Malaria: current status of control, diagnosis, treatment, and a proposed agenda for research and development

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Rolling back malaria is possible. Tools are available but they are not used. Several countries deploy, as their national malaria control treatment policy, drugs that are no longer effective. New and innovative methods of vector control, diagnosis, and treatment should be developed, and work towards development of new drugs and a vaccine should receive much greater support. But the pressing need, in the face of increasing global mortality and general lack of progress in malaria control, is research into the best methods of deploying and using existing approaches, particularly insecticide-treated mosquito nets, rapid methods of diagnosis, and artemisinin-based combination treatments. Evidence on these approaches should provide national governments and international donors with the cost-benefit information that would justify much-needed increases in global support for appropriate and effective malaria control.

Lancet Infect Dis 2002; **2:** 564–73

Malaria is the world's most important parasitic infection, ranking among the major health and developmental challenges for the poor countries of the world.[1] Four parasite species of the genus *Plasmodium* infect human beings, but two cause the majority of infections. Nearly all malaria deaths and a large proportion of morbidity are caused by *Plasmodium falciparum*. During the "eradication era", half a century ago, malaria was eliminated or effectively suppressed in many parts of the world, particularly subtropical regions. Malaria is now on the rise again; since it is appearing in areas where it had disappeared, it is classified by some as a re-emerging disease. In general though, malaria has been a submerged disease, because lack of investment even in data collection has led people to conclude that it is being tackled effectively.[2] Despite global economic development, more people die from malaria nowadays than 40 years ago.

The current failure to control malaria through effective vector control and treatment of the disease results mainly from an inability to deliver appropriate case-management to a significant proportion of patients, particularly at the periphery of health systems. This paper attempts to define some of the essential research questions that must be addressed if we are to combat malaria.

Incidence, burden, and economic consequences

More than a third of the world's population (about 2 billion people) live in malaria-endemic areas, and 1 billion people are estimated to carry parasites at any one time. In Africa alone, there are an estimated 200–450 million cases of fever in children infected with malaria parasites each year.[3] Estimates for annual malaria mortality range from 0·5 to 3·0 million people.[4] These are imprecise estimates because there has been little investment in proper documentation of the epidemiology and burden of malaria.[3,5] Malaria-related mortality is particularly difficult to measure because the symptoms of the disease are non-specific and most deaths occur at home. Although use of ineffective drugs for a potentially lethal disease will inevitably result in an increase in mortality, there are few reliable data on the extent of the problem.[6] Data from control programmes and research are rarely compiled together. Both researchers and control experts share responsibility for this failure.

In general, the effects of resistance to antimalarial drugs on malaria morbidity and mortality are underestimated.[7] The single well-documented study to date on the effect on mortality of resistance to chloroquine concluded that the development of resistance had resulted in a four to eight fold increase in mortality.[8] Inadequate epidemiological data create many problems, justifying inaction and preventing the policy changes that would allow deployment of effective treatments.

Malaria-endemic countries are among the poorest in the world. In 1995, income was only a third that of non-endemic countries, irrespective of geographical location.[9]

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Malaria has both short-term and long-term health costs and economic consequences. In addition to traditional measures of morbidity and mortality, disease burden in these countries can be quantified through disability-adjusted life years (DALYs),[10] effect on health systems, and socioeconomic impact, but these estimates also suffer from the general lack of high-quality data. In 2000, malaria was estimated to be the cause for the loss of nearly 45 million DALYs (13% of all infectious diseases).[10,11] In addition to the more routinely measured costs associated with malaria, such as the cost of prevention activities, lost workdays for both patients and caregivers, and treatment seeking and medication, malaria-related costs in endemic countries also include those associated with suffering, retarded physical and cognitive development in children and consequently poor educational performance, related malnutrition, anaemia, and potential increases in vulnerability to other diseases.[12–15] Malaria incapacitates the labour force, lowers educational achievement, discourages tourism and business investment, and reduces opportunities for specialisation both within the household and for the economy as a whole.

Estimates of the economic burden of malaria measured in terms of lost opportunities for economic growth range from 0·25% to 1·30% of a country's per-person GNP growth rate, even after control for factors such as initial income level, geographical location, and overall life expectancy.[16–18] Slow economic growth prevents improvements in living standards and places a serious constraint on countries' ability to fund and maintain malaria-control efforts, thereby creating a vicious cycle of high disease prevalence and low economic growth.

