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SPECIAL FEATURE: MILTEFOSINE

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NEW TOOL

Oral miltefosine may revolutionize treatment of visceral leishmaniasis

The potential impact of miltefosine on visceral leishmaniasis in India

N. K. Ganguly

India is one of the world’s hotbeds of visceral leishmaniasis (VL). Along with Brazil, Sudan and Bangladesh, India contributes to 90% of the global burden of VL.1 India has taken up the challenge to eliminate VL by 2010. Soon, its National Leishmaniasis Control Programme may have a new drug to fight VL - miltefosine.

Miltefosine is the first oral drug for leishmaniasis, giving cure rates of about 98%. It has negligible side-effects, does not require refrigeration for storage, and has been used successfully to treat cases resistant to conventional antimony therapy. Since the drug can be administered orally, it has the potential to be used as a simple and affordable public health tool to treat patients effectively at the community level and even during epidemics.

India has been home to VL since the mid-18th century. Even the ancient Indian scriptures mention ‘kala-azar’ – or ‘black fever’ – which discourser the skin black (referring to post-kala-azar dermal leishmaniasis – PKDL). The first VL epidemic was reported in 1870. Since then, several epidemics have swept the Ganga-Brahmputra plains of northern India, taking a huge toll of human lives and inflicting unimaginable misery.

The currently-used drugs are toxic, and have severe adverse reactions. The parasite in India has also developed varying degrees of drug resistance. Conventional therapy for VL consists of parenteral pentavalent antimony (sodium stibogluconate and meglumine antimoniate), given for 28 days (20 mg/kg/day). Severe adverse reactions such as pancreatitis and cardiac toxicity have limited its use. Relapse is common and resistance to antimony is alarming (about 50%). Alternative drugs too are not free from disturbing side-effects. Pentamidine isethionate has been shown to cause diabetes mellitus in over 10% of cases. These and other similar drugs are administered parenterally, often under strict medical supervision. The treatment costs are high and therapeutic efficacy is limited.

The research and development efforts for a cost-effective, safe and oral treatment for VL bore fruit when Professor Hansjorg Eibl, (Max Planck Institute for Biophysical Chemistry), and Professor Clemens Unger in Göttingen, Germany, discovered a structurally simple molecule, miltefosine.

Initially, miltefosine was tried for the management of cancer patients. The dose required for such treatment had pronounced side-effects, limiting its usefulness. Simultaneously, in vitro studies showed that it had striking activity against Leishmania donovani and L. infantum. Preclinical studies using the same dosage as for anti-cancer treatment indicated that the drug had teratogenic effects, renal toxicity, and adverse effects on fertility in males. The dosage of the drug required for treatment of VL is, however, far less than that required for management of cancer, and consequently has reduced adverse reactions. The results of Phase III clinical trials of miltefosine in India have shown that this oral drug is very effective for treating VL in both adults and children, and has limited side-reactions. It produced cure rates of 98%.

The availability of the drug is the culmination of concerted efforts by several Indian scientists and Zentaris (previously ASTA Medica) in Germany, supported and coordinated by TDR. Currently, the Indian Council of Medical Research (ICMR), supported by Zentaris and TDR, is planning to carry out a Phase IV operational trial in several districts of Bihar (India). The drug has now been licensed in India. After completion of the Phase IV trial, the Government of India proposes to use miltefosine as first-line drug for its kala-azar elimination programme.

From the country where Leishman and Donovan independently isolated the parasite for the first time, another first is emerging. The availability of an oral anti-leishmaniasis drug may revolutionize the treatment and control of kala-azar and alleviate the sufferings of the millions of adults and children in affected countries.
Miltefosine discovery and development and the TDR product development paradigm

Six years of discovery and development research in TDR leads to registration of the first oral drug for the treatment of visceral leishmaniasis

Robert G. Ridley, Juntra Karbwang

Miltefosine is a marvellous example of what can be achieved through public/private partnership in the area of product research and development for neglected diseases. Miltefosine was prioritized for development in TDR, in partnership with ASTA Medica (now Zentaris), in 1996. Six years later it has been registered for use in India as the first oral drug for the treatment of visceral leishmaniasis. This development is as rapid an achievement as would normally be anticipated in the pharmaceutical industry and has been carried out to full international standards, compatible with ICH (International Conference on Harmonisation) regulatory guidelines. Furthermore, because of the close involvement of Indian scientists and Indian institutions in the compound’s development, there is a deep understanding of miltefosine and its potential in India. There will therefore be a very thorough and rapid evaluation of its utility for India’s National Leishmaniasis Control Programme.

The reasons for the successful development of miltefosine are several:

• TDR’s commitment to drug discovery research, and its funding of laboratories to test and evaluate compounds against all the TDR target diseases, allowed thorough evaluation of the compound’s potential as a clinical development candidate for leishmaniasis.

• A legal agreement, clearly specifying the relative responsibilities of the partners and guaranteeing preferential pricing of the product for public sector use in developing countries, allowed a firm and committed partnership to be established between TDR and Zentaris.

• The establishment, under the auspices of TDR, of a powerful and professionally managed product development team, with significant contributions from Prof. Anthony Bryceson and Dr. Jonathan Berman, meant that all the essential expertise to manage the project was available. This facilitated management of the Zentaris work, the outsourced work of non-clinical investigators, and the clinical trials initiated and supported by TDR. The principal investigators of all trials were Indian investigators living in the disease endemic areas, and the studies were utilized to build national research and development capacity, especially in the area of good clinical practice.

• Being able to access, inform and collaborate with national authorities through WHO has allowed TDR to keep the Government of India fully briefed on all aspects of the studies, and to respond to their requirements and needs. This has resulted in a very rapid transition from pre-registration studies to post-registration studies where the drug’s value can be assessed in a ‘real world’ setting.

In essence, through this activity, TDR has demonstrated its ability to move projects from ‘bench’ research, through product development, to ‘implementation’ research by creating appropriate partnerships with industrial and public sector organizations. The development of miltefosine builds on past TDR experience, notably the development of ivermectin for onchocerciasis and the development of eflornithine for African trypanosomiasis.1 The success of the miltefosine project will help lay the foundations for similar activities that can provide useful tools (drugs, vaccines and diagnostics) to fight other diseases in the TDR portfolio.

