Malaria: past problems and future prospects

After more than a decade of neglect, malaria is finally back on the agenda for both biomedical research and public health politics

Janet Hemingway & Imelda Bates

Malaria is one of the world's biggest killers. In areas where it is highly endemic, young children bear the brunt of the disease. Last year, between 1 and 2 million children below the age of 5 years died of malaria, most of them in Africa. The statistic itself is telling: if malaria were a disease found predominantly in developed countries, then this huge margin of error would be much smaller. The reality is that in the poorest countries, where malaria takes its highest toll, it is difficult to collect accurate data and to derive meaningful statistics about malaria (Trigg & Kondrachine, 1998). Most malaria deaths occur at home, without confirmation of the diagnosis. During their illness, many patients struggle, often unsuccessfully, to access even basic health care. For those that succeed, the care they receive may be of dubious quality and ineffective. To tackle these important problems there is an obvious need for better implementation of our current methods for malaria prevention, diagnosis and treatment, as well as an urgent requirement for new methods to reduce the malaria burden (Hommel, 2002). The publication of the genomes of *Plasmodium falciparum* and *Anopheles gambiae* in October 2002 has given new hope for the development of new anti-malarial drugs that may ultimately help to control the disease.

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Why is malaria still such a huge problem, 105 years after Ross discovered how the malaria parasite is transmitted by the mosquito vector and a century after he received a Nobel Prize for this seminal discovery? Eradication of malaria was promoted in the 1960s, when indoor residual spraying with

Fig. 1 | Insecticide-impregnated bednet trials are underway in Nane-Janania village near Navrongo, Ghana. Drying the nets on sleeping mats also helps to kill any insects in the mat. © WHO/TDR/Ane Haaland.

DDT and prophylaxis using chloroquine were a powerful combination for reducing malaria transmission. On the fringes of the malaria belt in Europe and in parts of Southeast Asia, this campaign was a spectacular success, but in the African and Asian malaria heartlands, it soon became clear that eradication with the available tools, expertise, manpower and funding would be impossible. The emerging resistance of the parasites to the available drugs and of the mosquito vectors to DDT compounded the situation, and the euphoria about the proposed eradication gave way to efforts to sustainably control malaria. Furthermore, the poverty of the areas where malaria transmission is highest, and the unwillingness of richer countries to support open-ended control programmes, means that it is crucial to allocate resources for malaria control to clearly defined priorities that are based on established evidence.

Good leadership and political will are essential to implement evidence-based malaria control on a national scale, but these are often lacking. In April 2000 in Abuja, Nigeria, delegations from 44 African nations met in the largest-ever heads-of-state summit focused on a single health issue. They pledged to take decisive steps towards halving the world's malaria burden by 2010, and to ensure that 60% of those

affected have access to treatment, are particularly protected during pregnancy, and sleep under insecticide-treated nets (ITNs; Figs 1,2). These promises were made as the African leaders signed up to 'Roll Back Malaria' (RBM), a global partnership created in 1998 by the World Health Organization (WHO), the United Nations (UN) Development Programme, the UN Children's Fund and the World Bank. Despite such initiatives, there is little sign of progress towards the Abuja goals.

Current malaria programmes attempt to address both prevention and treatment. Prevention of disease transmission is through the control of the insect vectors at the population level, and through the use of ITNs and other materials to prevent mosquito biting at the individual and household level (Neville *et al.*, 1996; Curtis & Townson, 1998). Prophylaxis of malaria with drugs can be used to provide additional protection for groups at particular risk, such as pregnant women living in, and travellers to, countries where the disease is endemic. Successful operational implementation of each of these malaria prevention strategies is subject to constraints, with problems occurring in some areas more than others. For example, a central plank of RBM strategy is the operational, large-scale

Fig. 2 | Ronei do Silva Rodrigues and his migrant parents in Candeias township close to Porto Velho, Brazil, habitually sleep under bednets to avoid being bitten by mosquitoes. © WHO/TDR/Mark Edwards.

