# Malaria

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**Malaria is the most important parasitic infection in people, accounting for more than 1 million deaths a year. Malaria has become a priority for the international health community and is now the focus of several new initiatives. Prevention and treatment of malaria could be greatly improved with existing methods if increased financial and labour resources were available. However, new approaches for prevention and treatment are needed. Several new drugs are under development, which are likely to be used in combinations to slow the spread of resistance, but the high cost of treatments would make sustainability difficult. Insecticide-treated bed-nets provide a simple but effective means of preventing malaria, especially with the development of longlasting nets in which insecticide is incorporated into the net fibres. One malaria vaccine, RTS,S/AS02, has shown promise in endemic areas and will shortly enter further trials. Other vaccines are being studied in clinical trials, but it will probably be at least 10 years before a malaria vaccine is ready for widespread use.**

Malaria is caused by protozoan parasites belonging to the genus *Plasmodium*. Four species account for almost all human infections (*P falciparum*, *P vivax*, *P malariae*, and *P ovale*). *P falciparum* causes the majority of infections in Africa and is responsible for most severe disease and mortality. *P vivax* and *P ovale* form resting stages in the liver (hypnozoites) that, once reactivated, can cause a clinical relapse many months after the initial event. Malaria can be transmitted by several species of female anopheline mosquitoes that differ in behaviour. This contributes to the varying epidemiological patterns of the disease seen worldwide. Because *P vivax* can develop in mosquitoes at a lower temperature than can *P falciparum*, its geographical range is wider. Figure 1 summarises the malaria life cycle. We present updated information about the challenges and opportunities for improved treatment and control.

After World War II, strenuous efforts were made to eradicate malaria.[1] Although these efforts were successful over large geographical areas, they did not succeed in tropical Africa or in many parts of Asia. The subsequent primary health-care initiative, which placed the main responsibility for malaria control on peripheral health-care workers, was equally unsuccessful. In the past few years, malaria has once again attracted more attention with the establishment of several new initiatives such as the Roll Back Malaria Partnership,[2] partly because of increasing recognition that the malaria situation in sub-Saharan Africa has deteriorated during the past decade, for several reasons (panel 1).[3] The importance of climatic warming is debated.[4,5] War and civil unrest has led to an upsurge of malaria in many parts of Africa where health services have broken down.[6] Malaria and HIV interact in several ways; malaria could adversely affect HIV infection by increasing viral load,[7] whereas HIV increases malaria fevers[8,9] and interacts adversely with malaria during pregnancy.[10] However, the main cause of the worsened malaria situation recorded in recent years has been the spread of drug-resistant parasites, which has led to rising malaria-associated mortality, especially in east Africa, even though overall child mortality has fallen (figure 2).[11,12]

## The burden of malaria

To estimate accurately how many people die from malaria per year is important now that international organisations are setting specific targets for control programmes, but this measurement is difficult to achieve.[13] Most deaths from malaria occur at home, so that information for these events can only come from use of the post-mortem questionnaire technique, an imprecise method. Attempts have been made to improve the reliability of this approach that take into account the sensitivity and specificity of the technique[12] and combine epidemiological, geographic, and demographic data.[14] Most estimates suggest that malaria directly causes about 1 million deaths per year or 3000 deaths a day, and that most of these deaths occur in African children (figure 3).[14] Results of effective intervention studies suggest that the true number could be even higher because of indirect effects of the disease on nutrition and other infections.

Accurate determination of the extent of morbidity caused by malaria is also difficult. Strenuous efforts are being made to measure the morbidity due to malaria by collation of all published reports and unpublished records by groups such as Malaria Risk Across Africa (MARA) and the Child Health Epidemiology Reference Group (CHERG).[14–16] The consensus is that about 0·5 billion clinical attacks of malaria take place every year, including 2–3 million severe attacks (figure 3). In

### Search strategy and selection criteria

In addition to the review of key papers, we undertook searches of electronic databases. For PubMed, the search items were "malaria" restricted to the past 5 years, "malaria and trial", "malaria and pathophysiology", "malaria and diagnosis", "malaria and vectors", and "malaria and vaccines" without a time restriction. The Cochrane database of systematic reviews was searched by use of the term "malaria". Articles were selected on the basis of their effect on malaria treatment or control. When more than one paper illustrated a specific point, the most representative paper was chosen.