Credit for the success of the partnership rests in part on the research and development structure in TDR, which enables projects to move from

1 Morel CM. Reaching maturity - 25 years of the TDR. Parasitology Today, 2000, 16(12):522-528.
strategic and drug discovery research into focused drug development projects that can link downstream to implementation research (see figure). It also rests on TDR’s ability to link such studies to utilizing and building on existing research capacities in developing countries. Primarily however, credit is due to the enthusiasm and goodwill of the institutional partners involved, notably Zentaris, and to the tremendous commitment of all individuals involved, whether they be laboratory scientists, technicians, clinicians or administrators, or whether they be from industry or academia, from the North or the South. Special recognition must also be given to the Government of India, which actively engaged in and supported this project from an early stage, and continues to support evaluation of the drug for its potential use in the National Leishmaniasis Control Programme.

AWARD

Piero Olliaro of TDR granted two visiting professorships

We are pleased to announce that Dr Piero Olliaro has been awarded two non-stipendiary visiting professorships; one from the University of Bordeaux 2, France, and the other from the University of Oxford, UK. The University of Bordeaux awarded the title of ‘Visiting Professor de l’Université Victor Segalen Bordeaux 2’ to Dr Olliaro in February this year. The title, to be held for the 2001-2002 academic year, was given in recognition of Dr Olliaro’s contribution to teaching and research in the University’s work in the implementation and evaluation of new diagnostics and drugs for parasitic diseases. At the same time, the Medical Sciences Board of the University of Oxford conferred on Dr Olliaro the title of ‘Visiting Professor in Tropical Medicine’ for a period of three years from 1 April 2002. This was given in recognition of Dr Olliaro’s contribution to teaching and research in the Nuffield Department of Clinical Medicine in Oxford. Dr Olliaro has worked in TDR for almost 10 years. An expert on drug development, registration, post-registration and implementation studies, he joined TDR in 1993 as manager of the Steering Committee on Drugs for Malaria, and later became manager of Drug Discovery Research. Since 1998, Dr Olliaro has been responsible for managing research activities related to drug resistance and policies, which is part of the TDR unit on Intervention Development and Implementation Research. He continues to be involved in various areas of research and to publish actively in scientific journals.
Miltefosine, the story of a successful partnership: disease endemic country - TDR - pharmaceutical industry (Zentaris)

J. Engel, Zentaris AG (Frankfurt, Germany)

Miltefosine was originally developed as an anticancer agent, first by ASTA Medica and, since 2001, by its spin-off biotech company Zentaris AG, Frankfurt, in collaboration with the Max-Planck-Institut in Göttingen (Prof. H.-J. Eibl) and the Universitätsklinik in Göttingen (Prof. G. Nagel, Prof. C. Unger). The drug, a membrane signalling pathway inhibitor, was successfully developed as a formulation for application to the skin in certain forms of cutaneous cancer, and was launched as such in several countries. An oral formulation of the drug was also used to treat cancer patients in clinical Phase I and Phase II studies, but the high and prolonged dosages required (up to 200 mg/day) to achieve meaningful clinical activity in these patients, and the resulting gastrointestinal side-effects, ultimately meant the drug was superseded by a more efficient anticancer candidate (perifosine).

In 1988, Simon Croft1 and his group reported anti-leishmaniasis activity of miltefosine and related compounds after parenteral use in mice. Considering the good oral bioavailability of miltefosine, as evident from our studies in tumour patients, Kulencord, Unger and others demonstrated for the first time an excellent oral activity in their leishmaniasis models.2

In 1995, ASTA Medica/Zentaris signed an agreement with TDR/W HO for the clinical development of miltefosine for visceral leishmaniasis. The Task Force for this development was introduced by TDR, with Prof. Anthony Bryceson as chairman, Dr Jonathan Berman as co-chair, clinical investigators from India (Prof. C.P. Thakur, Dr TK Jha, Prof. S Sundar), as well as members from ASTA Medica/Zentaris (including myself). O n the basis of a small-scale proof-of-concept study in India, which was organized by ASTA Medica/Zentaris, Prof. Shyam Sundar, and Prof. Henry Murray of Cornell University, a clinical development programme was initiated under the supervision of the TDR Task Force. A dose-ranging and pharmacokinetic Phase I/II study and a large Phase III trial comparing miltefosine with Amphotericin B were organized, initiated, and completed in adult patients. In addition, a dose-ranging and pharmacokinetie study, and a confirmatory Phase III study, were conducted in children. The centres worked according to current GCP standards; TDR/W HO and Zentaris cooperated closely in the monitoring of the studies. Recently, the Indian Council of Medical Research (ICMR) has become involved in developing the drug and a Phase IV study, to be conducted under the auspices of ICMR, has been organized jointly by ICMR, TDR/W HO, Zentaris, and German Remedies Ltd., the Indian partner company of Zentaris that received the approval for miltefosine for the treatment of visceral leishmaniasis in India.

Zentaris will continue to help in the development of this important first oral treatment against leishmaniasis. In a compassionate use programme, we have supplied the drug for treatment of patients with HIV/visceral leishmaniasis co-infection who were resistant to the classical treatment including ambisome (the liposomal formulation of Amphotericin B). Very encouraging therapeutic responses have been seen even in patients with multiple pre-treatment. In addition, a placebo-controlled Phase III study in cutaneous leishmaniasis is currently ongoing in South America, with the aim to confirm the efficacy seen in an earlier dose-finding study. Finally, a multinational programme is now being sponsored by the European Community to study the mechanism of action of miltefosine in leishmaniasis.

To my knowledge it is the first time that a drug has been developed in such close collaboration between the pharmaceutical industry, academia, TDR/W HO, and medical and regulatory bodies in India, the country that is most severely suffering from visceral leishmaniasis. The quality of this joint development has also been acknowledged by a series of publications in prestigious medical journals.3,4

UPDATE

Genomics and bioinformatics for tropical diseases

Ayo Oduola, Steven Wayling, Carlos Morel

TDR’s role in parasite genome sequencing
TDR has played an important role in the generation of knowledge about the parasite genomes for African trypanosomiasis, Chagas disease, leishmaniasis, schistosomiasis, and lymphatic filariasis. Starting in 1994, TDR helped establish five international parasite genome networks and opened the door for scientists from disease endemic countries (DECs) to participate and collaborate in genome and post-genome projects. Following on with training, TDR helped DEC scientists acquire the expertise needed to exploit advances in biotechnology and applied genomics, fostered partnerships with agencies and institutions to enable access of information in public databases, and facilitated a forum for discussion of progress.

Knowledge of the human genome will speed the search for new drugs, diagnostics and vaccines...

Now, TDR is enhancing DEC capacity to use the parasite genome data, and is supporting developments in applied genomics and bioinformatics.