Fig. 3 | Female *Anopheles gambiae* mosquito feeding. © WHO/TDR/Sinclair Stammers.

use of ITNs; the only insecticides authorized by the WHO for use on nets, at present, are the pyrethroids. In 1998, when large-scale ITN use was proposed, it was assumed that the main African vectors (*Anopheles gambiae* (Fig. 3) and *A. funestus*) were fully susceptible to these insecticides (Malcolm, 1988). Since 1998, monitoring through the Multilateral Initiative on Malaria (MIM) scheme has demonstrated that serious resistance problems are present in both vectors. *A. gambiae* has a high frequency of *kdr* (knock-down resistance) throughout much of West Africa; this resistance results from a point mutation in the sodium channels that are the target sites of pyrethroids and DDT. *A. funestus*, by contrast, produces detoxifying enzymes, which also gives rise to metabolic resistance to pyrethroids (Chandre *et al.*, 1999; Brooke *et al.*, 2001). We may have been lucky with *A. gambiae*, because the *kdr* mechanism is functionally recessive and the behavioural change it produces in the homozygous *kdr* mosquitoes results in only minor changes in the efficacy of ITNs to reduce malarial transmission. Nevertheless, the situation in southern Africa is more worrying because resistance in *A. funestus* has severely compromised the use of pyrethroids for both residual spraying and the impregnation of ITNs. An obvious fear is that this metabolic pyrethroid resistance mechanism will eventually be selected in *A. gambiae*, and there is now evidence of this in parts of West Africa and in Kenya (Ranson *et al.*, 2002).

One of the main goals of malaria control programmes is to improve access to prompt drug treatment for initial infections, to prevent the development of life-threatening complications requiring hospital admission. But access to treatment is often problematic, particularly in low-income areas. The problem is compounded by the

spread of drug resistance, which affects many malaria-endemic countries. Chloroquine, the cheapest of the anti-malarial drugs, is now ineffective in many regions. Several African countries have replaced it with sulphadoxine pyrimethamine, but this too has been associated with reduced efficacy during the past few years, with evidence that resistant parasites are being spread rapidly throughout the world. New cost-effective and simple drug regimes are urgently needed; to reduce the development of resistance they will need to be based on rational combinations of drugs (that is, combinations that are affordable, that, ideally, act both synergistically and within similar time-frames, and that can be co-formulated), rather than single agents (Mutabingwa *et al.*, 2001).

What prospects are there for overcoming these and other problems involved in malaria, so that we can make progress towards the now seemingly idealistic targets that were set in Abuja? A malaria vaccine has been a long-standing research goal, but there is little prospect of one becoming available within the next decade (Riley, 1997). Delivery of such a vaccine into poor rural areas, particularly if regular boosters are required, will also need a much better logistical framework than exists at present. In addition, change is needed in many countries to improve the acceptance of ITNs, and we need to resolve the long-standing debates over who should pay for this type of intervention. Long-lasting nets that do not need regular retreatment with insecticide every six months would increase their effectiveness and open up the possibility of using mosaic treatments on nets as a form of resistance management. This would allow carbamates, for example, to be used on the upper sections of nets, and pyrethroids on the lower sections that are more likely to come into contact with the skin.

Many of the current treatments depend on a presumptive diagnosis of malaria based on a combination of clinical features. As there are no features that are specific for malaria this results in considerable over-diagnosis, particularly where malaria is seasonal. We therefore need better methods to diagnose malaria accurately, especially in rural settings where microscopy is impractical. Promising, rapid diagnostic tests are being developed and their relatively high

cost might be offset by reducing the waste associated with using anti-malarial drugs to treat non-malarial illness. This balance might be tilted further in favour of these tests if expensive drug combinations are introduced as first-line therapy for malaria.

