follow-up in order to reduce the duration of clinical care.
10. Combination of mapping of endemicity of African trypanosomiasis with other programme information such as dracunculiasis eradication and onchocerciasis elimination.
11. Development of decision analysis tools for the determination of a cost-effective sequence of diagnostic tests and case management.

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

Dr Alvaro Moncayo
Manager
Task Force on Intervention Research on African Trypanosomiasis
TDR, World Health Organization
1211 Geneva 27
Tel: (41-22) 791-3865/3903 Fax: (41-22) 791-4774
E-mail: moncayoa@who.ch

## Filariasis intervention research

Following a recent review of filariasis and onchocerciasis research needs (see page 12), the Task Force on Filariasis Intervention Research has developed a new workplan. The following are research activities in the workplan for which the Task Force invites proposals for review during its next meeting in September 2000:

- Research on integration of drug delivery for lymphatic filariasis and onchocerciasis with other disease control programmes, studies on optimal integration of ComDT of onchocerciasis within the health system, and evaluations of ongoing experiments in different countries in which community directed distributors are given additional health care responsibilities (e.g. treatment of malaria).
- Drug delivery in India: (i) studies on methods for identifying target populations for treatment and drug delivery in urban areas, and (ii) studies on drug delivery in rural areas that build on the recommendations of a recently completed multicentre study in India (recommendations available from the TF manager).
- Studies to assess trends in levels of transmission and infection with W. bancrofti during 4-6 years of mass treatment with ivermectin and albendazole in areas with Anopheles transmitted filariasis in Africa.
- Studies on community-based management of lymphedema and related adenolymphangitis (the TF intends to launch a multi-country study on this issue. The teams that will be invited to join the study will be selected on the basis of the received proposals. A draft protocol for the study is available from the TF manager).
- Development of simple methods for monitoring coverage, including rapid assessment methods for identifying low coverage villages and reliable methods for community census.
- Field testing of existing diagnostics and other monitoring tools for both W. bancrofti and B. malayi, and development of more effective approaches to their application.
- Development and testing of methods for community self-monitoring.
- Development and field testing of rapid assessment methods for Loa loa.

The next meeting of the Task Force is in September 2000 and the deadline for submission of proposals is 15 August 2000. Researchers interested in collaborating in the above activities should write to:

Dr Hans Remmej, Manager, Task Force on Filariasis Intervention Research, WHO/TDR, 1211 Geneva 27, Switzerland. Tel. (41 22) 791 3815 Fax (41 22) 791 4774 - E-mail: Remmej@who.int
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* Tentative

** IDE Task Forces may call for specific research proposals at any time of the year according to their workplans

*** Progress reports and renewals only
Africa is the continent most severely affected by malaria. It is for this reason that Roll Back Malaria (RBM) has Africa as its main focus. The RBM movement has now been in existence for 18 months or so. What has been happening in Africa under this banner?

From the vantage point of building on past initiatives in malaria in Africa, of which a not insignificant number have materialized in recent years, several indicators of RBM activity are apparent. A prime sign is that greater political will has manifested. Of the 50 countries and territories in Africa affected by malaria, 24 heads of state have committed themselves to active participation in the RBM partnership. Ministers of health have taken part in RBM inception activities, and governments have taken steps to increase financial and human resources for malaria.

In April 2000, the government of Nigeria hosted the African Summit on RBM in Abuja, demonstrating political commitment at the highest level (see box).

Another indicator of RBM action is that, in the last 18 months, existing partnerships in malaria have been strengthened and new partners have become involved - at global, regional and country levels. In African countries, there has been an increase in NGO, private sector, and non-health sector involvement (e.g. collaboration with ministries of education, communication, finance, agriculture, environment), and non-traditional partners have become involved too e.g. UNESCO (United Nations Educational, Scientific and Cultural Organization) in Sudan. Also, joint actions in malaria between neighbouring countries have taken shape, e.g. the Health for Peace Initiative in West Africa (The Gambia, Senegal, Guinea-Bissau, Guinea Conakry), the Lumbombo Development Initiative in Southern Africa (South Africa, Mozambique, Swaziland), and a North African initiative (Morocco, Algeria, Tunisia, Libya, Egypt).

Countries have also begun to develop RBM strategy. Whereas many countries in Africa are hyperendemic for malaria, others, in the North, have already eradicated, or nearly eradicated, the disease – so the strategy varies with the local situation. Within countries, technical committees and networks have sprung up to help develop local strategies to roll back malaria, or prevent its return, according to the situation. So far five countries have completed strategy development while many others are reviewing their national strategies in line with RBM. Most are placing emphasis on boosting interventions based on evidence.

Africa is a continent which often faces complex emergency situations in malaria, e.g. drug resistance, epidemics, war situations - at least ten countries south of the Sahara have experienced malaria epidemics with unacceptably high mortality rates in the last few years. Under the RBM banner, two of these countries were able to report, by the end of 1999, adequate preparedness for complex emergency situations, and at least ten others are in the process of doing so.

These activities so far constitute the ‘inception’ phase of RBM. Soon the ‘implementation’ phase will commence, when the strategies will be implemented. This will be the real testing ground for the RBM concept and strategy, when mortality and morbidity indicators become important.

Is there any reason to believe that these latest WHO efforts, under RBM, will have more lasting effects than earlier WHO efforts in Africa? ‘The beauty of RBM is that there is no blueprint’, says Dr Kabir Cham of RBM/WHO. ‘There is no one way of going about things any longer - challenges are addressed depending on the situation

African children can now look towards a healthier future? Continued on page 15
Chlorproguanil/dapsone (LAPDAP) multicentre phase III clinical trial under way in Africa

In March 2000, the pivotal Phase III clinical trial of chlorproguanil/dapsone (LAPDAP) for the treatment of uncomplicated *Plasmodium falciparum* malaria was initiated in five African clinical trial sites.