Control strategies

Prevention of infection

After World War II, widespread use of DDT coupled with the covering and draining of breeding grounds resulted in a substantial reduction in mosquito populations and, together with effective treatment, eradicated malaria in southern Europe, Russia, and parts of Asia. Although substantial successes were achieved in subtropical regions, control of malaria in the tropics proved far more challenging. The effectiveness of the control effort was undermined through a combination of difficult access to health facilities, the deterioration of health infrastructures, and the gradual development of insecticide resistance. As a consequence, plans for eradication of malaria through vector control had to be abandoned in the late 1960s.

Malaria-prevention efforts have since shifted toward more appropriate local protection methods, focusing on partial control of breeding grounds and, in particular, on the use of insecticide-treated mosquito nets, which both reduce the number of infective bites for a given mosquito population and have important mass insecticidal effects. Deployment of impregnated bednets in China and Africa has been successful in reducing malaria morbidity, mortality, or both,[19–21] although the resulting decrease in naturally occurring immunity may limit this effect in the medium term.[22] Resistance of the vectors to insecticides is generally increasing. Moreover, even in areas where the benefits are substantial and bednets have been deployed through national programmes, community uptake has been disappointing. The reasons why need to be examined and lessons learned to improve sustainability. The effectiveness of insecticide-treated mosquito nets varies with the rate of malaria transmission; the nets do not work well in many areas of low and unstable transmission, where malaria vectors bite in the early evening and morning.[23] Further work remains to be done on new combinations of insecticides and fabrics. More information is also needed on the relation between the extent of community use of insecticide-treated mosquito nets and malaria morbidity, mortality, and transmission.

Vaccines

With an increase in both insecticide and antimalarial-drug resistance, the development of a malaria vaccine carries huge expectations. However, vaccine research over the past three decades has been characterised by lack of funding, a serious underestimation of the complexity of the parasite, faith in technology above scientific understanding, lack of appropriate models, and above all a lack of adequate knowledge about the immune mechanisms underlying protection.

As a reflection of these uncertainties, there has recently been a move away from animal models and an emphasis on clinical trials.[24] Of the 6000–8000 malaria proteins so far identified, the few that have been the subject of clinical trials are outlined below.

Vaccines can target different stages of the parasite cycle, each with a distinct antigenic repertoire.[25] The pre-erythrocytic stage (sporozoite and liver-stage) vaccines are those best supported financially, perhaps because there is a potential market in the more developed countries (armed forces, tourists, short-term visitors such as business people and field researchers). Immunisation with sporozoites can produce protective immunity, but the experimental means of conferring protection, multiple repeated exposures to bites of hundreds of irradiated mosquitoes,[26] is not practicable, and efforts to produce the same degree of protection with vaccines based on sporozoite proteins have so far failed.[27–29] Difficulties include substantial polymorphism in immunologically important regions of the proteins (epitopes) and low immunogenicity. Irradiated sporozoites are now known to transform into young liver forms, and emphasis is being placed on molecules deriving from the latter stages.[22]

Asexual blood-stage vaccines aim at reproducing the situation that occurs in adults in hyperendemic areas—ie, predominantly antibody-mediated protection acquired through repeated exposure to infection. The goal is more modest, because in human beings any reduction of the parasite load will decrease or abrogate symptoms. However, since the mechanism of antibody-mediated protection is not agreed on, which of the current vaccine candidates should be developed is not clear, and the results obtained in models cannot be extrapolated to human beings with certainty.

A gamete-stage vaccine aims to prevent mosquitoes that are feeding on an infected individual from acquiring and

transmitting the parasite. This altruistic approach does not protect the vaccinated individual but contributes to protection in the community.[30] In the absence of complete coverage, such a vaccine would be expected to decrease the number of infections only in low-transmission areas. Despite its efficacy in models, this approach is limited by overall poor immunogenicity and lack of natural boosting.

One of the few vaccines to undergo large-scale clinical trials, the three-component vaccine (SPf66) developed by Pattaroyo,[31] did not show any efficacy.[32,33] The most advanced development to date is the RTS'S, based on a particulate construct of the circumsporozoite protein fused to the hepatitis B surface antigen. Because of polymorphisms in the critical epitopes of the circumsporozoite protein, clinical trials showed protection only to a strain homologous to that used in the vaccine design.[34] Field trials, in which heterologous strains would have been encountered, have shown protection in some volunteer vaccine recipients, but it waned after 1–2 months, and a design limitation was that the control group was not given the adjuvant given to the experimental group.[35]

Among blood-stage molecules, MSP1, alone or combined with MSP2, has been included in several human trials. However, the inhibition of merozoite invasion obtained with monoclonal antibodies has not been induced to date by immunisation.[36–38] Several other molecules are being channelled into human trials on the basis of results considered promising and obtained in one of the primate, mouse, or in-vitro models (figure 1).[39–43] Clinical trials will be essential to show whether these results can be extended to human beings.