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In addition, there is a need to ascertain drug resistance patterns regularly so that treatment recommendations can be adjusted appropriately. Although combination therapy, using a mixture of anti-malarial drugs, should slow down the development of drug resistance, this comes at a significant financial cost. There are other issues, such as correct dosage and compliance, adequate financing of drugs for poor communities and quality control of drugs sold over the counter, that need to be tackled urgently. On a positive note, the recent publication of the *P. falciparum* and *A. gambiae* genomes will facilitate the rapid identification of targets for the development of new drugs and insecticides (Hemingway *et al.*, 2002; Holt *et al.*, 2002). Proteomic approaches will speed up the process of designing small-molecule inhibitors against these targets, and initiatives such as the 'Medicines for Malaria' public-private partnership should ensure the rapid development and production of these new drugs. Their introduction then needs to be managed in a cost-effective and appropriate manner to achieve maximum long-term

Fig. 4 | A young girl experiencing a clinical attack of malaria in a Health Centre in The Gambia. © WHO/TDR/Dr Steven Lindsay.

Fig. 5 | Relatives carry a young Yanomami girl, seriously ill with cerebral malaria, from a field clinic to an aeroplane for transfer to a hospital.
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sustainable malaria control benefits. The availability of the genome sequence might also allow us to rapidly develop novel synergists, or 'resistance breakers', to restore the efficacy of the pyrethroids and other insecticides. Targeting such molecules against the insect-specific regulators of the metabolic resistance mechanism should avoid the problems of increased human toxicity that are common to synergists available at present.

We also need new approaches to address the lack of blood available for emergency transfusions. Anaemia is one of the main life-threatening complications of malaria, and one that mostly affects young children who do not receive adequate early treatment (Fig. 4). Children with severe anaemia have a high mortality rate if a blood transfusion is not available within the first few hours after admission to hospital (Fig. 5; English *et al.*, 2002). However, the marked increase in HIV has made this process far more risky in rural African settings. The reorganization of transfusion services to facilitate the screening of donors for viral markers could improve the safety and reduce the overall costs of the service. This approach needs to be evaluated in a typical developing-country setting. Transfusions of blood from newborn umbilical cords could save the lives of children in hospital with acute anaemia due to malaria when emergency supplies of donated blood are not available. Sufficient blood can be collected from an umbilical cord to save the life of a child with severe malaria-related anaemia. A study in a large hospital in Ghana showed that umbilical cord blood collected from 67% of vaginal deliveries could provide all the transfusion requirements for the paediatric unit at the same hospital.

Other potential uses of modern genomic and transgenic technology might provide new solutions to malaria control in the longer term. Not all mosquito species are able to transmit the malaria parasite, and we are now about to characterize the genes that encode the refractory phenotype (Collins, 1994). These genes, or genes that encode single-chain variant-fragment antibodies against the parasite, could be inserted into the genomes of major mosquito vectors to block transmission (Capurro *et al.*, 2000). Although such transgenic technology was close to science fiction a decade ago, we now have all the necessary technology to produce refractory mosquitoes and a proof of principle in both *A. gambiae* and *A. aegypti*—the latter for bird malaria—that the technology will work. However, the main hurdles that still need to be overcome before it can be introduced are the development of rapid mosquito population replacement and the acceptance of the technology by the human population living in the regions where malaria is endemic.

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After a decade or more of neglect and underfunding, malaria is now firmly back on political and health agendas. New alliances and funding initiatives, such as RBM, the Global Fund for HIV/AIDs, TB and Malaria, Medicines for Malaria and MIM, should provide the impetus to strive to achieve the Abuja targets and support the development of new tools and techniques for the control and treatment of malaria. These initiatives also provide a much-needed opportunity to train the next generation of African malaria researchers, technicians and operational control specialists, and should start to redress the loss of capacity in this area that has been apparent in the past decade.

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Janet Hemingway and Imelda Bates are at the Liverpool School of Tropical Medicine, Liverpool, UK.

E-mail: hemingway@liverpool.ac.uk

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