The goal is to develop a ‘new’ safe and effective alternative to chloroquine and sulphadoxine/pyrimethamine (S/P) for the treatment of falciparum malaria in Africa. Chloroquine has been the principal drug for decades, but it no longer achieves adequate cure rates across much of the continent. However, it remains the first-line drug in many national malaria control programmes. Some African countries, such as Malawi, have replaced chloroquine with S/P, but unfortunately this compound has the drawback of rapidly selecting resistant organisms, due to its slow elimination from the body and simple molecular mechanism of resistance. This was the case in Thailand where S/P had a useful lifetime of less than 10 years.

This double blind Phase III trial is designed to measure the safety and efficacy of LAPDAP for 3 days as compared to treatment with a single dose (the standard course) of S/P. The trial will randomize - in a 4:1 ratio of LAPDAP:S/P - 2000 African children aged 12-120 months. The trial sites are in Gabon, Kenya, Malawi, Nigeria and United Republic of Tanzania.

Both chlorproguanil and dapsone, which work by inhibition of folate metabolism, are agents with a long history of safe and efficacious use for malaria and leprosy respectively. The hypothesis that these two agents in combination would be effective against falciparum malaria, was proven by Watkins, Winstanley and colleagues at the Wellcome Trust laboratories in Nairobi. It has been proposed that LAPDAP may have the following significant advantages over the existing S/P treatment regimen: more rapid elimination of chlorproguanil, chlorocyloguanil (its active metabolite), and dapsone; and retention of activity of chlorocyloguanil against certain pyrimethamine resistant parasites.

The LAPDAP development project is a public/private sector collaboration between WHO/TDR, the UK Department for International Development, and SmithKline Beecham.

A suitable macrofilaricide?

A drug that is used in veterinary medicine has been shown to have interesting macrofilaricidal activity in animal models of onchocerciasis and lymphatic filariasis, and is now ready for evaluation in humans.

Final results of moxidectin trials in animal models were presented to the TDR Product Research and Development Committee in March 2000. These preclinical studies have shown that the compound fulfils the criteria for a potential macrofilaricide (i.e. a drug that kills adult filarial worms) and has unique ‘selling points’:

- a single treatment produces ‘slow’ death of adult worms in girds and dogs, and sterilization of worms in cattle.
- compared to ivermectin (a microfilaricide, which kills larval stages of filarial worms), moxidectin has a considerably longer half life in plasma - 20 days compared to 2 days - allowing for the possibility of either less frequent treatment, or ‘higher efficacy’ with similar frequency of treatment, compared to ivermectin.
- it is effective in animal helminth infections that are resistant to ivermectin.

Moxidectin is a fermentation product from *Streptomyces cyaenogriseus* spp noncyanogenus. Chemically it is related to other nematocides – the avermectins – but instead of a disaccharide side chain it has unique methoxine- and dimethylbutenyl-side chains.

A suitable, safe and effective macrofilaricide would allow more impact to be made on controlling filarial diseases than is currently possible using microfilaricides, even though the latter are effective. This is because adult worms can survive in the human host for a number of years (more than 10 in the case of onchocerciasis) and treatment with microfilaricides has to be maintained for the lifetime of the adult worm.

Currently moxidectin is only available in veterinary formulations, but discussions are under way with the company that produces them to obtain material for humans use. As soon as clinical grade moxidectin becomes available, clinical trials will start.
Filarial update

A poll of research needs for lymphatic filariasis

The bid to eliminate lymphatic filariasis is picking up speed, and, in order to ensure that the new TDR Task Force on Filariasis Intervention Research addresses priority needs of all partners involved, a poll of these needs has been carried out.

The survey began with the compilation of a list of 48 needs by a group from the research and control departments in WHO and associated external experts. After further review and updating in-house, the list was emailed to 81 experts in filariasis control and research around the world for their comments, additional needs, and ranking according to importance for filariasis elimination. Of the 50% who responded, half were experts from filariasis endemic countries. There was general agreement that the list of research needs is comprehensive.

The priority research needs, according to this census, are shown in the diagram.

The group reviewed the results and suggested who could or should address which priority needs, whether in WHO or elsewhere, and a workplan was developed for a TDR task force on filariasis elimination research. Briefly:

- **TDR Product Development** will test combinations of microfilaricides and look for a macrofilaricide (see page 11 for news of a potential macrofilaricide).
- **TDR Filaria Intervention Research** will address drug delivery strategies, strategies for filariasis elimination, methods and criteria for monitoring and evaluation, community-based management of chronic disease and methods of mapping. Most of these issues overlap with the research needs for onchocerciasis control and the Task Force will cover both diseases.

A number of other organizations have already expressed interest in addressing some of the remaining research needs.

Community directed treatment of lymphatic filariasis in Africa

A multicentre study has shown community directed treatment (ComDT - in which a community takes control of its own treatment) of lymphatic filariasis to be highly effective in Africa. In filariasis, ComDT is entirely feasible because the treatment is simple, consisting of a single dose taken just once a year. The study compared mass treatment of communities (with a single dose of ivermectin) through the public health system (HST) with mass treatment through a community directed system introduced by the public health services (ComDT/HS). In ComDT/HS, the community decides on and selects its own distributors, who distribute the drug at the convenience of the community, while the health services are responsible for introducing the concept to the community, training the distributors and helping with monitoring and supervision. The study was carried out in Kenya and Ghana.