In view of the failures with the initial available candidates there has been a recent trend towards multicomponent or multistage vaccines that use combinations of components that are individually not sufficiently effective. The difficulty of deciding which vaccine candidates to take through to clinical trials is best illustrated by the Nyvac-7, and NMRI "Must Do" programme, in which this choice is avoided by use of mixtures of five, seven, nine, or 15 different antigens.[29,44] This inclusive strategy carries the risk of significantly decreasing the immunogenicity of each individual antigen.[45]

Diagnosis

Access to medical care is limited in many malaria-endemic areas. Where medical services exist, they commonly lack facilities for laboratory diagnosis. As a result, malaria treatment is mostly given on the basis of clinical or self diagnosis. However, clinical diagnosis is very inaccurate, even in areas where malaria is a common cause of fever, because signs and symptoms of uncomplicated malaria are non-specific and overlap with those of other febrile infectious diseases,[46,47] and because the subjective sensation of fever is unreliable.[48,49]

The specificity of clinical diagnosis (ie, declared fever) is only 20-60% compared with microscopy.[50–54] Microscopy (Giemsa-stained thin and/or thick smears) is traditionally the gold standard for diagnosis. Under optimum conditions, microscopy can detect 20-50 parasites per μL blood, but such sensitivity is rarely achieved in routine diagnosis. Although microscopy is simple and inexpensive, to achieve high sensitivity requires training and quality control of microscopists, adequate equipment, and maintenance. These costs have not been documented adequately and vary from place to place.

Cost-effectiveness has been at the centre of the debate as to whether treatment should be provided on clinical or parasitological grounds, and in the latter case, which method should be used. The presence of parasites in a blood smear in low-transmission areas indicates that malaria is the cause of the illness, but this does not apply where transmission is intense and a large proportion of the population is infected at any one time (though not necessarily ill). Parasite counts above a threshold value (eg, 10 000/μL in an intense-transmission setting) are specific for malaria; therefore there is a need for less sensitive or semiquantitative dipsticks in these settings.

Microscopy is generally not available in most clinics in Africa; where it is available, the quality of microscopy is likely to be poor. As a result, antimalarial drugs are generally prescribed to treat fever, irrespective of the microscopy results. In areas or seasons of high malaria transmission, WHO recommends antimalarial treatment for all patients with fever or a history of fever.[55] However, this policy has been adopted much more widely, resulting in unnecessary treatment and inappropriate use of drugs, associated toxicity, and increased costs to both individuals and health systems (that again have not been documented adequately).

In addition, this policy relies on inexpensive drugs (chloroquine and sulfadoxine/pyrimethamine [SP]), the effectiveness of which has been greatly eroded by resistance. There are very few places where chloroquine can be relied on, and resistance to SP has developed rapidly nearly everywhere that it has been widely deployed. The next options for treatment are substantially more expensive.[56]

Several alternative laboratory methods have been developed, including the quantitative buffy-coat centrifugal haematology system, immunofluorescence, ELISA tests for the detection of *P falciparum* antigen, and use of PCR. None of these tests is used routinely because they are too complicated or too expensive. Rapid blood tests have lately become commercially available; these use a dipstick or test strip with monoclonal antibodies directed against the target parasite antigen, histidine-rich protein 2 (Pf HRP2) or parasite-specific lactate dehydrogenase (pLDH). The tests can be done in less than 15 min, require little training, and are subject to less investigator-related variation than microscopy. They are generally more than 90% sensitive and specific for falciparum malaria[57] compared with microscopy,[58–62] although HRP2 persistence for weeks after a malaria episode is a drawback for this test. The main limitation of these rapid tests is their cost (US$0·50–3·00), and their lower sensitivity in the diagnosis of the other human malaria infections. Dipstick antigen-capture assays are cost-effective for the management of *P falciparum* malaria in specific conditions: in epidemics and emergencies; in mobile clinics; where laboratory services are inadequate; where first-line treatment is much more expensive than the dipstick assay; and in previously treated severe cases for whom

blood films may have become negative.[63] Unit cost will determine the future choice in many geographical areas.[64]

Treatment

Treatment access

Prompt and effective treatment is probably the most cost-effective element of malaria control.[65] The bulk of antimalarial therapy worldwide is oral drugs for uncomplicated falciparum malaria. Oral treatment prevents progression to severe disease and complications, and, if the drugs are efficacious and applied effectively, they reduce overall malaria morbidity and mortality.[66,67] However, most people living in endemic areas have little or no access to diagnosis and treatment; moreover, treatment is commonly inadequate because quality-assured, effective drugs are not available, or if available they are not taken correctly (incorrect prescription or poor adherence) or they are taken when not needed (the patient does not have malaria). Most malaria-affected countries have, as their national treatment recommendations, drugs that are partly or even completely ineffective.