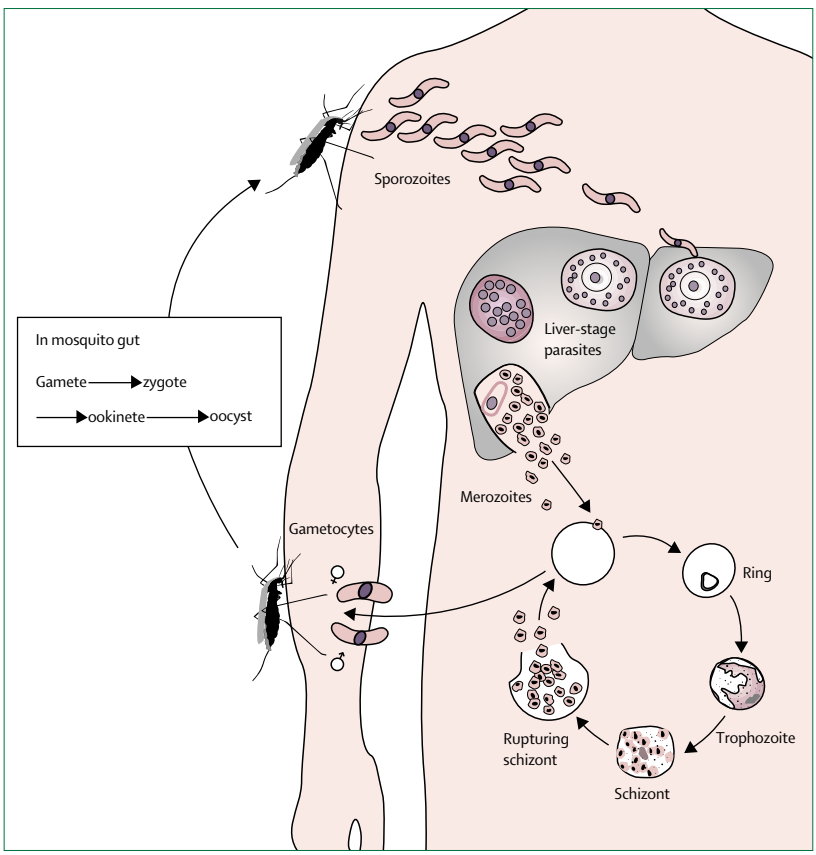



***Figure 1:*** **Life cycle of the malaria parasite**
Adapted from Good MF. Vaccine-induced immunity to malaria parasites and the need for novel strategies. *Trends Parasitol* 2005; **21:** 29–34.

malaria-endemic areas, malaria infection in pregnancy is believed to account for up to a quarter of all cases of severe maternal anaemia and for 10–20% of low birthweight babies.[17,18] In addition to its direct effect in infants, the disease could account for an additional 5–10% of neonatal and infant deaths based on its effect on birthweight.[19] Although most deaths from malaria arise in Africa, which justifies the focus of control efforts in Africa, evidence suggests that the number of clinical episodes of *P falciparum* malaria is higher than that widely quoted, and that morbidity due to malaria in Asia has been greatly underestimated,[20] including that due to *P vivax* infections.

The effect of malaria extends far beyond these direct measures of mortality and morbidity. Malaria can reduce attendance at school and productivity at work and evidence suggests that the disease can impair intellectual development.[21] Cerebral malaria can result in persisting developmental abnormalities.[22] The economic effect of malaria is immense;[23] estimations during the past 35 years indicate that the yearly gross national product (GNP) has risen 2% less in countries where malaria remains highly endemic than in countries with an otherwise similar background where malaria does not occur,[24] and that the disease costs Africa about US$12 billion every year. The burden of malaria falls disproportionately on poor and vulnerable individuals[25] and its social consequences are poorly understood.[26]

Geographical information systems are being used to estimate the prevalence of malaria in areas that have no survey data by matching geographic features (obtained by satellite or ground-based systems) with those in areas where the epidemiological pattern of malaria is known.[14,27] These information systems are also useful for the prediction of epidemics. Study of changes in global climatic patterns, such as El Niño activity, can provide medium-term warning of increased risk.[28] At the local level, new data-collection systems are being developed to allow early detection of local outbreaks, thus providing an opportunity for the rapid implementation of control measures.[29,30]

## The parasite

Malaria research has been transformed by the use of molecular genetic techniques.[31] An example of the value of this investigative approach in the epidemiology of malaria has been the demonstration that a cluster of cases in Kapit (Sarawak, Malaysia) were caused by infection with the monkey parasite *P knowlesi*, and not with the morphologically similar *P malariae* as had been previously thought (figure 4).[32]

***Panel 1:*** **Reasons for deterioration of malaria control**

- Climate instability: droughts and floods can increase malaria transmission in different epidemiological circumstances
- Global warming: global warming can increase transmission in some highland areas, but is unlikely to lead to a wide geographical spread of malaria
- Civil disturbances: civil unrest results in the collapse of malaria treatment programmes and crowding of refugees, some of whom might come from non-endemic areas, which enhances malaria transmission and can lead to epidemics
- Travel: increasing travel within endemic areas as well as by travellers from non-endemic to endemic areas puts many non-immune individuals at risk
- HIV: HIV increases susceptibility to malaria, raises the burden on the health services, and reduces the number of clinical staff available to treat malaria
- Drug resistance: drug resistance is probably the major cause of the deteriorating malaria situation in Africa
- Insecticide resistance: resistance to pyrethroids (used to treat bed-nets) has emerged in *Anopheles gambiae* in west Africa and in *An funestus* in southern Africa. Resistance in *An gambiae* is not yet severe enough to stop treated bed-nets from being effective, but resistance in *An funestus* is more substantial and had needed a change to DDT for household spraying in southern Africa