Results indicated that the HST system was not able to deliver sufficient treatment for elimination purposes, but that the ComDT/HS system was able to reach levels of treatment coverage that appeared to be sufficient for filariasis elimination. One factor in the success of ComDT/HS concerns distance of a community from the nearest health services facility – in villages located over 5km from a health facility, coverage is poor unless the community distributes the treatment. As one health worker commented ‘... going house to house was the best thing because you reach even those who cannot walk. The people liked it because they felt it was not interfering with their daily duties, the drug distributors were people they knew and thus had faith in’.

Key issues arising included lack of information – not only for the community, but also for many of those involved in delivery of treatment (from both the health services and community) who did not know the exact purpose of treatment.

Both communities and health staff appreciated the ComDT/HS approach, despite initial scepticism. Compliance with treatment was not a problem; as one man said ‘I think the drug is a very good one because my leg was getting swollen and very painful but now I can walk with very few problems, and so I am very happy. I was even going for more but they told me that I must take it only once a year’.

Recommendations included exploring to what extent ComDT introduced through the health services is relevant for drug distribution for other endemic diseases, and how the element of implementation through the health services can strengthen ComDT in onchocerciasis control.

A report of the study will soon be available from TDR on request: Community directed treatment of lymphatic filariasis in Africa: Report of a multicentre study.
Artemether protects against schistosomiasis infection

Since the early 1990s, evidence has been accumulating for the prophylactic effects of the artemisins (artesunate, artemether) against *Schistosoma japonicum* infections. In addition to their well-known effect against the malaria parasite, these drugs also kill juvenile forms (schistosomula) of schistosomes: artemisins have now been shown to be effective against *S. mansoni* in animals and humans, while laboratory work on *S. haematobium* has been completed and field studies are under way, with support from TDR. Since these schistosome species are responsible for the majority of infections worldwide, and are the predominant species in Africa, the outcome could be a major impact on control of schistosomiasis worldwide.

In a study on the use of artemether in *S. mansoni* infections in hamsters and mice, very few animals developed schistosomiasis when treated during the first month after infection. The parasite was particularly susceptible between weeks 3 and 4 after infection. Single treatment with artemether gave cure rates of up to 82%, but multiple therapy raised this to almost 100% in all cases. In animals with repeated infection, representing more closely the real situation in nature, there was almost complete protection. Previous studies using *S. mansoni* had shown no effect of artemether, but had concentrated on the adult parasite, not the schistosomula. A clinical trial in Côte d’Ivoire has confirmed this potential of artemether to significantly reduce *S. mansoni* infection.

Artemether is already in use as an antimalarial and has a good safety profile. Praziquantel is a drug that has been used for schistosomiasis for more than two decades. It also is safe and effective, but has to be given repeatedly due to rapid reinfec-
tion. Combined treatment with the two drugs has been studied in rabbits infected with *S. japonicum* parasites at different developmental stages (young stages and adults), representing the natural situation in areas where infection occurs throughout the year. Using this animal model, combined treatment with the two drugs significantly increased the effects of the individual drugs.

Praziquantel and artemether affect schistosomes at different developmental stages, and work surprisingly well together in this respect. Praziquantel affects the adult parasites, but also the very young stage (realistically only during the first day in the host) - the very times at which artemether has no effect. Conversely, artemether affects the juvenile stages (except immediately after infec-
tion), thereby blocking the development of the adult stages. Whether the two drugs can actually be given simultaneously - whether there is any pharmacological interaction - remains to be investigated. Since artemether blocks the development of adult worms, even a limited period of treatment with this drug could theoretically wipe out parasite transmission in certain areas. Praziquantel on the other hand, cannot stop the infection, but remains the cornerstone of control since it retards the development of morbidity.

The different species of parasite are sensitive to artemether for slightly different lengths of time. *S. japonicum* is susceptible up to 21 days of age, while *S. mansoni* responds to the drug for up to 42 days, and *S. haematobium*, due to the longer time it takes to develop into the adult, has an even longer period of sensitivity.

In areas that are endemic for both malaria and schistosomiasis, the use of artemether is precluded because of the possibility that its regular use might contribute to the development of resistance of the malaria parasite. On the other hand, the drug could safely be recommended for use in schistosomiasis in areas where there is no regular malaria transmission (e.g. in China, southern Brazil, countries north of the Sahara, parts of the Middle East). Of particular interest are those areas where human schistosomiasis has been very much reduced, but final eradication has proved difficult (e.g. in Saudi Arabia, Morocco), where artemether could contribute to breaking its transmission; it could also play an important role in the control of schistosomiasis in Egypt.

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**RCS grants, 2000-2001**

The Research Capability Strengthening (RCS) unit of the Special Programme for Research and Training in Tropical Diseases (TDR) is going through a strategic planning process to better define policies and priorities in relation to its funding and operating procedures.

Concerning applications for RCS grants, including Research Training Grants (RTG), a revised workplan will be issued by July 2000. The revised workplan and application forms will be available from the TDR website at [http://www.who.int/tdr/grants](http://www.who.int/tdr/grants), or by contacting TDR directly.

Applications submitted and received in RCS before the revised workplan is available will be retained by RCS and then reviewed in the light of the revised requirements when these are determined, after which the principal investigator will be contacted regarding eligibility of the proposal.

