Malaria in 2002

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The burden of malaria is increasing, especially in sub-Saharan Africa, because of drug and insecticide resistance and social and environmental changes. Thus, there is an urgent need for vaccines, new drugs and insecticides. Parasite, mosquito and human genome projects are helping in the search for new control tools and international donors are developing new funding mechanisms that could make them available to poor countries. But these new tools will achieve their maximum impact only if additional resources are deployed to strengthen malaria research and control communities in countries where the new tools will be used.

Malaria was eliminated from the United States and from most of Europe during the first half of the twentieth century as a result of changes in land use, agricultural practices and house construction and some targeted vector control. The development of the highly effective, residual insecticide DDT initiated a global eradication programme in the 1950s and 1960s which was initially very successful in many countries such as India, Sri Lanka and the former Soviet Union. However, this success was not sustained because of the costs of the programme, the resistance of many communities to repeated spraying of their houses and the emergence of resistance to DDT. Furthermore, with the exception of a few pilot schemes, no sustained effort was made to control malaria in sub-Saharan Africa.

The elimination of malaria from most of Europe and from North America and the failure of the global malaria eradication programme led to a loss of interest in malaria for a period of about 25 years from the early 1970s to the late 1990s. Only 3 of 1,223 new drugs developed during the period 1975–1996 were antimalarials[1]. Industry lost interest in the development of insecticides for public health use and support for research on malaria declined. Furthermore, in many malaria-endemic countries, national malaria control programmes, established during the colonial period and sustained during the period when elimination of malaria was considered to be an achievable goal, collapsed. Thus, for many years, there was little change in mortality and morbidity from malaria, especially in Africa. Recently, the malaria situation has deteriorated and mortality from malaria is probably increasing in sub-Saharan Africa. Some of the reasons for this are shown in Box 1. By far the most important is the development by *Plasmodium falciparum* of resistance to cheap and effective drugs such as chloroquine and sulphadoxine/pyrimethamine.

The burden of malaria

Although malaria remains an important health problem in some parts of Asia and South America, its main impact is in sub-Saharan Africa where at least 90% of deaths from malaria occur. The most important reason for the persistence of malaria in Africa is the presence of the vector *Anopheles gambiae,* although social and economic factors are also important. *A. gambiae* feeds preferentially on humans and is long-lived, making it particularly effective at transmitting malaria from one person to another. The entomological inoculation rate (EIR), a measure of the frequency with which an individual is bitten by an infectious mosquito, rarely exceeds 5 per year in Asia or South America. In contrast, EIRs of over 1,000 have been recorded in several parts of sub-Saharan Africa. In savannah areas of West Africa, it is not unusual to collect in one room during the course of a single night several hundred mosquitoes of the *A. gambiae* complex, 1–5% of which are infectious. The task of interrupting transmission in such a situation is daunting.

There are major differences in the prevalence of malaria between countries in Africa, between districts in the same country and even between villages situated only a mile or two apart (Fig. 1). Consideration of the whole of tropical Africa as an area of hyper-endemic malaria transmission is a simplification of a very complex epidemiological situation. Fortunately, new techniques, including satellite imagery, are making it possible to construct much more accurate maps of the distribution of malaria in Africa than have been available in the past (see review in this issue by Rogers *et al.*, pages 710–715). Superimposition of plots of population density and of the distribution of health facilities on maps of malaria risk may identify imbalances between needs and resources. For example, a study in Kenya showed that insecticide-treated bednet (ITN) programmes were concentrated in areas where nongovernmental organizations had strong links, rather than in areas where malaria risk was greatest[2].

Assessing the burden of malaria accurately is difficult because most deaths from malaria occur at home, the clinical features of malaria are very similar to those of many other infectious diseases and good quality microscopy is available in only a few centres. Despite these limitations, attempts have been made recently to estimate the global burden of malaria more accurately than had been done previously[3,4]. It is now believed that at least one million deaths occur from malaria each year — a death from malaria every 30 seconds. However, when successful interventions have been introduced into malaria-endemic areas, their impact on overall mortality has usually been more marked than would have been expected. Thus, an effective intervention, such as a highly protective malaria vaccine, might save many more deaths than expected.