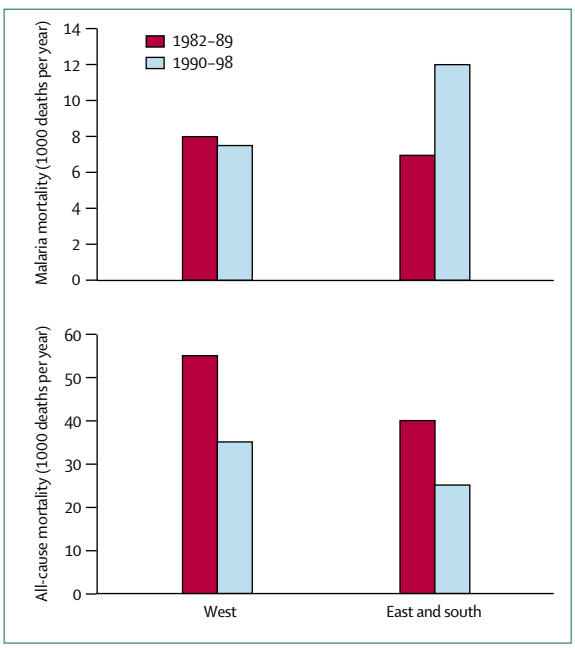



*Figure 2:* **Malaria mortality in Africa**
Adapted from reference 12, with permission from Elsevier.

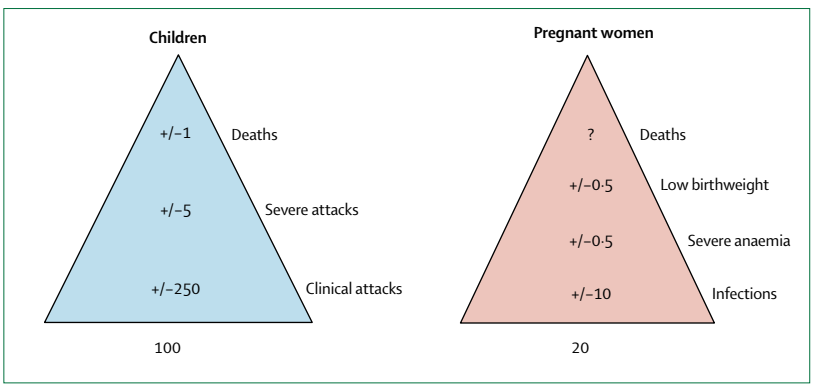



*Figure 3:* **Number of malaria episodes and complications occurring every year in children younger than 5 years in sub-Saharan Africa and in African pregnant women**
Numbers are in millions. Severe attacks in children include about 1 million cases of cerebral malaria and 4 million cases of severe anaemia. Of children with clinical attacks, several thousand have neurological damage and up to 250 000 will have developmental problems. In pregnant women, low birthweight associated with anaemia is thought to contribute to 100 000 infant deaths every year.

Several studies have focused on genetic markers that characterise parasite virulence. The best studied of these is the *P falciparum* erythrocyte–membrane-protein-1 family that are responsible for antigenic variation and for cytoadherence of parasitised erythrocytes to endothelial cells and to cells of the placental syncytiotrophoblast. Parasites that cause severe malaria in non-immune patients tend to express a small subset of these proteins that differ from those expressed by parasites that cause uncomplicated infections.[33] There is also increasing evidence for the virulence of another subset of these variant proteins that mediate sequestration of *P falciparum* in the placenta.[34] More virulence proteins are probably yet to be identified.[35]

Valuable information on the selection, transmission, and clearance of drug-resistant parasites has been obtained by the identification of molecular markers of drug resistance.[36,37] Resistance to the antifolate drug combination sulfadoxine-pyrimethamine is linked to three or four mutations in the dihydrofolate reductase (*dhfr*) gene and to one or two mutations in the dihydropteroate synthase (*dhps*) gene. Surprisingly, these mutations have arisen infrequently and their current widespread distribution is due to gene flow.[38] Resistance of *P falciparum* to chloroquine is largely due to mutations affecting the *pfcrt* and *pfmdr1* genes that have also arisen only infrequently but are now widely distributed.[39] Both chloroquine and sulfadoxine-pyrimethamine have long half-lives; therefore, drug-resistant parasites are at a selective advantage in communities where these drugs are widely used.[40,41] However, in the absence of drug use, resistant parasites seem not to be as well transmitted as wild-type parasites. Complete discontinuation of the use of these drugs (although not easy to achieve) might allow them to become useful again, especially if used in a combination.[42]

Vaccination with polymorphic proteins could lead to the selection of parasite populations that evade the immune response induced by the vaccine; this event can now be monitored by use of molecular techniques.[43] Selection of parasite subpopulations was not reported in a trial[44] of the pre-erythrocytic vaccine RTS,S/AS02 (discussed in detail later), but was recorded in a small trial[45] of the blood-stage vaccine MSP (merozoite surface protein)-2 in Papua New Guinea.

## Pathogenesis and clinical features of malaria

Although the clinical features of malaria have been well-described, severe malaria (predominantly due to *P falciparum*) is now known to be much more complicated