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Brazil to be declared free of Chagas disease

Epidemiological and entomological data presented by the Brazilian Ministry of Health at the Ninth Meeting of the Intergovernmental Commission of the Southern Cone Initiative, held in Rio de Janeiro in March 2000, confirmed that six of the twelve endemic states in Brazil are free of vectorial transmission of Chagas disease and that a further four states will become free during this year. The total ten states are: Goias, Matto Grosso, Matto Grosso do Sul, Paraiba, Sao Paulo, Rio de Janeiro, Minas Gerais, Piaui, Pernambuco and Rio Grande do Sul. The remaining two states are Bahia and Tocantins. An international commission in charge of evaluating the interruption of vectorial transmission in the ten states will make a field visit to confirm the above report. Certification is expected to be phased - state by state - until the end of 2000.

The number of domiciliated Triatoma infestans (the main vector of Chagas disease in Brazil) captured by the control programme in the whole country in 1998 was only 562. This represents an average of one insect per 10,000 houses surveyed, i.e. an infestation rate far below the minimum required for effective transmission of the parasite to new patients. This result confirms the interruption of vectorial transmission of Chagas disease in Brazil.

The prevalence of human Trypanosoma cruzi infection in the 0-7 year age group for the whole country in 1999 was 0.28% as compared with 5.0% in 1980. This represents a 95% reduction of incidence since 1980 (see Graph).

Furthermore, the prevalence rate of infected blood in blood banks in the country has decreased by 90%, from 7.0% in 1980 to 0.73% in 1998. Spraying activities are now concentrated in the states of Bahia and Tocantins, where the municipalities that are still positive for the vector are clustered.

Improving good clinical practices

Research in developing countries is becoming increasingly important for solving urgent health problems. Consequently, it is necessary to strengthen good clinical practice (GCP) and capacity for reviewing research ethics in these countries. TDR and UNAIDS have already launched a number of initiatives aimed at strengthening capacities for implementing GCP (see TDRnews No. 59) and the ethical review process (see TDRnews No. 61).

A recent (January 2000) meeting in Bangkok, Thailand, was convened to help strengthen ethics committees in Asian and Western Pacific countries. The focus was on developing internationally operational, country- and institution-specific guidelines and standard operating procedures.

Participants commented on the draft TDR/WHO Operational guidelines for ethics committees that review biomedical research, which were finalized by the drafting committees of these guidelines the next day. Another activity that took place at the same time was to establish the Forum on Ethics Committees in Asia and the Western Pacific (FERCAP) in order to foster improved understanding and implementation of ethical review of biomedical research in Asian and Western Pacific countries.

Earlier meetings on this theme have included the Seminar on Ethical Review of Biomedical Research in Asia and Western Pacific Countries, August 1999, organized by TDR/WHO and held in Chiang Mai, Thailand; an Interim Meeting of the Asian and Western Pacific Forum for Members of Ethical Review Committees, held in November 1999 in Bethesda, USA, in the context of the Global Forum on Bioethics in Research; and the Seminar on Ethical Review of Biomedical Research in African Countries held in November 1999 in Arusha, United Republic of Tanzania, which followed the Health Research Ethics in Africa Seminar organized by the African Malaria Vaccine Testing Network.

TDR has, since the Bangkok meeting, published the Operational guidelines for ethics committees that review biomedical research (see page 20) and distributed them to all WHO member countries. This is a first step. More crucial is to build capacity among both researchers and research ethics committee members, and TDR plans to hold a first workshop for implementing the guidelines in Asia during July 27-8, 2000, followed by a training course (July 31-August 4) in ethics for researchers, ethics committee members and medical students. The course will cover the ethics of research on human subjects and scientific integrity. It is an attempt to begin the process of strengthening ethical review in biomedical research in developing countries.

Bourses RCS, 2000-2001

L’unité Renforcement du potentiel de recherche (RCS) du Programme spécial de recherche et de formation concernant les maladies tropicales (TDR) a entamé un processus de planification stratégique afin de mieux définir ses politiques et priorités de financement et ses modalités de fonctionnement.

En ce qui concerne les demandes de bourses RCS, y compris les bourses de formation à la recherche (RTG), un plan de travail révisé sera publié d’ici juillet 2000. Le plan de travail révisé et les formulaires de demande seront disponibles sur le site Web du TDR, à l’adresse: http://www.who.int/tdr/grants, ou directement auprès du TDR.

Les candidatures déposées à RCS avant que le plan de travail révisé ne soit disponible seront conservées et examinées au vu des nouvelles conditions une fois qu’elles auront été fixées. Il sera pris contact avec le chercheur principal pour lui faire savoir si sa demande est recevable.
Roll Back Malaria
Continued from page 10

and resources of the country; the emphasis is on dialogue and flexibility. RBM targets high-risk populations - such as under-fives and pregnant women - so today the country and its people are the centre of the action. Another new focus is on processes leading to sustainability rather than sustainability itself.

How much emphasis is placed on research in RBM in Africa? TDR and RBM work together in a number of areas, such as product research and home management of malaria. The Abuja plan of action promotes, amongst other things, strengthening of research, and in particular, development of vaccines and exploration of traditional medicines for malaria. At the summit, the heads of state and government in African countries called upon development partners, amongst other things, to:

- invest additional resources to stimulate the development of malaria vaccines appropriate for Africa and provide similar incentives for other anti-malaria technologies
- strengthen and sustain collaboration of research institutions within Africa and with partner institutions throughout the world, and
- foster the collaboration of research institutions with agencies implementing Roll Back Malaria to ensure full utilization of research knowledge and programme experience.