Why bioinformatics in the disease endemic countries?
Bioinformatics provides opportunities in health research and development. For new drug research and development, this includes identification of novel drug targets, structural predictions, tapping into biodiversity, reconstruction of metabolic pathways, and systems biology. Bioinformatics may also contribute to the identification of vaccine candidates through analysis of surface antigens and epitopes.

Bioinformatics is a window of opportunity for DEC. It is ‘people-intensive’, and less affected by infrastructure and economics than other areas of biological research. Further, the ‘critical mass’ issue is less critical – a worldwide community is within reach through the Internet. Bioinformatics requires relatively modest hardware and technical support. There is a vast repository of public domain software for computational biology and individual accounts for remote access and data processing can be opened at high-performance computer facilities and bioinformatics regional centres including EMB network nodes, FIO CRUZ, SAN BI, CECaULa (Venezuela), and ICGEB (Italy and India). Powerful searches are possible using public websites such as NCBI, EMB electromagnetic book nodes, Sanger Centre, ExPASy/SW ISS-PROT, and KEGG database.

The TDR initiative on bioinformatics
TDR’s programme for developing capacity in bioinformatics was initiated in 2001. The rationale was that bioinformatics – or computational biology - plays a key role in molecular biology, genome sciences, post-genomics, and functional genomics. Bioinformatics levels the playing field for developed and developing countries, and has a direct impact on basic research and on the development of new tools in biotechnology and for disease control.

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The objectives of the TDR initiative are to:

- support 20-30 DEC scientists to a top level of competence in bioinformatics (‘trainers’) with the capability to conduct local bioinformatics training in Africa, Asia and Latin America in the next five years;
- further establish sustainable regional networks of centres and expertise for the promotion and integration of bioinformatics and DNA technology in basic research and management of tropical diseases in endemic countries; and
- establish a distance learning programme for bioinformatics in disease endemic countries.

The strategy is to build an integrated and sustainable network of centres in DECs utilizing existing and/or newly developed infrastructure including the World Bank’s Distance Learning Program, NCBI, SANBI, and ONSA centres. TDR’s activities started with a ‘train-the-trainer’ workshop in bioinformatics and applied genomics. The next steps are to initiate regional training courses in Africa, Asia and Latin America, and a Bioinformatics Career Development Grant for exceptional individuals who emerge from these courses. In the longer term, Masters and Doctoral training programmes will be developed and/or expanded in DECs.

The first step, the train-the-trainers workshop, was the International Training Course on Bioinformatics and Computational Biology Applied to Genome Studies, held 21 May - 15 June 2001, in FIOCRUZ, Brazil. The objective was to develop a multidisciplinary and international network for bioinformatics applied to pathogen genome research. Amongst other things, the participants prepared themselves for teaching similar courses in their home countries, promoting South-South and South-North interactions in bioinformatics.

Four centres, selected from 18 responses to a Call for Application for regional training centres in bioinformatics, have offered, or will offer regional training courses as their first activities:

- for Africa:
  SAN BI, Cape Town, South Africa, 20/Jan-02/Feb/2002
  Course website: http://www.sanbi.ac.za/tdrcourse/
- for South America:
  USP, São Paulo, Brazil, 18/Feb-02/Mar/2002
  Course website: http://icb.ime.usp.br/tdr/
- for Asia:
  ICGEB, New Delhi, India, 26/April-09/May/2002
  Course website: http://www.icgeb.res.in/~whotdr/

and Mahidol University, Bangkok, Thailand, 09-23/Jul/2002
Course website: http://www.sc.mahidol.ac.th/scbc/cbag/index.htm

Therefore, while TDR’s bioinformatics initiative is in its early days, considerable progress has already been made. Through this initiative, TDR is strengthening institutions and training researchers from disease endemic countries, helping them to reach self-reliance in this important area of modern biological research.
There is much evidence that armed conflict and infectious diseases are intimately linked together (see Box 1). It has been suggested that 65% of infectious disease epidemics occur in unstable countries, while direct death from ‘war’ ranks in the top 12 most common causes of death worldwide and is projected to become the 8th most common cause of death by 2020. Despite the evidence, there has been limited research, at least from within the public health field, on how individuals, communities and health systems cope with adversity.

Exploring the interface of the TDR diseases with conflict and other crises in today’s uncertain world is an area that has been taken up by the TDR Steering Committee for Social, Economic and Behavioural Research (SEB). The first activity was to hold a workshop in Manila, April 2002, attended by 25 social scientists, epidemiologists and health systems researchers, from 12 different countries, including some which are currently unstable as a result of current or previous conflict. The aim of the workshop was to develop a framework for examining how communities and health systems cope with instability, insecurity and infectious diseases.

**BOX 1** Conflict and infectious diseases are interlinked

Forcibly displaced people typically experience high mortality, especially in the period immediately following their displacement, and infectious diseases and nutritional disadvantage are key factors. In conflict settings, the quantity and quality of health care available is usually greatly reduced; vector control programmes, outreach services, training, referral, and drugs distribution are all typically impeded. In Ethiopia and Mozambique, epidemics of malaria were associated with deterioration in disease control activities and, in Nicaragua, increased risk of malaria was associated with war-related population and troop movements, inability to carry out timely disease control activities, and shortages of health personnel needed to conduct control programmes in peripheral areas. Work presented at the SEB/TDR workshop highlighted the linkages between the spread of the Ebola virus and military movements in central Africa. In conflict settings, lack of resources and various other constraints including reduced motivation of health professionals, can have devastating consequences on the provision of care, while any pre-existing shortcomings of services, and any inequities in access to care, are exacerbated.
and infectious diseases with a view to identifying and supporting ‘resilience’ (see Box 2). Understanding how people cope would provide some guidance on how to better support health systems under threat.

Workshop participants spent the first two days exchanging ideas about the links between conflict and infectious diseases, and heard evidence from the Democratic Republic of Congo, Uganda, the Philippines, Afghanistan, Sri Lanka, Colombia, and Sudan regarding these relationships. Evidence was presented which highlighted the impact of conflict on health and health systems, through the destruction of health service activities, planning and policy-making, changes in the distribution of personnel, and the impact on logistic support, amongst others. Additional commentary and discussion focused on how communities and health systems survive such adversity, with some interesting examples emerging. Nomads in Afghanistan, for example, appeared to better preserve their health, given their knowledge of how to live in an insecure setting, knowledge of how to avoid disease while on the move, and better ability to make use of cross-border services that may be operating.