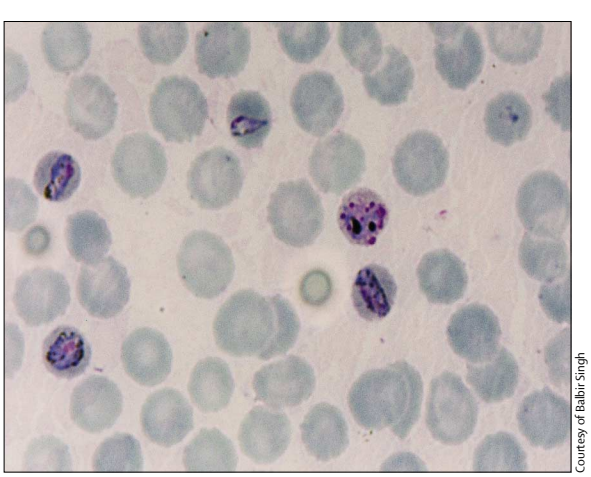



*Figure 4:* **Blood film from a patient with malaria in Kapit, Sarawak**
Trophozoites and schizonts of *P knowlesi*, morphologically similar to those of *P malariae*, are shown.[32]

than originally thought. The clinical pattern of severe malaria differs between non-immune adults and semi-immune African children in several ways, with organ failure being more common in adults than children. The two most frequent presentations of severe malaria in African children are severe anaemia and cerebral malaria, but respiratory distress is the most dangerous, especially in combination with other syndromes.[46]

Cerebral malaria is the best-known form of severe malaria. Carefully undertaken post-mortem and electrophysiological studies in children have shown that this disease is a heterogeneous syndrome in which sequestration probably has a major role in some cases but little in others.[47,48] Metabolic derangement including hypoglycaemia and subclinical convulsions are important in many cases. Sequestration is probably more consistently the cause in adults than in children.[49]

Severe malarial anaemia (figure 5) also consists of a group of conditions with different causes, including direct destruction of parasitised red blood cells, indirect destruction of non-parasitised red blood cells by immune mechanisms, and bone-marrow suppression associated with imbalances in cytokine concentrations.[50]

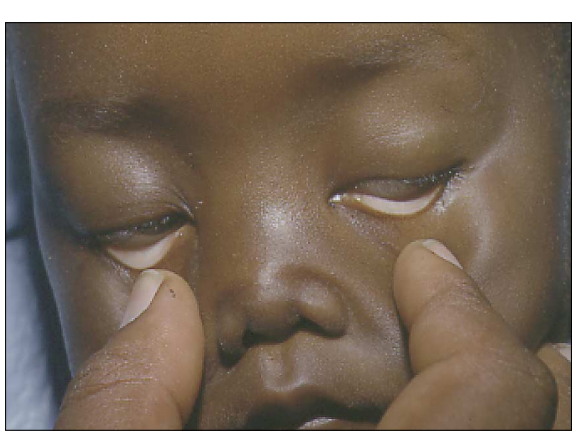
Pro-inflammatory cytokines such as tumour necrosis factor (TNF), nitric oxide, and various metabolic products, are associated with a poor prognosis in severe malaria, but whether this association is always causal is unclear.[51,52] Acidosis is a good marker of disease severity. Initially, this event was thought to be due mainly to lactic acidosis but (in adults at least) lactic acidaemia now seems to be only one of several metabolic causes.[53] In children, increasing evidence has shown that tissue hypoperfusion has a central role in disease severity; the relative importance of hypovolaemia and anaemia are uncertain.[54,55] Research in this area is important, since fluid and (to a lesser extent) blood replacement are the two adjunctive therapies that are available even in poorly resourced hospitals. An extensive search for other adjunctive therapies based on current understanding of the pathophysiology of severe malaria has not yet yielded any product of established benefit, but further study is ongoing.

## Diagnosis of malaria

In tropical Africa, many patients treated for mild or severe malaria do not actually have the disease,[56,57] especially in adults diagnosed as having cerebral malaria.[58] Conversely many cases of malaria are not diagnosed. Overdiagnosis and consequent overprescription of antimalarial drugs for the treatment of uncomplicated malaria was not a major problem when chloroquine was used as first-line treatment, since the drug was safe and cheap. However, over-diagnosis has become a major issue now that drug combinations, which are expensive and in relatively short supply, are the preferred form of first-line treatment. The issue of most concern for patients with severe febrile illness is that treatable alternative diagnoses are being missed. Good evidence now indicates that in Kenya, mortality due to bacterial disease is underestimated in febrile children.[59,60] In adults living in areas where HIV prevalence is high, much of the severe illness treated as malaria is probably HIV-related, although this assumption is not yet proven.[61] Algorithms that attempt to differentiate malaria from other causes of febrile illness in young children using clinical features alone have not proved sensitive or specific enough to guide treatment[62] and, where malaria is endemic but parasitological diagnosis cannot be undertaken, children with fever should be given antimalaria treatment according to Integrated Management of Childhood Illness (IMCI) guidelines, even if another diagnosis such as pneumonia is regarded as likely.

Accurate microscopy can be helpful in diagnosis, but maintenance of the microscopes and the quality of microscopy in peripheral clinics is difficult.[63] Alternatively, several rapid diagnostic tests based on antigen-capture techniques have been developed that have high sensitivity and specificity for falciparum malaria and that could contribute greatly to improving malaria diagnosis in some situations.[64,65] However, these tests have limitations. In highly malaria-endemic areas, many healthy individuals have parasitaemia; thus, although a negative test rules out malaria, a positive test does not prove that malaria is the cause of illness. Another limitation of rapid diagnostic tests is their cost. The introduction of artemisinin-based combination therapy (ACT) probably will make rapid diagnostic tests more cost-effective, but only if their use leads to a substantial reduction in overprescription of antimalarial drugs.