In many areas, illness and treatment tend to occur outside the formal health sector and are therefore not included in health statistics, and so little is known about the numbers and treatment-seeking behaviours of patients with uncomplicated malaria. These factors influence the effectiveness of malaria-control programmes. Failure to provide prompt treatment in the private or public sector leads to severe malaria. When the patient's condition deteriorates, oral treatment is no longer possible and injectable or rectal administration is required.[68,69] Delays in referral may be fatal. Therefore, attention has been given recently to ways of making treatment available close to or in the home,[70] with both oral drugs for patients with uncomplicated malaria and rectal formulations for incipient severe malaria (ie, for patients who cannot take oral medication and whose condition is deteriorating).

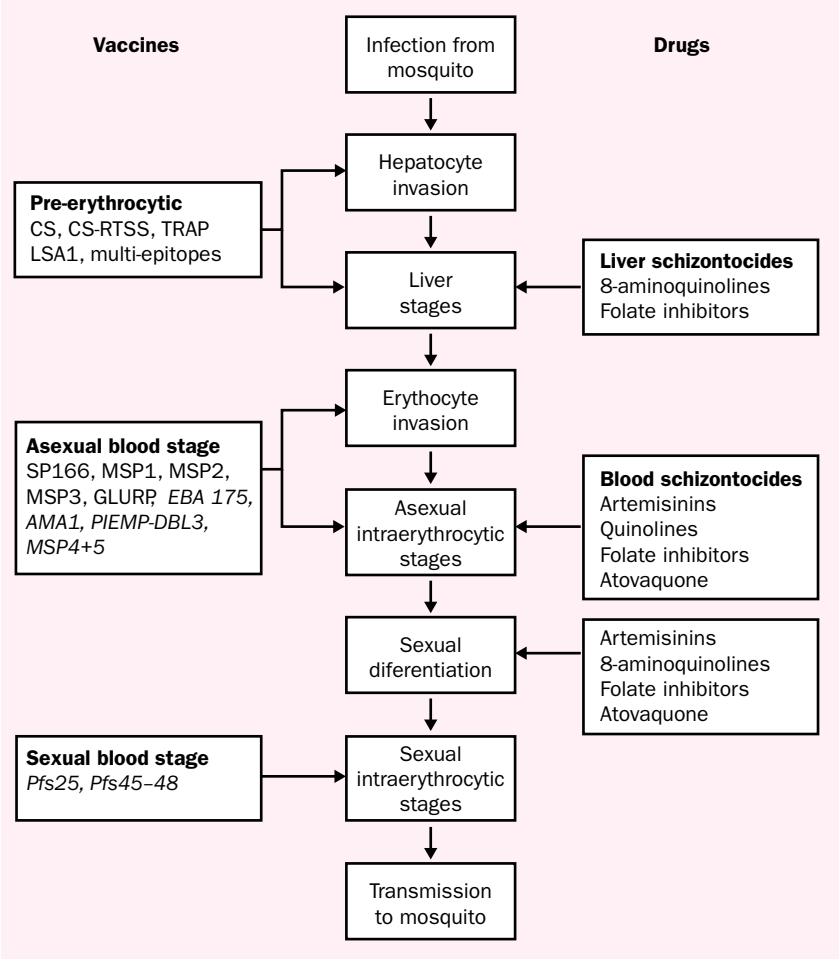

Figure 1. Target stages of vaccines and antimalarial drugs. The vaccine candidates that have undergone clinical trials are shown in capitals, and those that should do soon are in italics. Some, such as circumsporozoite protein (CS) and MSP1 cover several distinct formulations.

Resistance

Adequate malaria treatment requires that effective and safe drugs are available to patients in such a way that the useful lifespan of the drugs is maximised—ie, they are protected against the emergence of resistance.[71] Resistance is more likely to emerge when background immunity is weak, parasite numbers in an individual are high, transmission is low, and drug pressure is intense.[72] The propensity for resistance to develop also depends on the pharmacokinetic and pharmacodynamic properties of the drug;[73] drugs with long half-lives and for which resistance is conferred by single-point mutations select resistant parasites rapidly. Uncontrolled use and poor quality or fake drugs also contribute to the emergence of resistance. Problems with fake artesunate or mefloquine have been reported throughout southeast Asia.[74,75]

The use of a drug for which there is widespread resistance leads to increased malaria mortality and morbidity.[8,76] As resistance increases, the duration of clinical improvement is shortened and haematological recovery after treatment is impaired.[77] A shortened period of clinical relief means that many children never become truly healthy. Furthermore, the use of drugs with poor efficacy results in increased costs to the health-care system arising from frequent visits and the much higher costs of severe malaria.