Outputs of the workshop included:

- Initiation of country profiles development, focusing on conflict, infectious diseases, and health system and community responses. Papers were presented from a number of countries – edited conference proceedings will make these materials more widely available. Although the contexts differed substantially in each of the settings discussed, common threads were identified from which lessons could be learned.
Resilience vs. vulnerability

Sometimes conflict situations can have positive impacts on societies and health systems, as in Nicaragua, Mozambique, Viet Nam, Eritrea and Tigray. In the popular conflict against the Ethiopian Derg, community-based political movements in Eritrea and Tigray engaged strongly in building community structures for participation and decision-making, facilitated the development of multi-sectoral health promotion strategies, and identified innovative community-financing systems.

Despite the positive outcome in some situations however, the usual situation is that communities and health systems become more vulnerable. Vulnerability reflects the level of exposure to risk, shock and stress. People and health systems may be vulnerable because of poverty, gender, age, ethnicity and/or religious identity. Other threats in conflict include exposure to violence and armed attack, targeting of property and dispossession of assets, and undermining and direct targeting of service providers and services.

Ability to cope depends on a combination of factors including resilience, which has been defined broadly as the ability to recover from adversity. The ability of the health system to recover from the effects of conflict and improve its response to the community’s health needs is affected by factors such as pre-conflict status, level of preparedness and disaster planning, and degree of external support.

In addition, the ability to activate effective coping strategies may be in large part determined by the resilience of people and health systems. Resilience can be considered to reflect the support derived from such elements as traditional and formal institutions, social networks and social solidarity, cultural values, spirituality, economic resources, migration, life skills, and experience. The dynamics of the interplay between these factors in supporting (or undermining) the process of recovery are not well understood.

Political conflict ...

(continued)>

- Identification of a cohort of enthused research activists who are keen to explore, understand and promote improved policy responses to infectious diseases and conflict.
- A decision to commission a key review of how communities and health systems respond.
- Development of an agenda for research on conflict and health systems, around which further debate will be encouraged.
- Development of a proposal for a six-country (Afghanistan, Democratic Republic of Congo, Philippines, Sri Lanka, Sudan, Uganda) case study. If funded, this study will extend the boundaries of current knowledge about vulnerability and resilience at individual, community and health system levels. The overall objective is to elucidate which factors influence resilience and vulnerability of conflict-affected communities and health systems, and how these factors interact, in order to respond better to infectious disease, with specific reference to malaria.

15 Chambers, R. 1989 Vulnerability, coping and policy. IDS Bulletin 20
17 Cf. http://www.who.int/disasters/
world of tropical diseases research

worked on the island of Zanzibar, many scientists remain sceptical, considering the obstacles to be overcome using the method on such a large scale.

- **Computer models** indicate that introducing two copies of two genes into just 3% of a mosquito population would be enough to drive the gene through the population. Selection pressure would be created because, when only one of the genes is inherited, the mosquito dies, but when both genes are inherited, the mosquito survives. Only the offspring of some of the crosses will inherit one gene (crosses between hybrids and engineered flies will inherit both genes), so the offspring of wild flies will die more often than those of engineered or hybrid flies.

- A report on malaria resurgence in the East African highlands indicates that climate change is not responsible for the re-emergence of malaria, as many people believe. There is no evidence that warming has occurred in any of the four locations investigated, so other factors for the comeback of the disease must be considered instead (e.g. demographic change, drug resistance of the malaria parasite).

- The first human anti-parasitic vaccine has been registered for cutaneous leishmaniasis. It is not a preventive vaccine but a therapeutic vaccine, given in conjunction with drug treatment. This results in better cure in a shorter time than either treatment alone. The therapeutic vaccine is a new concept, already in use in many other countries. The leishmaniasis vaccine, developed with TDR support, was registered in Brazil in October 2001.

- Novartis, in collaboration with the Singapore Economic Development Board, has established a research institute for tropical diseases research in Singapore. Aimed at the discovery of novel treatment and prevention methods for diseases such as tuberculosis and dengue fever, the long-term aim is to help reduce the overall afflication of tropical diseases and improve the prosperity of developing countries. In those countries where the diseases are endemic, the Novartis Group intends to make treatments readily available and without profit. The Institute is looking to become a major centre of excellence and will offer exceptional teaching and training opportunities for postdoctoral fellows and graduate students.

- W HO has added Coartem, a combination of an artemisinin and a non-artemisinin compound (artemether/lumefantrine) in a single tablet, to its Essential Medicines List. W HO also recommends other combinations of artemisinin compounds with currently used medicines, such as amodiaquine or sulphadoxine pyrimethamine, for use where these medicines are still effective.

- W HO has issued a major new report on the impact of genomics. The report, *Genomics and World Health*, details the latest advances in genome research, and explains how this research could result in medical advances against many diseases, including those pandemic in poor countries. The report also warns about the potential risks of such research, and makes recommendations on how the fruits of this research can be brought to the developing world. It makes a major contribution to the debate on the ethics of genome research, and anticipates how the global community could use genetics to attack the unfinished agenda of infectious diseases such as malaria, TB and HIV/AIDS, helping to narrow the existing unethical inequities in global health. The need for public engagement on issues related to genomics in order to enable society to enter into informed debate on an uncertain, rapidly changing field with enormous potential for improving health.

- A step towards genetic control of malaria transmission was announced with the news that a malaria-inhibiting gene has been successfully introduced into a mosquito. The gene is expressed in the mosquito’s gut when the mosquito feeds on blood, causing production of a molecule known as SM1, which prevents the parasites from passing through the gut wall, and hence from invading the salivary glands, where they have to go before they can be transmitted to a person during mosquito feeding. After feeding on malaria-infected mice, mosquitoes with the introduced gene were 80% less likely to have malaria parasites in their salivary glands and were almost totally unable to transmit the infection on to other mice.

11. Free downloading and information: www.who.int/genomics
Malaria intermittent treatment in infants

Melba Gomes, Jane Crawley, Philippe Duclos, Mark Young

Severe anaemia exerts a heavy toll on African children in malaria endemic countries, a recent estimate suggesting that 1.4-5.7 million cases of anaemia each year kill 190 000-974 000 children under 5 years, with the highest mortality occurring in infants of less than 12 months.1 Although iron deficiency, intestinal helminth infections and HIV make significant contributions to the pathogenesis of anaemia in many African countries, there is now a substantial body of evidence to suggest that, in areas endemic for malaria (particularly those with high transmission intensity), malaria is a major underlying factor. WHO/TDR has therefore funded a number of studies to investigate the impact of antimalarial drug interventions on episodes of malaria and anaemia in infants during the first year of life.