Until recently, first-line treatment for falciparum and vivax malaria was the same (ie, chloroquine) in poorly resourced parts of Asia, such as Afghanistan, where both infections are found and where diagnostic services are scarce. Because *P falciparum* but not *P vivax* has become highly resistant to chloroquine in many of these areas, treatment for both infections is diverging and species diagnosis has now become increasingly important. Unfortunately, most rapid diagnostic tests do not detect vivax infections, and those that do are expensive.



Courtesy of Martin Weber

*Figure 5:* **Gambian child with severe malaria anaemia**

| | |
|---|---|
| **Non-artemisinin combinations** | |
| Quinine and sulfadoxine-pyrimethamine | Used effectively in Europe and parts of Asia. Long treatment course, cost and side-effects make combination inappropriate for the African market |
| Quinine and doxycycline | Similar to quinine and sulfadoxine-pyrimethamine, mainly used where sulfadoxine-pyrimethamine resistance is a problem (eg, historically in Thailand) |
| Sulfadoxine-pyrimethamine and chloroquine | Current policy used in some African countries, but is ineffective where resistance to both drugs is high |
| Sulfadoxine-pyrimethamine and amodiaquine | Substantially more effective than sulfadoxine-pyrimethamine and chloroquine in areas where amodiaquine resistance is low |
| **Artemisinin-based combination treatments (ACTs)** | |
| Artemether-lumefantrine | Currently the only internationally licenced coformulated ACT. Available in Asia and Africa |
| Artesunate and amodiaquine | Currently copackaged. Adopted as policy by some African counties. Effective where amodiaquine resistance is low |
| Dihydroartemisinin-piperaquine | Coformulated drug that has been used widely in Asia and is presently being assessed in a new formulation for licensing |
| Artesunate and mefloquine | Mainstay of antimalarial drug policy in much of southeast Asia. Regarded as too expensive for the African market |
| Artesunate and sulfadoxine-pyrimethamine | Treatment used in some Asian countries (eg, Afghanistan). Ineffective where sulfadoxine-pyrimethamine has failed |
| Dihydroartemisinin-napthoquine-trimethoprim | New formulation used in China and Vietnam. Early reports are encouraging |

***Table:*** **Examples of currently used combinations of antimalarial drugs**

## Treatment of malaria

Although chloroquine is still the first-line treatment for uncomplicated falciparum malaria in some countries, it now fails almost everywhere. Resistance to sulfadoxine-pyrimethamine has occurred in most countries where the drug has been introduced to replace chloroquine,[66] although not in all.[67] Some form of combination treatment is now clearly needed for the first-line treatment of falciparum malaria in Africa and Asia,[68] and in some countries a switch to combination treatment is well overdue. Combination therapy with drugs with different modes of action is now the preferred approach to malaria treatment to inhibit the emergence and spread of parasites resistant to one component of the combination. What combination of drugs should be used and how can such treatment be afforded? Combinations of drugs with similar half-lives are desirable so that parasites are not exposed to one component of the combination alone for long periods.

The most widely promoted combinations are ACTs (table). A coformulated ACT, artemether-lumefantrine, is already available with good efficacy data from Asia[69] and promising effectiveness data from east Africa,[70,71] although few published data support its use in some of the areas where its use is being considered.[72] A combination of artesunate and amodiaquine works well in areas where resistance to amodiaquine is modest.[73] In Africa, the addition of artemisinin to a drug that has failed locally only leads to a failed combination.[71,74] However, in southeast Asia, mefloquine resistance might have been reversed by combination with artemisinin.[75] Not all effective combinations have to contain artemisinin. The combination of amodiaquine and sulfadoxine-pyrimethamine is still efficacious in some areas of Africa where only moderate resistance to these drugs exists,[76] but will remain so only if the component drugs are not used widely for monotherapy.

Although the current choice of ACTs is restricted, the future is encouraging, with several new drugs at various stages of development.[77] Two have considerable promise. First, the fixed-dose combination dihydroartemisinin-piperaquine is already being used in much of southeast Asia and has proved very efficacious.[78] The second treatment, which is being designed for the African market where drugs must be cheap as well as effective, is a combination of artesunate and chlorproguanil-dapsone. The combination is cheap, well-tolerated, and works well even in areas where sulfadoxine-pyrimethamine has failed.[79,80] Questions about the safety of artemisinin in pregnancy[81] and of chlorproguanil-dapsone in those with glucose-6-dehydrogenase deficiency are being addressed. Other new drugs, including those that are modifications of existing antimalarial classes and others with a novel mode of action, are entering clinical trials and the prospects for effective new treatments are much more encouraging than they were a few years ago.[77]

The major obstacle to large-scale use of ACTs is their cost; they are up to ten times more expensive than current monotherapy, which is unrealistic in many settings unless subsidies are introduced.[82] A decision to encourage most African countries to change to ACTs simultaneously, irrespective of their immediate need, has contributed to a short-term quadrupling in the cost

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Courtesy of Brian Greenwood

***Figure 6:*** **Artemisinin suppositories for early management of severe malaria in a village in northern Ghana**

of artemisinins and a global shortage of raw materials. High costs of ACTs have encouraged the production of counterfeits.[83] Synthetic versions of artemisinins (that are being developed) could reduce costs,[84] but in the medium-term at least, improvement of the supply of *Artemisia* and substantial subsidies for ACTs are the only realistic options[85] if ACTs are to be used widely in the many parts of Asia and Africa where the treatment is needed most.