P falciparum has become variably resistant to all drug classes except the artemisinin derivatives. Currently, chloroquine-resistant *P falciparum* is widespread across all malaria-endemic areas. The efficacy of SP has declined rapidly in all regions where it has been introduced for

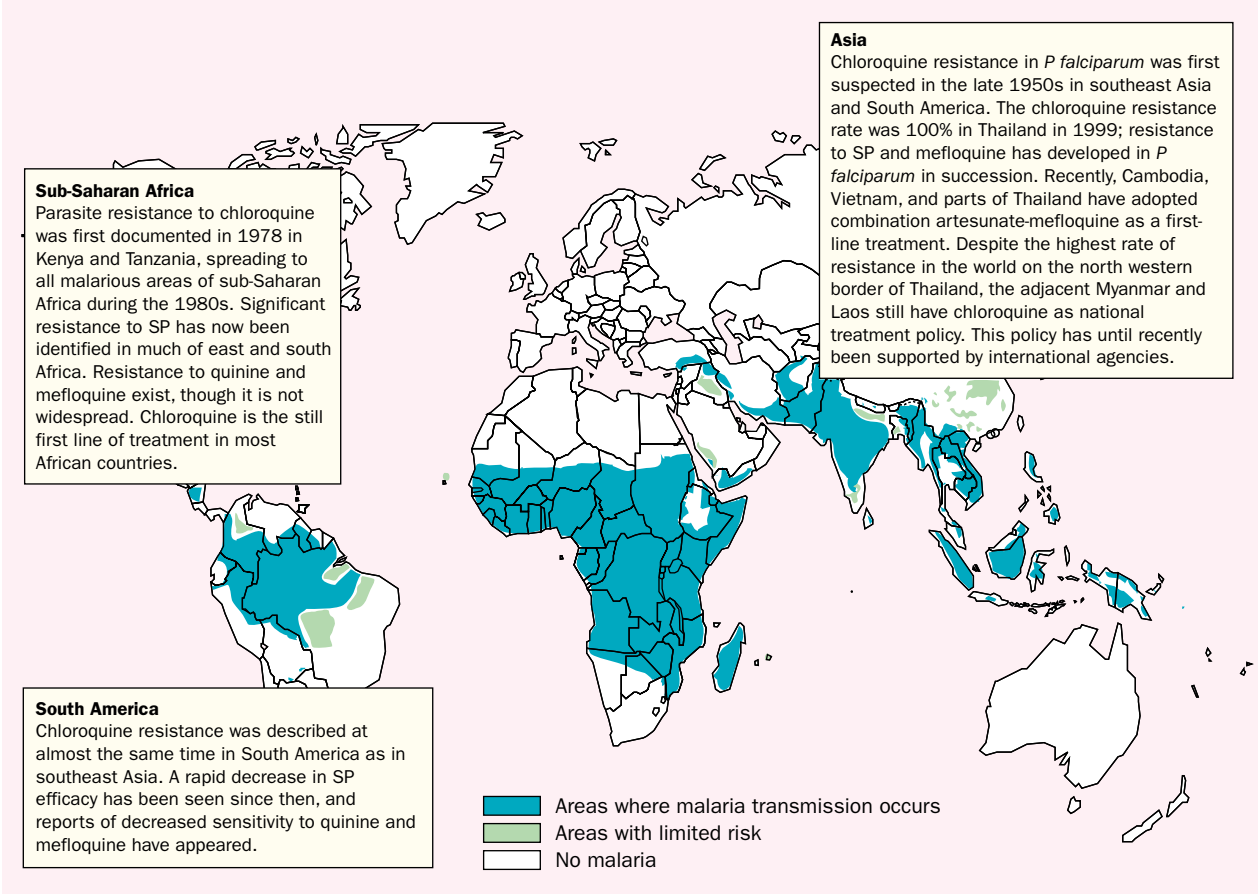

Figure 2. Antimalarial resistance by region. Reproduced with permission from WHO.

widespread use.[78] Multidrug resistance is established in southeast Asia, South America, and Africa (figure 2). Drugs currently in use are of a restricted range of chemical classes (figure 1, panel).[79–81] The over-reliance on the same classes of drugs (quinolines and folate inhibitors) is threatened by cross-resistance among closely related chemical entities. The sequential introduction of drugs as monotherapy has led to sequential selection and spread of mutant drug-resistant malaria parasites and ultimately to multidrug resistance.[82,83] Artemisinin-based combinations, which provide mutual protection against resistance, high efficacy, excellent tolerability, and reduced transmissibility, are judged the most effective strategy to provide highly effective treatment that will not fall to resistance.[84,85]

The artemisinin-based combinations also reduce the transmissibility of malaria by preventing gametocyte development. This feature, combined with high treatment efficacy, has led to a reduction in the incidence of falciparum malaria in areas of southeast Asia where artemisinin-based combinations have been deployed systematically. The effects of these combinations on disease incidence and on the emergence of resistance at higher rates of transmission requires further study, as does the relation between prevention of resistance and community coverage. However, they provide the best approach to antimalarial treatment, and are available now.