Initial studies focused on chemoprophylaxis, and a study from Tanzania demonstrated that weekly pyrimethamine-dapsone between the ages of 2-11 months reduced episodes of malaria by 60%, and episodes of anaemia (defined as a packed cell volume of < 25%) by 57%, during the first year of life.2 There was, however, a rebound in the number of episodes of malaria and anaemia in the year following cessation of chemoprophylaxis, suggesting that the development of natural immunity to malaria had been impaired.

Subsequent studies have assessed the impact of malaria intermittent treatment (MIT), i.e. of a full treatment dose of an antimalarial drug given at specific times during the first year of life, regardless of the presence or absence of malaria parasites. Since treatment is only given on an intermittent basis, this intervention is less likely to interfere with the development of immune responses to malaria. A promising result, published in The Lancet last year, showed that a single dose of sulphadoxine-pyrimethamine, administered to Tanzanian infants at 2, 3 and 9 months of age at the time of routine EPI vaccination, reduced episodes of malaria by 59%, and episodes of anaemia by 50%.3 These results appear to be confirmed by another, as yet unpublished, study from a different region of Tanzania, where amodiaquine was used for MIT. Confirmatory results from the three other studies currently under way (two in Ghana and one in Kenya), due to be completed mid 2003, are now awaited eagerly. Although we can infer a survival benefit based on protective efficacy against severe anaemia seen in the studies to date, in order to clearly establish survival benefit, dedicated, multi-country, large-scale, randomized controlled trials would be required. These studies are costly, however, and take time to do well.

Are further studies needed to assess whether MIT can reduce mortality among infants and young children? There are compelling arguments for moving rapidly from research into practice, without conducting large-scale, randomized, controlled trials to quantify survival benefit, which are likely to take at least three years to complete. WHO (EPI, RBM, and TDR), GAVI and UNICEF consider these results to be an indication of an important new method for preventing malaria deaths through EPI, and perhaps of increasing EPI adherence as well. UNICEF is committed to strengthening the delivery of maternal and child (MCH) services, with a focus on children and pregnant women in sub-Saharan Africa. Included as one of UNICEF’s
organizational priorities is 'Immunization Plus', linking other interventions (such as vitamin A supplementation) to EPI points of contact. Infant MIT would be a natural and logical addition to this package, and UNICEF stands ready to proceed to programme implementation as soon as this is possible.

There are, however, equally strong arguments for providing a solid base of evidence on which the future interventions of EPI, UNICEF and GAVI can stand:

- **First**, it is vital that MIT does not severely compromise the response to EPI vaccines. None of the studies currently being undertaken or completed were designed to fully assess the effect of MIT on EPI antigens, and TDR is therefore commissioning studies to assess this effect. The work will take at least 12 months to complete, in the context of a cohort being vaccinated during the first year of life.

- **Second**, as the introduction of vitamin A supplementation into EPI programmes has taught us, it is beneficial to ensure that new activities do not disrupt or add additional burden to routine services. For instance, it may be necessary to have an antimalarial drug available in a formulation which can be easily used by EPI programmes in routine circumstances. Development of a suitable infant formulation for use by EPI will not be immediate.

- **Third**, there are a number of practical issues associated with the introduction of new interventions into EPI, and we have a lot to learn regarding the logistics of delivering immunization and malaria interventions simultaneously and systematically. These 'linkage' issues can be explored at programme level while awaiting further research results.

- **Fourth**, we need to understand the impact that the introduction of MIT might have on the attitude of local communities to EPI vaccination. There is, for example, a remote possibility that MIT might be perceived as a vaccine against malaria, and adversely affect subsequent treatment-seeking behaviour during episodes of fever. Vaccination programmes can be damaged by misinformation and misunderstanding, and it will be crucial to carry out targeted social science research in this important area. This research should not delay implementation, but may be done in the context of implementation.

- **Finally**, although there is a strong interest in implementing MIT before definitive evidence on the survival benefit is obtained, it is not obvious that this interest will be sustained by governments without clear evidence of the survival benefit of this intervention, and the clear calculation of the costs per avoided death through MIT compared with alternative means of avoiding deaths, and without clear evidence on whether an EPI plus (+MIT) will increase adherence and coverage of EPI vaccination programmes.

GAVI/UNICEF/WHO (EPI-RBM-TDR) eagerly await the results of ongoing trials, and are using the intervening time period to: (i) obtain definitive evidence of the impact of MIT on EPI antigens, (ii) fund large-scale randomized controlled trials that can quantify survival benefit, and (iii), once vaccine efficacy has been assured, to simultaneously introduce MIT into EPI programmes in a limited number of districts under well monitored conditions. This will provide an opportunity to assess the problems that occur in introducing malaria interventions into EPI, the changing perceptions and adherence to EPI when MIT is introduced, and the most effective ways that these potential problems can be addressed.
Recognizing the worsening epidemiological trends for dengue globally with the growing burden of epidemic disease, particularly among children, the 55th World Health Assembly held recently in Geneva passed a Resolution on dengue fever and dengue haemorrhagic fever prevention and control.

The Resolution presented three main requests:

**First**, it urged member States:

- to advocate increased commitment and acquisition of additional human and other resources for improved and sustained prevention and control efforts and for strengthened research;
- to build and strengthen the capacity of health systems for management, surveillance, prevention and control and management of dengue fever and dengue haemorrhagic fever;
- to strengthen the capacity of diagnostic laboratories, taking into account the fundamental importance of laboratory diagnosis to confirm etiology and to strengthen clinical and epidemiological surveillance for dengue fever and dengue haemorrhagic fever;
- to promote active intersectoral partnerships involving international, regional, national and local agencies, nongovernmental organizations, foundations, the private sector, community and civic organizations;
- to pursue, encourage and support the development, application, evaluation and research of new and improved tools and strategies for prevention and control of dengue fever and dengue haemorrhagic fever;
- to strengthen health measures at borders for vector control and opportunities for diagnosis and treatment in order to optimize regional resources;
- to mobilize financial resources to be spent on vector control and research into vaccines.

**Second**, it urged other specialized agencies, bodies and programmes of the United Nations system, bilateral development agencies, nongovernmental organizations and other concerned groups to increase their cooperation in dengue fever prevention and control, through both continued support for general health and social development and specific support to national and international prevention and control programmes, including emergency control;

**Third**, it requested the Director-General:

- to develop further and support implementation of the global strategy for prevention and control of dengue fever and dengue haemorrhagic fever through integrated environmental management;
- to continue to seek resources for advocacy and research on improved and new tools and methods for dengue fever prevention and control and their application;
- to study the need for and feasibility of incorporating the surveillance and research of other arthropod-borne viral infections, such as Japanese encephalitis, W est N ile, and other emerging diseases, in the surveillance system for dengue haemorrhagic fever;
- to mobilize financial resources to be spent on vector control and research into vaccines.