Many deaths from malaria occur in the community before any contact is made with the formal health sector. Several developments have the potential to improve this situation. These advances include home-based management that provides effective treatment as close to home as possible,[86] training of shopkeepers who sell drugs,[87] packaging of drugs,[88] and development of artemisinin suppositories, which can be given to the community for initial treatment of severe malaria before transfer to a treatment centre (figure 6).[89] Achievement of a good balance between the provision of presumptive treatment close to home (to ensure rapid treatment) and the reduction in overprescription of increasingly costly antimalarial drugs is a major challenge.

## Antimalarial drugs and the prevention of malaria

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Several million non-immune people travel to malaria-endemic areas every year for business or pleasure, and they need to be protected. The decision on the most appropriate drug for particular travellers to take for chemoprophylaxis needs a detailed knowledge of their medical history and of the places they will visit. Guidelines on chemoprophylaxis for travellers are provided by several national and international organisations.[90,91]

Early studies in endemic areas showed that chemoprophylaxis during pregnancy reduced the incidence of severe maternal anaemia and improved birthweight. In children, chemoprophylaxis lowered mortality and morbidity from malaria substantially, but it is difficult to sustain over long periods, could encourage drug resistance, and could impede the development of natural immunity.[92] Thus, the discovery that sulfadoxine-pyrimethamine given on two or three occasions during pregnancy was more effective at preventing infection of the placenta than chemoprophylaxis with chloroquine was a breakthrough.[93] Subsequent studies have shown that this approach, now known as intermittent preventive therapy in pregnancy (IPTp), protects against maternal anaemia[94] and low birthweight,[95] especially in primigravidae and secundigravidae, and its use in areas of medium or high transmission is recommended by WHO. Unfortunately, the efficacy of IPTp is reduced in HIV-positive women.[96] Whether IPTp with sulfadoxine-pyrimethamine is effective through prevention of infection or intermittent clearance of parasites from the placenta is not known. This issue is important since increasing resistance to sulfadoxine-pyrimethamine makes the search more urgent for a safe and effective alternative therapy.

**Panel 2: Key questions to be answered before IPTi can be recommended for routine implementation**

- Is IPTi safe?
- Will the administration of drugs at the time of vaccination impair the immune response to routine vaccines?
- Does IPTi require a longlasting drug and, if this is the case, which drug could be used to replace sulfphadoxine-pyrimethamine in areas where this drug is losing efficacy?
- What effect will IPTi have on the development of natural immunity to malaria?
- Will implementation of IPTi encourage or discourage parents from bringing their children for vaccination?
- Can IPTi be introduced into routine EPI (Expanded Programme on Immunization [WHO]) clinics without causing disruption?

IPT has also been used to protect children. Two studies undertaken in Tanzania[97,98] showed that use of sulfadoxine-pyrimethamine or amodiaquine at specific times during the first year of life (IPTi) lowered the incidence of malaria and severe anaemia without any rebound in clinical malaria the following year.[99] These encouraging results have led to the creation of an IPTi consortium addressing several important issues related to the approach (panel 2).[100]

In areas where malaria is highly seasonal and affects older children, a different approach to IPT is needed. Preliminary results are encouraging from studies in Senegal and Mali, in which antimalarial drugs were given to children (younger than 5 years) at set times during the short transmission season.[101,102] IPT is also being investigated as a means of protecting other groups at risk, such as children with anaemia.[103]

Vitamin and mineral supplements have been used to reduce the incidence of clinical attacks of malaria with success for vitamin A,[104] but with conflicting results for zinc.[105,106]

## Vector control

The genome of *Anopheles gambiae* has now been sequenced,[107] providing opportunities for new, targeted measures for control. For example, use of olfactory cues by female mosquitoes to find their human hosts and identification of odorant-binding proteins in the antennae of mosquitoes that respond to components of human sweat could lead to development of new types of insect traps or repellents.[108] A 20-year programme aims to develop and release mosquitoes that are fully refractory to *Plasmodium*. Although refractory strains have been produced in laboratories, the challenge is to find ways to drive resistance mechanisms into the wild mosquito population, without the genetically altered

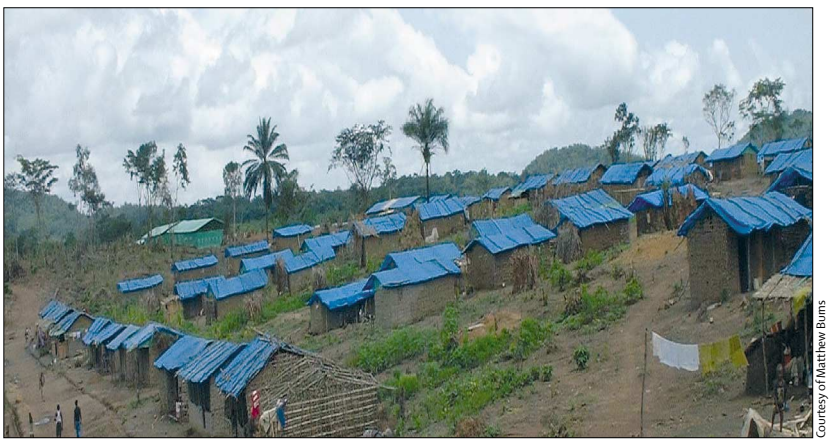
mosquitoes being at a selective disadvantage and being quickly eliminated.[109] Alternative genetic modifications that are lethal to female mosquitoes could be more effective.[110]