Severe malaria

In the treatment of severe malaria, the artemisinin derivatives have diverse advantages over injectable quinine, which otherwise remains effective in most areas.[86] In large randomised trials artemether proved certainly as good as quinine, and in southeast Asian adults better, but it is an oil-based intramuscular formulation that is erratically absorbed, and may not have been the best formulation to test. There are few data on the immediately bioavailable water-soluble parenteral artesunate, and there is still only one manufacturing source: this drug urgently needs further assessment. Mortality from severe malaria continues to be high even when effective drugs are used in the best facilities (14–17% in the above-mentioned study),[86] mainly because patients arrive in health centres in an advanced state of disease that cannot be reversed by the antimalarial and ancillary therapies. Home or village-based rectal administration of artesunate is a very promising approach for the treatment of patients who cannot take oral antimalarials to prevent latent progression, and optimising deployment and use of rectal artesunate is an important research priority.

Severe malaria includes organ failure, cerebral malaria, and severe anaemia.[12] Management of cerebral malaria requires more sophisticated training and devices for parenteral and ancillary treatment.[87] Certain groups of

patients (pregnant women, infants) are at particular risk and require special care. Animal models and various theories of severe malaria pathogenesis have not yielded therapeutic benefits. To date, no adjuvant treatment has proved effective in severe malaria; all have been ineffective or harmful.[88–90]

Malaria in pregnancy

Pregnant women are more susceptible than the general population to malaria and its consequences.[91–93] Malaria-related maternal mortality can be very high,[15] particularly in epidemics and in areas of low transmission and therefore low immunity. The economic burden on households resulting from the illness or death of a mother is devastating, and the need for effective diagnosis and treatment is a desperate priority for this high-risk group. However, pregnant women are systematically excluded from drug trials for fear of toxicity to the fetus (and, less openly, for fear of liability by the pharmaceutical industry or investigators). As a result, new, safe, and effective drugs for pregnant women are unlikely in the near future. The prospective assessment of the safety and efficacy of existing drugs must become a research priority.

Artemisinin combination therapy is needed to slow the rate of development of drug resistance in Africa, but embryotoxicity remains a concern for this drug class. The use of artemisinin derivatives in pregnant women has, thus far, been safe for this group, and WHO is currently examining the reproductive risks.[94,95] Obtaining further clinical information in exposed pregnancies is a research priority.

Plasmodium vivax *malaria*

P vivax predominates in South America and parts of Asia. Resistance of this parasite to chloroquine is geographically still limited,[96] though likely to increase. Although it causes recurring and debilitating infections, *P vivax* rarely kills. In contrast to falciparum malaria, treatment must clear not only blood-stage parasites but also 'dormant' parasites (hypnozoites) in the liver, which cause relapse. Therefore, chloroquine should be combined with primaquine. A 2-week treatment course is needed; adherence to a 14-day regimen is likely to be poor, but there is no convincing evidence that shorter courses are as effective. The inconvenience of a 2-week treatment course and contraindications to primaquine account for a high rate of relapse. More information on the relation between dose, duration, and anti-relapse effect of primaquine is needed in different geographical areas since the relapse characteristics of *P vivax* vary. Primaquine cannot be used in people with severe variants of glucose-6-phosphate dehydrogenase deficiency. Pretreatment screening would be a requirement but is seldom possible in tropical settings. The use of primaquine in programmes depends on the background prevalence and severity of glucose-6-phosphate dehydrogenase deficiency in the general population.

Prospects for new drugs

The current most urgent need in malaria control is to provide effective treatment. Antimalarial drugs that are effective against all malaria parasites are available now, and their lifespan of effective use will be greatly extended if they are used in combination. We already have several highly effective artemisinin combination treatments, although further development work in dosing, coformulation, packaging, and delivery is still urgently needed. These combinations include artesunate with mefloquine, amodiaquine, SP, and atovaquone-proguanil, artemether with lumefantrine, and dihydroartemisinin with piperaquine.[7,73,97–100] The safety of these combinations needs to be further assessed.