In addition to WHO's recognition of the urgent need to renew or intensify efforts to reduce the public health and economic burdens associated with this epidemic disease, based on deliberations of a recent International dengue vaccine meeting held in Ho Chi Minh City, Vietnam, the establishment of a decentralized consortium has been proposed, called the "Pediatric Dengue Vaccine Initiative" (PDVI), with a secretariat to be housed at the International Vaccine Institute in Seoul, Korea. An eight member International PDVI Board of Councillors has recently been selected to oversee the consortium activities.
New research awards

Renewals: Research Group Development (RGD)

- **970684** EN RIO UE MEDINA-ACOSTA, Universidade Estadual do Norte Fluminense, Brazil. Development of a chimaeric plant virus-derived vaccine against experimental leishmaniasis (budget: US$ 24 000)

- **990893** ANDREA MAREA MACEDO Universidade Federal de Minas Gerais, Instituto de Ciencias e Immunologia, Brazil. Genetic variability and population structure of Trypanosoma cruzi revealed by microsatellite analysis (budget: US$ 35 000)

- **990948** BARBARA JUDITH MEN DIO LA MARTINEZ Instituto de Medicina Tropical “Pedro Kouri”, Cuba. Isolation of new aspartic proteinase inhibitors with potential effectiveness as antimalarial drugs (budget: US$ 21 000)

- **971102** ABRAHAM ISRAEL SHUMA MURO National Institute for Medical Research, Tanzania. Epidemiology and integrated control of human schistosomiasis in Ukerewe district, Tanzania (budget: US$ 35 000)

- **991066** SHYAM SUNDAR Banaras Hindu University, Institute of Medical Sciences, India. Visceral leishmaniasis and PKDL: new therapeutic, immunologic and diagnostic studies and site preparation for vaccine trial (budget: US$ 35 000)

- **A00903** THELMA E. TUPASI Tropical Disease Foundation Inc., The Philippines. Community-based DOTS-plus programme for management of MDR-TB: pilot project, Makati (budget: US$ 25 000)

Renewals: standard capacity building grants (RCS)

- **991006** MYRIAM AREVALO-HERRERA, Universidad del Valle, Fundacion Centro de Primates, Colombia. Establishment of an international research centre for malaria vaccine and drug testing (budget: US$ 60 000)

- **A00884** WEBER CHELI BATISTA Centro de Pesquisa em Medicina Tropical, Brazil. Isolation and molecular typing of dengue virus circulating in urban and rural areas of Rondonia, Brazil (budget: US$ 35 000)

- **980947** IBRAHIM MO HAMED ELHASSAN University of Khartoum, Institute of Endemic Diseases, Sudan. Natural history of PKDL and its role in transmission (budget: US$ 35 000)

- **971178** SHAVKAT ABLAKULOVICH RAZAKOV Uzbekistan. Vaccine development against ZCL: Evaluation malaria threat/strengthening of preventive capacity (budget: US$ 30 000)

- **990106** MAGDI MAHMOUD ISMAIL Zagazig University, Faculty of Medicine, Egypt. Resistance to praziquantel: an emerging problem (budget: US$ 25 000)

- **990965** THERESA KEMBENG NKUO-AKENJI University of Buea, Faculty of Science, Department of Life Sciences, Cameroon. Malaria pilot centre in rural setting of Mount Cameroon through multidisciplinary approach studies (budget: US$ 35 000)

- **990891** ALEXANDRE AFRA NIO PEIXOTO Fundacao O swaldo Cruz, Bioquimica e Biologia Molecular, Brazil. Molecular, evolutionary and population genetics of circadian rhythms in sandflies (budget: US$ 27 500)

- **971178** SHAVKAT ABLAKULOVICH RAZAKOV Isaev Research Institute of Medical Parasitology, Uzbekistan. Vaccine development against ZCL: Evaluation malaria threat/strengthening of preventive capacity (budget: US$ 30 000)

Renewals: Re-entry Grants (REG)

- **A00720** GETAHUN ABATE Armauer Hansen Research Institute, Ethiopia. The development and implementation of a colorometric assay for a rapid detection of multidrug-resistant TB (budget: US$ 14 000)

- **A00781** OLUSEGUN GEO RGE ADEMO WO University of Ibadan, College of Medicine, Nigeria. CQ resistant *P. falciparum*: an evaluation of Pfmdr 1 and Pfcr polymorphisms and effect of host red cell genetic factors (budget: US$ 11 000)
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New Research Awards (continued)

- **A00752** IRENE E AKUA A
  AGYEONG Ministry of Health, Dangme West District Health, Ghana.
  Evaluation of impact of continuous quality improvement on design, management and outcome of malaria control in Ghana (budget: US$ 16 962)

- **A00789** ABRAHAM A SEFFA
  Armwarou Hansen Research Institute, Ethiopia.
  Improving the performance of clinical laboratories in the implementation of the national TB control programme (budget: US$ 18 500)

- **A00964** ANILZA BON ELO
  Universidad del Valle, Instituto de Inmunologia, Colombia.
  P. falciparum CS protein CTL epitopes: influence of natural polymorphism on immunogenicity (budget: US$ 20 000)

- **A00753** MARIA ISABEL NOGUEIRA CANO
  Universidade Estadual de Campinas, Brazil.
  Identification and characterization of telomere binding proteins in extracts of Leishmania amazonensis (budget: US$ 15 000)

- **990773** GUIMOGO DOLLO
  Universite du Mali, MRTC, Faculte de Medecine, de Pharmacie et d’O donto-Stomatologie, Mali.
  Chromosomal and molecular genetics of Anopheles gambiae complex in Mali (budget: US$ 15 200)

- **A00790** VANESSA CARLA FURTADO MOSQUEIRA
  Federal University of Ouro Preto (UFO P), Brazil.
  Development of new formulations that reduce toxicity and improve efficacy of the anti-parasitic drugs (budget: US$ 20 000)

- **A00700** MARCELA DE FREITAS LO PES
  Federal University of Rio de Janeiro, Brazil.
  Immunopathogenesis mediated by apoptosis: selective blockade of T cell apoptosis in experimental Chagas disease (budget: US$ 20 000)