Mosquito control has been at the centre of past efforts to eradicate malaria, mainly through the use of the insecticide DDT (dichloro-diphenyl-trichloroethane) for indoor residual house-spraying. Notable successes were achieved, but the programme was not sustainable. Despite attempts to ban DDT completely, the compound continues to be used for vector control although arguments about issues such as the effect on preterm births and the duration of lactation continue.[111] In some southern African countries (mainly those with unstable patterns of malaria), indoor house-spraying with DDT, carbamates, or pyrethroids, used alone or with ACTs has substantially improved malaria control.[112]

Trials of insecticide-treated nets (ITNs) have consistently shown reductions in overall child mortality and in episodes of clinical malaria during a 1–2 year period.[113] In a major study in Kenya,[114] there were substantial health gains in both children and pregnant women, and protection extended from homes with ITNs to adjacent homes without nets.[115] Encouragingly, use of ITNs for 6–7 years has not shown a shift in child mortality from younger to older children.[116,117] Regular re-treatment of nets with insecticide has proved difficult to sustain on a large scale, especially if users are required to pay for it. This problem should be overcome by the development of longlasting insecticidal nets, in which insecticide is incorporated into the net fibres. Different prototypes are being produced, two of which have now been approved by WHO and are undergoing large-scale production.[118] In emergency situations, insecticide-treated tarpaulins have proved very effective (figure 7), and materials that have long-acting insecticidal action are being developed for use in this way. Repellents could provide useful protection against malaria,[119] especially in places where vector mosquitos bite early in the evening. In such situations they might add benefit to ITNs.

Inevitably, resistance to pyrethroids is emerging,[120] but progress is being made in the identification of alternative insecticides that could be used to treat nets and other materials.[121] One approach to prevent insecticide resistance is the use of mixtures or mosaics of insecticides on nets. This method would be difficult to sustain if repeated re-treatment of nets was needed, but trials of this process would be worthwhile for longlasting insecticidal nets.

Despite the proven benefits and cost-effectiveness of ITNs, achievement of widespread use has proved difficult. In most sub-Saharan countries, only a small percentage of individuals who should be protected by nets actually use them.[122] Full cost recovery for nets and insecticides makes them unavailable to the most vulnerable groups. Part cost recovery by use of vouchers and often combined with social marketing[123] solves the problem to some extent. Free provision of ITNs, sometimes linked to other initiatives such as vaccination or attendance to antenatal clinics, has strong advocates[124] and is gaining support, but this approach needs a major and sustained commitment from international donors.[125]



Courtesy of Matthew Bums

*Figure 7:* **Insecticide-treated tarpaulins used for malaria prevention in a refugee camp in Sierra Leone (Tobanda)**

Environmental management (including drainage of breeding sites), improvements to house design, use of larvivorous fish, and zooprophylaxis have proved effective in some specific epidemiological situations but must be based on detailed behavioural knowledge of the main local vectors.

## Malaria vaccines

Vaccine development against both falciparum and vivax malaria is ongoing.[126,127] The decision on which parasite antigens are to undergo clinical development is difficult. Criteria for development include evidence showing that the antigen serves a function critical to the parasite, is associated with naturally acquired immunity, or is protective in animal models.[128]

So far, most efforts have been directed at the development of pre-erythrocytic stage vaccines designed to prevent invasion of hepatocytes by sporozoites or to destroy infected hepatocytes (figure 8). RTS,S/AS02A is the most advanced pre-erythrocytic vaccine, and is a hybrid molecule in which the circumsporozoite protein of *P falciparum* is expressed with hepatitis-B surface antigen (HBsAg) in yeast.[129] The vaccine is given with AS02, a complex three-component adjuvant. RTS,S/ AS02A has provided substantial, short-lived protection in volunteers, exposed experimentally to bites by infected mosquitoes,[130] and substantial (71%) but only short-term protection in naturally exposed, semi-immune adults from The Gambia.[131] Some protection was restored by one booster dose of vaccine given the next year. In a subsequent trial in Mozambican children,[132] RTS,S/AS02A gave 30% protection against the first clinical episode of malaria and 58% protection against severe malaria.

Comparison of different methods of immunisation with pre-erythrocytic vaccines has shown that schedules that