Families of antimalarial drugs in current use

Blood schizontocides, acting on intraerythrocytic (asexual and partly also sexual) parasites

Quinoline-containing drugs

- Type 1: the 4-aminoquinolines chloroquine and Mannich base amodiaquine, pyronaridine
- Type 2: the aryl-amino alcohols quinine and quinidine, mefloquine, halofantrine, lumefantrine (benflumetol)

Artemisinin-type compounds, including the natural extract artemisinin and semisynthetic derivatives (dihydroartemisinin, artesunate, artemether, arteether)

Nucleic acid inhibitors

Antifolates, mostly in the form of a combination between a sulfa-drug and a biguanide (SP is the commonest drug of this class)

- Type 1: sulphonamides and sulphones
- Type 2: pyrimethamine, biguanides and triazine metabolites, quinazolines

Atovaquone combined with proguanil is a more recent drug of this class though not widely used.

Tissue schizontocides, acting on liver stages 8-aminoquinolines (primaquine)

Nevertheless, new drugs are needed. Several improved treatments are in the development pipeline (table 1). Of the 17 drug projects identified, 11 involve peroxides, either alone or in combination. Apart from this research, there is very little innovation in the drug development pipeline, which continues to rely on the quinoline and biguanide families. Although new targets and molecules are being identified, the struggle seems to be to consolidate such findings into formal development. In addition, more slowly eliminated long-acting 8-aminoquinolines are under development (tafenoquine) or locally available (bulaquine) as alternatives to primaquine for both malaria prevention and the radical cure of *P vivax*.

With the sequencing of the malaria genome and technological advances in target and drug discovery, it is hoped that new classes of drugs will be developed.[101,102] For such discoveries to happen and for these drugs to become available to patients, an international commitment to provide adequate funding and coordination must occur at all levels from upstream research through development to deployment.[103] But, in all probability, none of the potential new compounds will be available for general use for 10 years—even if they are safe, effective, and affordable.

How can research help?

The quality of care for people with malaria today is simply unacceptable, and the global response to this crisis has been

inadequate. The reasons for the failure are a complex mixture of financial, political, logistic, and operational factors: the main target populations live in the poorest countries, and even within these countries the rural poor are often under-represented in the corridors of power. And so malaria escapes the normal laws of supply and demand, while ineffective treatments are recommended and provided on a massive scale. International agencies must bear much responsibility for continuing to endorse and support ineffective control measures.

Studies on malaria economics have mostly focused on country-specific analyses of the cost of illness associated with malaria and the cost-effectiveness of various interventions. This research can be particularly influential for policy-makers. More is needed on how economic analysis can be applied to help make intervention choices, to clarify the role of the public and private sectors in malaria treatment and prevention, and to assess the role of different regulatory policies such as treatment subsidies and user fees in a policy mix to achieve real control of malaria. For example, there is currently little information available on how responsive the degree of coverage with medications (ie, the proportion of affected people who will take appropriate treatment) will be to the price of these medications. Such information is essential for determining the optimum subsidy for antimalarial treatments, keeping in mind that the short-term objective of increasing treatment coverage, by increasing subsidies for treatment, has to balance against the long-term objective of financial sustainability. These crucial economic analyses must be closely integrated with information on the local epidemiology of malaria and the behaviour of local vectors to promote an efficient allocation of limited resources.

Appropriate epidemiological data are needed for adequate planning and measurement of the effect of interventions. But such systems must be fed with thorough information, which requires systematic collection and correct interpretation of reliable data on the population, disease distribution and prevalence, and treatment efficacy.

A consequence of the prevailing practice of treating malaria on clinical grounds, which inevitably leads to much over-treatment, is that little investment has been made into study of field-adapted diagnostic methods. More information is needed on the overall performance and costs of different methods, making parasitological diagnosis available in the field, and measuring its effects. The cost-effectiveness of diagnosis for a given situation of disease prevalence and treatment costs can be predicted.[65]

Vaccine development will require continued efforts and further financial support, and should be based on a strong rationale for selection of particular vaccine candidates. It requires investment in investigations on the relevance of available models, the development of improved models, and above all the identification of surrogates of protection, preferably defined in human beings. Assays relevant to protection are crucial at all steps, from the selection of candidates and relevant epitopes, the choice of constructs, delivery systems, and adjuvants, to the assessment of results obtained in clinical trials. The need for both higher throughput and more relevant tools is even more pressing as study of the malaria genomes unveils many new molecules to be tested.