New drug targets and leads for kinetoplastid drug discovery

Of the 1223 new drugs (new chemical entities) which entered the market between 1975 and 1996, only 11 were directed against parasites responsible for the diseases in TDR’s mandate. Of these, only three were for treatment of diseases caused by kinetoplastid organisms: eflornithine for African trypanosomiasis, and benzimidazole and nifurtimox, both for Chagas disease. The current treatments for kinetoplastid-caused diseases are not ideal: they are either very expensive, not effective in many patients, or have severe side-effects. To consider ways of improving this situation, TDR’s Drug Discovery Research team organized a meeting on new chemical leads for kinetoplastid diseases, which was held in Heidelberg in October 1999. Sixteen researchers from Europe, North and South America, China and Africa met to review kinetoplastid drug discovery, present their latest results and discuss ways of improving the current situation.

The immediate outlook is best for Chagas disease. On the one hand, control efforts are not ideal: they are either very expensive, not effective in many patients, or have severe side-effects. To consider ways of improving this situation, TDR’s Drug Discovery Research team organized a meeting on new chemical leads for kinetoplastid diseases, which was held in Heidelberg in October 1999. Sixteen researchers from Europe, North and South America, China and Africa met to review kinetoplastid drug discovery, present their latest results and discuss ways of improving the current situation.

The immediate outlook is best for Chagas disease. On the one hand, control efforts have been very successful in reducing transmission in large areas of the southern cone of South America (see page 14 and earlier issues of TDR news), and on the other hand, there are some promising new anti-fungal azoles which, in animal models, can clearly establish Trypanosoma cruzi infections. It may be possible to move one or more of these drugs rapidly into clinical testing for these infections.

In contrast, the situation is not so promising for chronic African trypanosomiasis. As reported in TDR news No. 61, the production of eflornithine - an effective but expensive drug - has been guaranteed for the next five years by an agreement between WHO, Médecins sans Frontières and the producing company (Hoechst Marion Roussel). However, the drug is expensive to manufacture, and is not effective against the Trypanosoma brucei rhodesiense form of the disease prevalent in central and eastern Africa. Trybazine, a lead molecule developed in China, is effective against acute trypanosomiasis in rodents and cattle, and ongoing work on the development of analogues that effectively cross the blood-brain barrier and show less toxicity, may produce drugs suitable for use in humans.

Current treatments for the life-threatening, visceral form of leishmaniasis (antimonials or the expensive amphotericin B/lipid formulation) are administered by a series of injections over several weeks. However, recent clinical trials of an oral formulation of miltefosine have given promising results in treatment of visceral leishmaniasis. Nevertheless, there is still a need for treatments which have fewer side effects and shorter treatment courses.

Participants at the meeting presented work on several promising target molecules or metabolic pathways of kinetoplastids: trypanothione reductase and polyamine metabolism, farnesyl transferase and protein prenylation, sterol metabolism, topoisomerases, proteases, and cAMP signalling pathways. However, the number of interesting lead molecules based on selective interference with these targets or pathways is very small. Manufacturers do not find the economic prospects of developing such leads attractive, and academic laboratories have difficulties in funding and patenting such work. In some cases, if a lead is found, further development can be undertaken by innovative public/private partnerships involving manufacturers and public agencies (see TDR news No. 61). Additional efforts, particularly in the form of collaborations between medicinal chemistry and biological laboratories, to find interesting lead molecules for anti-kinetoplastid drug development are needed.

Scientists who believe they have projects that are relevant to drug discovery for any of the kinetoplastid diseases, and for which molecular targets and/or lead molecules have been identified, are urged to contact Richard Pink (pinkr@who.int) for advice and information on TDR’s potential ability to advance the project.

1 Lancet 1999, 354: 164

TDR research on dengue
Continued from page 3

Research Capability Strengthening activities supported by TDR are needed for all areas of research outlined above (e.g. field research capability for vector control and entomology, and training in clinical epidemiology, basic flavivirology and cellular and humoral immunology). Finally, it was recommended that other important needed research on dengue, such as case management, clinico-epidemiological diagnosis, and surveillance, should be addressed by other players in the dengue research arena.
In memoriam:
Dr Robert N. Mshana

It was with the deepest sadness that WHO/TDR staff and fellow committee members learned of the tragic loss of Dr Robert N. Mshana and his assistant executive secretary in the crash of Kenya Airways Flight KQ 431 off the coast of Abidjan, Côte d’Ivoire, Sunday 30th January 2000. Dr Mshana was returning to Lagos from Harare on an official mission in his capacity as Executive Secretary of the Organization of African Unity (OAU)/Scientific, Technical and Research Commission (STRC).

Dr Mshana was born in 1954 in Arusha, Tanzania, and studied medicine in Dar-es-Salaam. He obtained his MSc and PhD degrees in Oslo, Norway, in the field of mycobacterial immunology, followed by additional short-term training in Switzerland, London and New York. Robert was a truly international person, working as a research scientist in Ethiopia, Gabon and Côte d’Ivoire before moving on to develop policies and guidelines on behalf of the STRC of the OAU in Lagos, Nigeria.

Dr Mshana also contributed immensely to WHO/TDR’s R&D activities from 1982 onwards, serving on the Steering Committees for Immunology of Leprosy (IMMLEP), Immunology of Mycobacterial Infections (IMMYC) and Vaccine Discovery Research (VDR).

We will greatly miss Robert, with his keen sense of humour and his modest, quiet but always constructive contributions to the scientific and political discussions. Our thoughts and prayers go out to his wife Marjorie and their children.