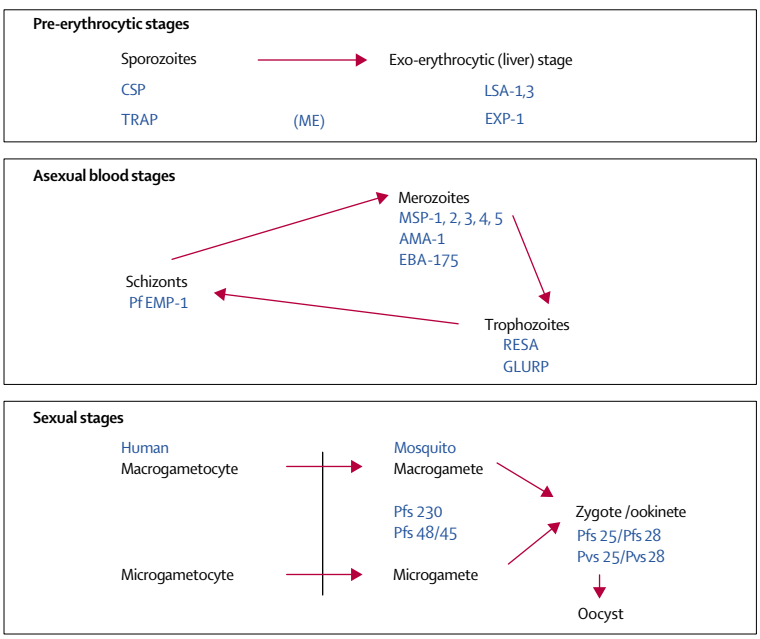



***Figure 8:*** **Malaria vaccines under development**
CSP=circumsporozoite protein. TRAP=thrombospondin-related adhesion protein. LSA=liver-stage antigen. EXP=exported antigen. ME=multiple-epitope string based on T-cell and B-cell epitopes of pre-erythrocytic stage antigens. MSP=merozoite surface protein. AMA=apical merozoite antigen. EBA=erythrocyte-binding antigen. RESA=ring-infected erythrocyte surface antigen. GLURP=glutamine-rich protein. Pf EMP=*P falciparum* erythrocyte-membrane protein. Pfs 230 and Pfs 48/45=antigens located on the surface of *P falciparum* gametocytes. Pfs 25/Pfs 28 and Pvs 25/Pvs 28=antigens located on the surface of ookinetes of *P falciparum* and *P vivax*, respectively.

use different presentations of the same antigen for different doses (prime-boost immunisation) are especially effective in inducing T-cell responses.[133,134] DNA, modified vaccinia and fowlpox vaccines encoding identical DNA sequences of epitopes from pre-erythrocytic antigens, and the entire sequence of the thrombospondin-related adhesion protein (TRAP) have undergone clinical trials. Several phase I studies have generated data showing the safety and strong immunogenicity of these vaccines.[135] Results of a phase IIb trial in semi-immune adult men in The Gambia were disappointing,[136] but additional trials based on this strategy, including a phase IIb trial in Kenyan children, are ongoing.

The aim of blood-stage vaccines is to eliminate or reduce the number of blood-stage parasites. Efforts to develop blood-stage vaccines have focused mainly on antigens contributing to erythrocyte invasion (figure 8).[137] A combination vaccine of three blood-stage antigens reduced parasite density in a strain-specific manner but had no pronounced effect on the overall number of clinical malaria episodes.[45] Vaccines based on the blood-stage vaccines MSP-1 and AMA (apical merozoite antigen)-1 are currently undergoing clinical trials.

Multicomponent vaccines will probably be needed to cope with the problem of antigenic polymorphism. An alternative is whole-organism vaccines—sporozoite or blood stage. Surprisingly a combination of very low doses of infection and drug treatment gave complete protection against challenge in volunteers.[138]

Transmission-blocking vaccines are designed to prevent mosquitoes that feed on vaccinated individuals from becoming infected, reducing transmission and providing indirect protection to the entire population.[139] Transmission-blocking vaccines against *P falciparum* and *P vivax* are well in advance and phase I trials are taking place.

Malarial vaccine research has progressed rapidly over the past few years, helped by the availability of more funds and by improved organisation mediated through organisations such as the Malaria Vaccine Initiative.[140] However, it is likely to be at least a decade before an efficacious vaccine is available for widespread use in malaria-endemic countries.

## Conclusions

There is no clear, single path to improve malaria control. Such an approach will probably come from a series of incremental steps involving better and more widespread use of the methods that have already been shown to be effective, as well as the step-wise introduction of new treatments and partly effective control measures shown to be of benefit.

Establishment of an effective malaria control programme—eg, one based on ACTs for treatment of diagnosed cases or on ITNs and IPTp for prevention—costs about $2–5 per person per year, a month's wages for many average-sized families. Thus, if wide coverage is to be obtained with these simple interventions, subsidies will be needed for poor and vulnerable individuals. For the first time, the international health community could be prepared to make this possible. The formation of the Global Fund Against AIDS, Tuberculosis and Malaria was an important first step in this direction and the group has committed nearly $1 billion to malaria control for the next 2 years.[141] It is essential that the international community continues to support this initiative.

Although much more can be done with existing measures, new methods for malaria control are needed. Development of new antimalarial drugs or malaria vaccines is not an attractive financial option for large pharmaceutical companies. Thus, the creation of public-private partnerships such as the Medicines for Malaria Venture[77] and the Malaria Vaccine Initiative,[140] in which major pharmaceutical companies can participate, is an important step forward. New drugs, vaccines, and vector control measures will need evaluation, both alone and, increasingly, in combination, which will need innovative research designs. Such studies, carried out to full international standards will have to be done in malaria-endemic areas. Currently few centres in endemic areas have the infrastructure or staff to take this on. Increased investment in more centres and scientists from malaria-endemic countries is urgent.

Major efforts are being made to develop new procedures for malaria treatment and control. However, these approaches will only achieve their maximum potential if a functioning health-care system can deliver them.[142] Improved treatment throughout the malaria-endemic areas of Africa will need a major increase in staff numbers, provision of appropriate training, and provision of sufficient monetary and non-financial incentives to retain key staff in post.

**Conflict of interest statement**

We declare that we have no conflict of interest.

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