- **990894** GERARDO A. MIRKIN
  Universidad de Buenos Aires, Facultad de Medicina, Microbiologia Parasitologia e Inmunologia, Argentina.
  Function of tissue-infiltrating V beta 9+ T cells in Trypanosoma cruzi infection (budget: US$ 16 100)

- **A00725** CHARLES SMITI
  Medical Research Institute, Centre for Microbiology Research, Kenya.
  Evaluation of anti-flarial regimens in reduction of infection and their effect on survival and fertility of vector mosquitoes (budget: US$ 6 000)

- **A00718** SWATI PATANKAR
  Institute of Life Sciences, India.
  Screening a natural compound library for molecules with anti-malarial activity (budget: US$ 20 000)

- **A00772** CHARLES SMITI
  Medical Research Institute, Centre for Microbiology Research, Kenya.
  Evaluation of anti-flarial regimens in reduction of infection and their effect on survival and fertility of vector mosquitoes (budget: US$ 6 000)

- **A00718** SWATI PATANKAR
  Institute of Life Sciences, India.
  Screening a natural compound library for molecules with anti-malarial activity (budget: US$ 20 000)

- **A00577** SISIRA LAL PATHIRANA
  University of Colombo, Faculty of Medicine, Sri Lanka.
  Studies on “strain”-specific protective immunity to Plasmodium cynomolgi infection (budget: US$ 18 020)

- **A00732** EDUARDO ALPHonso REBOLLARTELLEZ
  Universidad Autonoma de Yucatan, Centro de Investigaciones Regionales, Mexico.
  Vector capacity of allopatric populations of Lutzomyia o. olmeca and distribution of leishmaniasis in Yucatan, Mexico (budget: US$ 12 100)

- **A00892** N’FALE SAGNON
  Centre National de Recherche de Formation sur le Paludisme, Burkina Faso.
  Evaluation de la distribution des membres du complexe An. gambiae à travers différents types de gîtes de reproduction (budget: US$ 21 000)

- **A00750** J. EN RIQUE SALCEDO
  Universidad Militar Nueva Granada, Colombia.

- **A00731** AMIT SHARMA
  International Centre for Genetic Engineering and Biotechnology (ICGEB), India.
  Molecular cloning and biochemical characterization of a sexual stage-specific protein from P. vivax (budget: US$ 4 000)

- **A00769** VIVIAN E HELEN ETCHINGA
  University of Yaounde I, Biotechnology Center, Cameroon.
  Severe malaria in Cameroonian children: circulating adhesion molecules and disease severity (budget: US$ 9 500)

- **990881** LUIZ RICARDO
  Universidade de Sao Paulo, Faculdade de Medicina de Ribeirao Preto, Brazil.
  Use of transposable elements for functional genomics in Leishmania spp (budget: US$ 20 000)

New grants: Institutional Programme Grants (LDC)

- **A10491** ALI MO HAMED ASSABRI
  Assa’ri University, Faculty of Medicine and Health Sciences, Yemen.
  The epidemiology of severe malaria in children in Yemen (budget: US$ 30 000)

- **A10499** FENG ZHEN
  Institute of Parasitic Diseases, Chinese Academy of Preventive Medicine, P.R. China.
  Strengthening regional network for Asian schistosomiasis (SRNAS) (budget: US$ 50 000)

A10917 MON MON Department of Medical Research, Myanmar. Institutional capability strengthening on tuberculosis research in Myanmar (budget: US$ 50 000)

A11037 KAKARLA SATYANARAYANA Centre for Research in Medical Entomology (ICMR), India. Community-based dengue vector control under health system in one district (south India) and transfer of technology (budget: US$ 44 000)

New grants:
Re-entry Grants (REG)

A10935 SAYERA BANU International Centre for Diarrhoeal Disease Research, Bangladesh. Study on molecular epidemiology of tuberculosis and molecular mechanism of drug resistance of Mycobacterium tuberculosis (budget: US$ 13 700)

A10924 LUZIA HELENA CARVALHO Fundacao Oswaldo Cruz, Centro de Pesquisas René Rachou, Brazil. Molecular and immunological characterization of P. vivax Duffy binding protein in endemic areas of the Brazilian Amazon (budget: US$ 20 000)

A10937 CHO-MIN-NAING National Malaria Control Project, Disease Control Programme, Department of Health, Myanmar. Comparative economic and epidemiological analysis of malaria control in Myanmar and the Mekong region (budget: US$ 15 710)

A10828 A LA S A N E D I C K O Universite du Mali, Faculte de Medecine, de Pharmacie et d’O donto-Stomatologie, Mali. Evaluation of malaria transmission target strategy based on periodic treatment with S-P vs early case management (budget: US$ 21 800)

A10830 DANIEL DODOO Noguchi Memorial Institute for Medical Research, Ghana. The role of cellular and humoral responses against the glutamate rich protein (GLURP) in malaria immunity (budget: US$ 19 930)

A10931 MARCELO ROSADO FANTAPPIE Universidade Federal do Rio de Janeiro, Brazil. Cloning and functional characterization of high mobility group (HMG) proteins from Schistosoma mansoni (budget: US$ 20 400)

A10938 BEN ADU GYAN Noguchi Memorial Institute for Medical Research, Ghana. Haptoglobin polymorphism, immune function and malaria severity (budget: US$ 20 000)

A10804 LE THANH HOA Institute of Biotechnology (IBT), Viet Nam. Diversity in mitochondrial genomes of Asian and Indian Schistosoma species for evolutionary and genetic studies (budget: US$ 20 600)

A10756 ENOCK MATOVU Livestock Health Research Institute, Uganda. Investigating the distribution of meflarsoprof refractory T. b. gambiense in North-West Uganda (budget: US$ 32 700)

A10802 OSCAR RWEGA SILA MUKASA Ifakara Health Research and Development Centre, Tanzania. Information system for evaluation of malaria control tools: software development and hardware review (budget: US$ 25 700)

A10858 JIRA PRA PA IPASA Chiang Mai University, Research Institute for Health Sciences, Thailand. Factors involved in development and lifespan of memory T cells in immunity to blood stage malaria (budget: US$ 20 588)

A10825 WAN DEE VIN DEEYO UN GYEO National Center for Genetic Engineering and Biotechnology, National Science and Technology Development Agency, Thailand. Identification of essential genes of Mycobacterium tuberculosis by antisense RNA (budget: US$ 20 000)

New grants: Project Development Grant (PDG)

A10490 BACHTI ALISJAHBANA Padjadjaran University, TIU-RATH/WHO CC-PMC, Indonesia. Improved tuberculosis control and capacity strengthening for tuberculosis research in a rural community in Indonesia (budget: US$ 10 000)

A10503 VINOD JOshi Desert Medicine Research Centre, India. Studies on dengue and dengue haemorrhagic fever in Rajasthan, India (budget: US$ 5000)
Tuberculosis

Tuberculosis threatens one-third of the world's population. The World Health Organization declared tuberculosis a global health emergency in 1993. The magnitude of tuberculosis poses a threat particularly in poor parts of the world (notably eastern Europe and the former Soviet Union), the spread of which is rapid, especially among populations living in poverty.