Fumigant canister active against vectors of Chagas disease & dengue

The fumigant canister CIPEIN Pf-6, developed with TDR support for use against the triatomine insects that transmit Chagas disease, is manufactured by a local industry in Argentina and widely used for controlling these vectors. The simple and safe use of this insecticide tool opened vector control activities to community participation. Taking this into account, the canister was investigated against Aedes aegypti, the vector of dengue virus, in Argentina and Cuba. Good results have been obtained in different entomological and climatic conditions. In Argentina, knock down and mortality responses of adult A. aegypti were evaluated in laboratory and pre-field tests. Mortality of adult mosquitoes 24 hours after 15 minutes of exposure to fumes from the canister was 100%. After one hour of exposure to fumes and another hour of ventilation, mosquito mortality was also 100%. Field trials are now in progress to corroborate the indoor efficacy of the canisters against A. aegypti.

In Cuba, where the canisters were tested in rural houses with mud and thatch walls, there was also 100% mortality of adult mosquitoes after 30 minutes exposure to fumes. Fumes from the canister reached mosquito resting places high up on the walls.

This is very good news for control programmes and communities - the tool is inexpensive and can be used to control the vectors of two major tropical diseases.

Conference on health research

Ten years after the Karolinska Nobel Conference on health research for development, four leading partners in the field - the World Health Organization (WHO), the World Bank, the Global Forum for Health Research (GFHR), and the Council on Health Research for Development (COHRED) - have joined forces for the first time to draw up a common agenda for the International Conference on Health Research for Development, to be held in Bangkok, Thailand from 10 to 13 October 2000. During the conference, a number of International Health Research Awards, funded by the Rockefeller Foundation, will be announced. These awards are intended to encourage cooperation between institutions in developing countries, to enable the environment for health research. Proposals will be judged on the basis of partnerships of institutions representing, or proposing to create, national or regional initiatives targeting several of the following themes:

- strengthening national or regional health research agendas.
- increasing awareness of the importance of research among stakeholders.
- promoting good ethical practices in health research.
- improving communication and dissemination of research results.
- translating research into action.
- improving the processes and indicators for evaluating the impact of research.
- strengthening capacity in the management of research.

TB transplant to TDR

Continued from page 3

Research capability strengthening activities should be aimed at supporting research throughout these two main areas (HSSR and R&D of new tools). In particular, there is a need to build capacity for conducting field trials of new diagnostics, drugs and vaccines, and for carrying out post-regulatory assessments and functional genomics research.

TB was welcomed into the TDR disease portfolio by the Joint Coordinating Board (TDR’s top governing body) in 1999, which requested STAC to prepare plans of action and a focus for TB research, assuming that a budget of US$5.5 million for 2000-2001 could be raised. Already some of these funds are available, from, amongst others, the Rockefeller Foundation, Sweden (SIDA/SAREC), the Swiss Development Agency, Stop TB and WHO.
Trypanosomiase africaine

1. Évaluation de la rentabilité de l’intégration des stratégies d’adaptation et de surveillance passives et active dans les soins de santé primaires et non spécialisés en vue d’améliorer la couverture de la surveillance.


3. Évaluation de l’efficacité et de la rentabilité de l’utilisation du CATT et du CIATT pour le sérodiagnostic au niveau communautaire et évaluation comparative comme suit :
   - Le CATT dans la standardisation des tests sur sang total.
   - Comparaison entre le CATT PBS et le CATT EDTA.
   - Comparaison du CATT sang total et du CATT Latex.
4. Études prospectives de cohorte sur des sujets séropositifs mais parasitologiquement non confirmés pour évaluer l’impact épidémiologique du traitement.

5. Mise au point de nouveaux protocoles thérapeutiques (pou les formulations anciennes et nouvelles) tenant compte de l’efficacité, de l’innocuité et de considérations socio-économiques.

6. Création d’un réseau de surveillance de la pharmacorésistance à l’aide d’outils simples de détection et de cartographie.

7. Détermination de l’impact de la décentralisation de la lutte contre la maladie du sommeil et élaboration de stratégies de lutte en milieu urbain.

8. Définition de nouveaux critères normalisés pour prévoir l’évolution vers les stades tardifs de la maladie et mise au point de tests diagnostiques simples réalisés sur l’urine et la salive.

9. Définition de critères normalisés pour écouter le suivi du patient.

10. Association de la cartographie des régions d’endémie de la trypanosomiase africaine et d’informations émanant d’autres programmes comme ceux d’éradication de la dracunculose et d’élimination de l’onchocercose.

11. Mise au point d’outils d’analyse décisionnelle pour convenir d’une séquence rentable de tests diagnostiques et d’étapes de prise en charge. Les chercheurs qui souhaitent collaborer aux activités énumérées ci-dessus sont priés de s’adresser au :
Dr Alvaro Moncayo
Administrateur
Groupe spécial de recherche sur les interventions de lutte contre la trypanosomiase africaine
TDR, Organisation mondiale de la Santé
1211 Genève 27
Tél : (41-22) 791-3865/3903
Fax : (41-22) 791-4774
E-mail : moncayo@who.ch

Maladie de Chagas

Le Groupe spécial sur la maladie de Chagas va axer ses efforts sur l’étude de la dynamique des populations de triatomes non domiciliaires, vecteurs à la maladie de Chagas dans le nord de l’Amérique du Sud et en Amérique centrale. On peut espérer que les données entomologiques ainsi obtenues aideront les programmes de lutte nationaux de cette région à adapter aux conditions locales les stratégies de lutte antivectorielle qui ont si bien réussi à interrompre la transmission de la maladie dans les pays du Cône austral.