In many parts of Africa, young children experience several clinical attacks of malaria each year. Fortunately, only a small proportion of these attacks (1–2%) leads to severe complications. Why some children infected with *P. falciparum* develop a life-threatening illness whereas others experience only a febrile illness is still not fully understood. Parasite, host genetic and socioeconomic factors are all likely to have a role (see review in this issue by Miller *et al.*, pages 673–679). Deaths from severe malaria anaemia are increasing because of drug resistance and concerns over

Box 1
Factors contributing to the increasing burden of malaria

Drug resistance. In parts of Southeast Asia, *P. falciparum* is now resistant to almost all antimalarial drugs and strains of chloroquine-resistant *P. vivax* have emerged[6]. In Africa, chloroquine resistance is widespread and resistance to sulphadoxine/pyrimethamine is being detected increasingly frequently (ref. 7; and see review in this issue by Ridley, pages 686–693). Spread of highly resistant parasites of the type found in Southeast Asia to Africa could herald a medical disaster[8].

Insecticide resistance. The emergence of mosquitoes resistant to pyrethroid insecticides in West and South Africa now threatens insecticide-treated bednet programmes[9].

War and civil disturbance. Wars in Africa and elsewhere have led to major problems of malaria transmission in refugee populations. Collapse of health services has led to a resurgence of malaria in some parts of the former Soviet Union[10].

Environmental changes. In Thailand, malaria vectors have established themselves in rubber plantations[11] and construction of small dams has led to an increase in malaria transmission in Ethiopia[12].

Climatic changes. Global warming may have contributed to the spread of malaria into some previously malaria-free mountainous areas of Asia, Africa and South America, but other environmental factors are likely to be involved in this process[13]. Floods associated with increased El Niño rains have precipitated epidemics of malaria in Africa[14].

Travel. About 7,000 imported cases of malaria are recorded in Europe each year[15]. In malaria-endemic countries, travel from malaria-free areas to malaria-endemic areas for work is probably an increasingly important, and largely unrecognized, cause of severe malaria[16].

Population increase. During the past two decades the population of many malaria-endemic countries has doubled, thus greatly increasing absolute numbers of those at risk.

transfusion in communities where the prevalence of infection with human immunodeficiency virus (HIV) is high. Mortality from cerebral malaria remains at about 20%, even in hospitals with good facilities, and about 10% of children who survive are left with neurological defects which may interfere with their education and subsequent chances of employment[5].

Malaria is especially dangerous during pregnancy when some of the immunity acquired by adults as a result of repeated infections is lost. In areas of low transmission, malaria in pregnancy may lead to death of the mother, abortion of the fetus or a stillbirth. In areas of high malaria transmission, heavy parasitization of the placenta with *P. falciparum* may occur (see review in this issue by Miller *et al.*), especially in early pregnancies, impairing placental function and resulting in a low birth weight baby. Because infant survival is so sensitive to even small reductions in birth weight, malaria infection during pregnancy almost certainly increases infant mortality, although this has never been demonstrated directly.

The direct economic costs of malaria that result from treatment and from time away from work or school are enormous, but the overall economic impact of malaria is likely to be much more substantial than suggested by estimates of direct costs alone (see review in this issue by Sachs and Malaney, pages 680–685).

A more hopeful future?

The past five years has seen a pronounced re-awakening of interest in malaria in the richer countries of the world. Statements on the need for greater efforts to control malaria have been made at a number of high-profile political meetings in Africa and in industrialized countries.

Figure 1 The risk of malaria varies from area to area across Africa. In areas of relatively low endemicity, such as highland areas of Tanzania, the whole family is at risk. (Figure courtesy of C. Drakeley.)

Research scientists have had an important catalytic role in this process. In 1997, a meeting was held in Dakar, Senegal, attended by most of the small number of scientists undertaking malaria research in Africa and by their sponsors, which established priorities for a multidisciplinary programme of research. This meeting was held under the auspices of a new organization — the Multilateral Initiative on Malaria (MIM) — which has subsequently supported a number of important initiatives in research, training and information technology.

Since the Dakar meeting, increased funds for malaria research have been provided by established donors such as the National Institutes for Health and the Wellcome Trust, and by new donors such as The Gates Foundation. Another important new initiative has been the creation by the World Health Organization of the Roll Back Malaria (RBM) initiative, a partnership that is drawing together all the main groups interested in malaria control at international and national levels. RBM has raised the profile of malaria control during the past two years and it has set itself ambitious targets. These include achieving 60% access to effective treatment, protection during pregnancy, use of ITN or other appropriate measures of vector control by at-risk groups across Africa by 2005, and a reduction in global mortality from malaria by a half by 2010. RBM now faces the difficult task of delivering on the expectations that have been raised.