**Distribution**

- Americas – 18%
- Western Pacific – 35%
- Europe
- South-East Asia

**Causative agent**

The causative agent of tuberculosis is Mycobacterium tuberculosis. The bacterium is resistant to many antibiotics and the disease can evolve into drug-resistant forms, which are then difficult to treat.

**Transmission**

Tuberculosis is a contagious, airborne infection. A patient with tuberculosis can infect others through sneezing, talking or spitting. Infection occurs when these bacilli are inhaled by a susceptible person. A person will become infected with tuberculosis only if the infection is acquired during childhood.

**Issues**

- About 2 billion people are infected, mainly in developing countries.
- Infections are common among children in developing countries.
- The disease is the world's leading opportunistic killer, following AIDS.

**Global Status**

**Disease burden**

1. Incidence of TB cases: 5 million annually
2. Incidence of new cases: 32%
3. New cases: 3.4 million annually
4. New cases and thus limiting the risk of acquiring infection. Directly observed treatment, short-course (DOTS) is a proven system for treatment.

**Tuberculosis Treatment**

- DOTS has shown cure rates of up to 95% in countries such as China, Peru and Vietnam. However, DOTS has not reached many parts of the world.

**Drug Resistance**

Drug-resistant strains of tuberculosis have recently appeared. These strains are resistant to one or more of the main drugs used to treat tuberculosis, which makes treatment more difficult, lengthy and expensive, placing an even greater burden on patients and health care systems.

**Latest Advances**

- The discovery of new drugs and more effective vaccines for tuberculosis is hoped to help control the spread of the disease.

**Future Challenges**

- New drugs are needed to combat tuberculosis.
- Community education and awareness campaigns are necessary to combat the disease.
- Early detection and treatment are crucial.

**Conclusion**

Tuberculosis remains a global health challenge, and concerted efforts are needed to control its spread and improve treatment outcomes.
Books/reports

- **Special focus: Malaria Re-advertisement 2000**
  *Nature Medicine*
  Sponsored by the Medicines for Malaria Venture (MMV) and TDR.
  30 pages

- **Economics of malaria control in China: cost, performance and effectiveness of Henan’s consolidation programme.**
  Sukhan Jackson, Adrian C Sleigh, X-i-Li Liu.
  TDR/STR/SEB/RP/02.1
  The first in a new series of TDR monographs on Social, Economic and Behavioural (SEB) Research, this study of a malaria control programme in mainland China focuses on the cost-performance of case-management for suspected vivax malaria, a very important cause of malaria morbidity outside of Africa. At the time of the study, 25 years of malaria control in the study area had reduced transmission of vivax malaria by more than 99% and the control programme had now reached the consolidation stage. Data on all costs of control were obtained prospectively over two years from the government and community. Overall, malaria control and case-management were found to be a good buy in Henan, with balanced community and government costs and benefits. The methods used will be valuable for evaluating the economics of other malaria and health programmes.

- **Report of the Scientific Working Group meeting on African trypanosomiasis, 4-8 June 2001.**
  TDR/TRY/SWG/O2.1
  The first in a new series of reports of TDR scientific working group (SWG) meetings, the SWG on African trypanosomiasis charted out a global research agenda on African trypanosomiasis, closely linked to control needs and open to opportunities arising from basic science, to guide TDR and others interested in this disease. The meeting brought together a multidisciplinary group of scientists, partners and collaborators from academic, public and private sectors, sleeping sickness control programmes, and endemic and non-endemic countries.

- **Guidelines for the rapid assessment of Loa loa**
  TDR/IDE/RAPLOA/02.1
  In communities with high levels of loiasis endemicity, there is a risk of severe adverse reactions to the drug ivermectin, used as treatment for onchocerciasis or lymphatic filariasis. RAPLOA is a rapid assessment procedure for Loa loa. It uses a simple questionnaire on the history of eye worm to predict whether or not loiasis is present at high levels in a community. RAPLOA will facilitate the planning of ivermectin distribution programmes by predicting in which communities ivermectin treatment for onchocerciasis can be safely implemented. This document describes the RAPLOA method, and provides guidelines on how to implement RAPLOA and how to interpret the results. The guidelines are intended for planners and implementers of ivermectin distribution programmes in Africa.

The report reviews the current status of knowledge and makes recommendations for research in three broad areas:
- epidemiology, disease surveillance and control
- drug development, preclinical and clinical studies, drug resistance
- pathogenesis and applied genomics.
Steering Committee meetings

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

**BASIC AND STRATEGIC RESEARCH**
- Molecular Entomology: 31 Aug - 4 Sept 2003*  June 2003*
- Pathogenesis and Applied Genomics: 31 Aug - 4 Sept 2003*  June 2003*
- Strategic Social, Economic and Behavioural Research: 1-4 Sept 2003  27 June 2003

**PRODUCT RESEARCH AND DEVELOPMENT**
- Drug Discovery Research: March 2003*  Jan 2003*
- Vaccine Discovery Research: May 2003*  March 2003*
- Diagnostics Research and Development: 18-20 Sept 2002  18 July 2002

**INTERVENTION DEVELOPMENT AND IMPLEMENTATION RESEARCH**
- Implementation Research Steering Committee: 14-16 Oct 2002  1 Sept 2002
- Proof of Principle Steering Committee: 16-18 Oct 2002  1 Sept 2002

These two steering committees met for the first time in October 2001; incorporated into their activities are those of the previous IDE task forces (Malaria Home Management; Severe Malaria; Research on Drug resistance and Policies; Filariasis Intervention Research; Intervention Research on Chagas Disease; Intervention Research on African Trypanosomiasis; Chemotherapy of Leprosy).

**RESEARCH CAPACITY STRENGTHENING**
  - letters of intent  30 Nov 2002
  - full proposals, progress reports and renewals requests  15 Aug 2002

* tentative