Les recherches sont nécessaires dans le cadre de :

- La distribution des triatomes et l’infestation des maisons et de la proximité immédiate des maisons par les espèces domiciliaires.
- La structure génétique des populations de triatomes non domiciliaires.
- La mobilité sylvatique/domestique des populations de vecteurs.

Recherche sur les interventions de lutte contre la filariose

Satie à un recensement récent des besoins en matière de recherche sur la filariose et l’onchocercose (page 12), le Groupe spécial de recherche sur les interventions de lutte contre la filariose a établi un nouveau plan de travail. Il invite les chercheurs à soumettre des projets entrant dans les activités de recherche ci-dessous, projets qui l’examinerà lors de sa prochaine réunion, en septembre 2000.

- Recherche sur l’intégration de la distribution des médicaments contre la filariose lymphatique et de l’onchocercose et des programmes de lutte contre d’autres maladies, études sur l’intégration optimale du ComDT contre l’onchocercose dans le système de santé, et évaluation des expériences en cours dans différents pays où les distributeurs relevant de la communauté dispensez aussi d’autres soins (par exemple le traitement antipaludique).
- Distribution des médicaments en Inde :
  1) études sur les méthodes permettant d’identifier les populations à traiter et sur la distribution des médicaments en zone urbaine, et ii) études sur la distribution des médicaments en milieu rural sur la base des recommandations d’une étude multicentrique récemment achevée en Inde (recommandations disponibles auprès de l’administrateur du Groupe spécial).
- Études pour évaluer les tendances des taux de transmission et de l’infection par W.bancrofti pendant 4 à 6 ans de traitement de masse par l’ivermectine et l’albendazole dans les zones d’Afrique où les anophèles transmettent la filariose.
- Mise au point de méthodes simples pour surveiller la couverture, y compris des méthodes d’évaluation rapide pour localiser les villages mal couverts et des méthodes fiables de recensement communautaire.
- Essai sur le terrain des tests diagnostiques existants et d’autres outils de surveillance de W.bancrofti et B. malayi, et définition de modalités d’application plus efficaces.
- Mise au point et essai de méthodes d’autosurveillance communautaire.
- Mise au point et essai sur le terrain de méthodes d’évaluation rapide pour le Loa loa.
- La prochaine réunion du Groupe spécial se tiendra en septembre 2000 et la date limite de dépôt des projets est le 15 août 2000. Les chercheurs qui souhaitent collaborer aux activités ci-dessus sont priés d’écrire au Dr Hans Remme, Administrateur, Groupe spécial de recherche sur les interventions de lutte contre la filariose, OMS/ TDR, 1211 Genève 27, Suisse. Tel. (41 22) 791 3815. Fax : (41 22) 791 4774. E-mail : Remme@who.int
Goings and Comings

The last two years have seen an unusual amount of staff changeover in TDR due to retirements and movement to and from the main WHO administration:

In the Director’s office:
Dr Paul Nunn was transferred from the main WHO administration to be Advisor/Coordinator of tuberculosis activities in TDR.

In Programme Planning and Monitoring (PPM):
Dr Pamela Hartigan, Programme Manager, left to take up a position as a director in the main WHO establishment.

Erik Blas became Programme Manager and also took over responsibilities as manager of health sector reform projects.

In Research Capability Strengthening (RCS):
Dr Farrokh Modabber, Coordinator of Research Capability Strengthening (RCS) and Manager of the Leishmaniasis Vaccine Development projects, retired.

Dr Fabio Zicker, Manager of the Task Force on Malaria Research Capability Strengthening in Africa, became Coordinator of the RCS functional area.

In Intervention Development and Evaluation (IDE):
Dr David Evans, manager of the health sector reform task force, left to take up a post in the Evidence and Information for Policy cluster of WHO.

Dr Hans Remme returned to the TDR fold (from secondment to Roll Back Malaria) as Manager of the Task Force on Filariasis Intervention Research.

Dr Jane Kengeya-Kayondo, Manager of the Task Force on Malaria Home Management, became Coordinator of the IDE functional area.

In Product Research and Development (PRD):
Dr Rob Ridley became Manager of the Steering Committee on Drug Discovery Research, and led MMV through to its launch.

Dr Beatrice Haepaap became planner for the PRD functional area.

WHO/TDR, in collaboration with the WHO Regional Office for the Americas, has completed an English language training package on epidemiology research methods for tropical diseases. The training package, originally developed in Portuguese, contains five modules (diagnostic tests, prevalence studies, case-control studies, cohort studies, and clinical trials) in addition to an introduction to epidemiology and a module on standard operating procedures for clinical investigation. Each module contains a written chapter on the topic of discussion with accompanying presentation overheads, an actual data set from a completed research project on infectious disease using the same study design, and the publication(s) resulting from the project. Participants are introduced to each topic through directed readings and a conceptual presentation (with discussion), then work with the data set to answer pre-determined questions. An integral part of the theoretical programme is the teaching and use of Epi Info software. After an initial introduction, the use of Epi Info is continually reinforced through the practical exercises associated with the theoretical presentations and data sets.

TDR field tested the training package at the Institute of Medicine, Tribhuvan University, Kathmandu, Nepal, in March 2000. The training course was facilitated by Dr Simone Almeida e Silva, Department of Tropical Medicine, Public Health and Dermatology, Federal University of Goias, Brazil, and Steven Wayling, TDR/RCS. Seventeen participants from Tribhuvan University, the MOH Epidemiology and Disease Control Division, and the Regional Health Directorates attended the training course. In spite of being a heterogeneous group in terms of education and experience, the training module proved to be highly effective in teaching both research epidemiology and the use of Epi Info. The modules greatest strength is in integrating these two topics — by using theoretical presentations as the basis of practical exercises in Epi Info, which use actual data sets from studies, supported by their resulting publications. The package is also available in Spanish and Portuguese.