The population at risk from malaria in Africa is large, around 500 million, and increasing rapidly; thus the costs of even a basic control programme that will cover the whole population will be substantial, perhaps as much as US$2 billion each year for an indefinite period. Where might this come from? A part might come from the users, as even poor people are prepared to pay for an intervention against mosquitoes (and malaria) that they perceive to be effective, such as a bednet, and substantial additional sums are spent on insecticide coils and other repellents. However, the poor who are at greatest risk are likely to remain unprotected. Additional funds could come from the government through the redistribution of budgets from unproductive areas and from funds released by debt relief. But there is little doubt that malaria will not be controlled effectively in the poorest countries of Africa unless financial help is provided by wealthy, industrialized countries. The recent creation of a Global Fund to support the purchase of goods needed for the management of HIV, tuberculosis and malaria is a promising step forward but it is unlikely to be sufficient by itself, especially if there are no parallel improvements in the healthcare systems that will be needed to deliver these commodities in the most effective way.

Are there adequate tools for the control of malaria in highly endemic areas if substantial additional funds were to be made available? There is little doubt that much could be achieved using the

Box 2
New developments in methods for malaria control

Vector control. The insecticide DDT, still a valuable control tool in some malaria situations when used for household spraying, has been saved from a global ban[17].

Interruption of human–vector contact. Insecticide-treated bednets and curtains have been shown to provide significant protection against malaria in almost all epidemiological situations[18]. Methods are being developed for incorporating insecticide into netting materials, so as to obviate the need for repeated re-treatment, and for increasing bednet usage[19].

Intermittent treatment for malaria in pregnancy. Administration of sulphadoxine/pyrimethamine once during the second and once during the third trimester of pregnancy protects pregnant women against severe malaria anaemia and improves birth weight, although HIV-positive women may require more frequent treatment[20–22].

Intermittent treatment in infancy. A recent study in Tanzania showed that treatment of infants with Fansidar at the time of vaccination reduced the incidence of malaria and anaemia substantially[23].

Improving access to treatment. As a result of training mothers how to treat malaria correctly, mortality was reduced substantially in Ethiopian children[24].

Improved compliance with treatment. It has been shown that training shopkeepers on the importance of selling a full course of treatment and packaging of tablets can help to ensure that full courses of treatment are given[25,26].

Development of artemisinin suppositories. Drugs derived from the plant *Artemisia annua* are effective when given as a suppository, thus providing a means of initial treatment for cases of severe malaria in peripheral clinics where injections cannot be given.

Combination therapy. There is increasing recognition that, as far as possible, antimalarials should be used in combination so as to improve therapeutic efficacy and to decrease the chance of resistant parasites emerging. However, the benefits of combination therapy must be balanced against the draw-back of increased costs[27].

existing tools, which have been shown to be at least partially effective (Box 2). The success of Vietnam in reducing mortality and morbidity from malaria by using ITN and artemisinin-based treatment of clinical cases serves as a model for what can be done.

The *Plasmodium* genome project (see review in this issue by Hoffman *et al.*, pages 702–709) is identifying potential new drug targets at an accelerating rate and this knowledge may allow a drug already in use for some other purpose to be developed as an antimalarial quickly and relatively cheaply (see review in this issue by Ridley, pages 686–693). In addition, a variety of public–private partnerships are being set up to develop drugs for poor countries in a more effective way than has been the case in the past, as exemplified by the development of the new antimalarial Lapdap (chlorproguanil/dapsone). Exploitation of the *Plasmodium* genome project will facilitate vaccine development (see review in this issue by Richie and Saul, pages 694–701) and the anopheline genome project may help to identify novel insecticides, ways of overcoming insecticide resistance and facilitate attempts to develop mosquitoes that are resistant to malaria infection (see review in this issue by Hoffman *et al.*). Thus, at a technical level, prospects for the control of malaria have never been brighter.

Capacity development in endemic countries

Effective national malaria control programmes must be able to detect outbreaks, to monitor parasite and mosquito populations for changes in drug and insecticide resistance, and to make changes in treatment and control guidelines in a rapid and responsible way based on sound scientific findings. Thus, operation of an effective malaria control programme requires trained staff at many levels, ranging from traditional healers and shopkeepers to programme managers. In addition, it is essential that developing country scientists should be given the training and resources needed to allow them to participate fully in the exciting developments that are taking place in many areas of malaria research. Unfortunately, few malaria-endemic countries have given sufficient support to their research scientists or malaria control teams in recent years. So far relatively little attention has been paid by the principal donors who are providing increasing levels of support for malaria research and control to capacity development in malaria-endemic countries. A major investment in staff recruitment, training and support after training is needed if the new tools that are being developed for malaria control are to be introduced and evaluated effectively in the areas where they are needed most. □

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