The intention is to make the training package widely available from TDR and on the Web. TDR will also continue to support workshops using the materials.
Tropical diseases and health sector reform 2000

A special session of the UN General Assembly, the so-called ‘Copenhagen Plus Five’, takes place in Geneva 26-30 June 2000. During the same period, TDR’s Joint Coordinating Board (JCB) will discuss the new strategy for TDR. There will be many similarities between the two discussions. Both have reduction in the number of people living in extreme poverty as their aim. While the ‘Copenhagen Plus Five’ will address a broad range of social and economic issues, the JCB discussion will concentrate on what can be done within the mandate of TDR. The goals of TDR’s new strategy are:

- To alleviate inequity and poverty and foster social and economic development in endemic countries through reduction of mortality, morbidity and disability caused by neglected infectious diseases which affect poor and marginalized populations.
- To increase research self-reliance in endemic countries for identifying needs and developing solutions to public health problems caused by neglected infectious diseases.

While these goals clearly cannot be achieved by TDR alone, the Programme can make an important contribution because the diseases in the TDR portfolio disproportionately affect poor countries and poor people. For the TDR group of diseases, the gap between the world’s 20% poorest and 20% richest is wide. If the disease, age, and gender specific death rates among the poorest were equal to those of the richest, the number of deaths among the poorest would be reduced by 97.5% for tuberculosis, 99.6% for malaria, and 99.9% for the other TDR diseases. Only diarrhoeal diseases (96.5%), childhood cluster diseases (97.5%) and maternal conditions (98.6%) come close to having the same gap between rich and poor as in the TDR diseases. The WHO proposal to the ‘Copenhagen Plus Five’ suggests that ‘The delivery of health care itself is often profoundly anti-poor. There is rarely, if ever, focus on the risk factors that are the root cause of the ill health of the poor. And services are rarely designed with the poor in mind’. The newly established TDR research area of social, economic, and behavioural research (SEB) will focus much of its effort on increasing our knowledge in this field. A first call for proposals, ‘Tropical Diseases and Health Sector Reform – 2000’, was made in March 2000 with a deadline for 15 July 2000. This call for proposals aims to support studies in developing disease-endemic countries (DECs) to increase the knowledge and understanding of how the design, and changes in the design, of health systems in DECs affect the ability to effectively reduce the public health problems posed by the TDR group of diseases.

The SEB Steering Committee will, in its review of proposals, give priority to multidisciplinary research teams and teams that build bridges between research, control, and policy, e.g. through including control managers or policy makers in the project steering committee, or as members of the team. Experience from three rounds of comparative studies on health sector reform has shown that it can be extremely difficult to conduct this type of study (see TDR news No. 60). There are often problems with choosing the right methods, getting people from different disciplines and backgrounds to develop a common approach, conflict of interests, etc. Also, there is often a communications gap between academic researchers, managers, and policy-makers regardless of what their affiliation is to the specific research study. TDR will therefore offer, in addition to the research grant, technical support in the form of a methods/writing workshop and linkage to international expertise. The results of these studies are expected to be published at the beginning of 2002. For further information please contact Erik Blas, blas@who.int.

4 Please refer to the TDR website

TDR Alumni database. Calling all current and former principal investigators and trainees of TDR projects - TDR alumni:

TDR’s integrated management system (TIMS) needs your email address for the creation of a TDR-Alumni database. Please send a message to: tdrgrant@who.int to make sure your email address is updated. It will help if you include the TDR-ID number of your current or former project (one ID suffices). And of course, your usual “signature” i.e. name, address, fax, etc. The information will be entered in TDR’s official management information system, TIMS.

‘tdr-scientists’ mailing list. Calling all tropical disease researchers and friends - ‘tdr-scientists’:

You are invited to join the internet mailing list called “tdr-scientists” - a clearing house, informal forum of the tropical disease research community, which began in 1993 and now has 1650 colleagues networked together, sharing news and opportunities. Send a blank email to: tdrscinf@who.ch to receive instructions on how to subscribe to “tdr-scientists”. The list is free of subscription charges. You need not fear spam mail or viruses in posted messages as the list is moderated by volunteers. Stay in touch with TDR and the “tdr” community via a few short messages a week.

Dr K.R. Hata, Management Officer, Planning and Internetworking, TDR, hatak@who.int
**TDR Information and Workplans**

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

**Language:**  □ English  □ French

- □ TDR's Management Structure
- □ Intervention Development and Evaluation in TDR
- □ Basic and Strategic Research in TDR
- □ Product Research and Development in TDR

**TDR Workplans**

**Basic & Strategic Research**

- □ Functional Genomics and Pathogenesis
- □ Molecular Entomology
- □ Social, Economic and Behavioural Research

**Product Research and Development**

- □ Drug Discovery Research
- □ Vaccine Discovery Research

**Intervention Development and Evaluation**

- □ Malaria Home Management
- □ Filariasis Intervention Research
- □ Severe Malaria
- □ Research on Drug Resistance and Policies
- □ Intervention Research on Chagas Disease

- □ Intervention Research on African Trypanosomiasis
- □ Leprosy
- □ Immunology (IMMYC)
- □ Chemotherapy (THEMYC)

**Research Capability Strengthening**

- □ Grant information and workplan

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**To our readers**

We are unfortunately unable to accept for publication in *TDR news* 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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