The number of effective drugs available in the field to treat malaria is small, and growing resistance to the few available compounds poses a significant threat to health in the tropics.[104] Ineffective treatments are used in most parts of the world. Newer drugs (eg, artemisinin-based combinations) are more expensive than traditional chloroquine and SP. Health systems and households cannot afford to use these more expensive new drugs on the basis of presumptive diagnosis. The price of effective antimalarial treatment and rapid diagnostic tests must be reduced. A small targeted increase in donor funding could help improve production, formulation,

Table 1. Potential candidates in the drug development pipeline

Class	Compound	Indication	Route of administration
Early development			
Newer artemisinin-type compounds	Artemisone	Uncomplicated malaria	Oral
	Artelinic acid (status unknown)	Severe malaria	Injectable intravenously
New biguanide combinations		Uncomplicated malaria	Oral
New quinolines	Isoquine	Uncomplicated malaria	Oral
Artemisinin single-agent and combinations	Chlorproguanil, dapsone, and artesunate	Uncomplicated malaria	Oral
	Pyronaridine and artesunate	Uncomplicated malaria	Oral
	Dihydroartemisinin and piperaquine	Uncomplicated malaria	Oral
	Dihydroartemisinin	Uncomplicated malaria	Oral
Quinolines	Modified side-chain chloroquine	Uncomplicated malaria	Oral
	Desbutyl halofantrine (status unknown)	Uncomplicated malaria	Oral
Other	Fosfmidomycin	Uncomplicated malaria	Oral
Mid-late development			
Antifolate combinations	Chlorproguanil/dapsone	Uncomplicated malaria	Oral
Artemisinin derivative	Artesunate rectal	Moderately severe malaria	Rectal
8-aminoquinoline	Tafenoquine (etaquine)	Malaria prophylaxis and vivax treatment	Oral
	Bulaquine (CDRI 80/53)		
Studies with registered entities			
Artemisinin-based combinations	Artemether and lumefantrine	Uncomplicated malaria	Oral
	Artesunate and mefloquine	Uncomplicated malaria	Oral
	Artesunate and SP	Uncomplicated malaria	Oral
	Artesunate and amodiaquine	Uncomplicated malaria	Oral

Table 2. Summary of the current situation and needs

Current situation, main problems	R&D needs
Burden of disease	
At least 500 000 children (by lowest estimates) die each year of severe malaria Rough estimates of malaria prevalence are 300–500 million cases per year Sub-Saharan Africa and southeast Asia are the most affected regions The economic burden of malaria is analysed poorly and is likely to be underestimated. Lack of high-quality data, especially in the most affected countries Poor epidemiological data undermine the ability to characterise the problem well and may lead to underestimates or flawed assessment of the needs	Field-based epidemiological research to obtain more accurate mortality and morbidity data, based on reliable geographical information Socioeconomic research on the burden of malaria
Vector control	
Demobilisation of vector-control programmes in the past three decades Increased resistance to insecticides High cost of individual preventive measures Uncertainty over the effectiveness of programmes for ITNs Poor data on cost-effectiveness of vector control	Larger scale studies to investigate: The relative roles of personal protection and mass insecticidal effects in reducing malaria incidence The promotion, distribution, and implementation of ITN programmes in operational situations The cost-effectiveness and cost-benefit of ITN programmes in various epidemiological settings The medium-term balance between reduction of sporozoite inoculations and immunity Research and evaluation of insecticide-incorporated bednets The relation between the extent of community bednet use and malaria morbidity, mortality, and transmission.
Prevention of disease	
No vaccine available	Development of an affordable and effective vaccine Improved rationale in vaccine discovery Improved models to assess efficacy of vaccine candidates Develop expertise for field clinical trials of vaccine candidates
Diagnosis	
Clinical diagnosis is unreliable, because the symptoms of malaria are non-specific, and promotes extensive use of drugs 50–75% of the patients treated for malaria on presumptive diagnosis do not have malaria Microscopic confirmation is not used widely enough because it requires regular training, quality control, and investment in costly equipment Use of other diagnostic methods (rapid tests) is restricted owing to prohibitive cost, lack of sensitivity (for *P vivax*, *P malariae*, and *P ovale*), and would need to be quantitative in high-transmission areas where most people have low-grade chronic parasitaemia	Actively deploy diagnostic tools (microscopy or rapid tests) Decrease the use of presumptive treatment to reduce selection pressure at the origin of resistance Improve the sensitivity and specificity of rapid tests and adapt them to field situations R&D is needed to decrease the cost of producing rapid tests
Treatment	
Widespread use of ineffective drugs, endorsed by national malaria control programmes and supported by international agencies Underestimation of the burden of disease that results from drug resistance and use of ineffective drugs Nearly all of the antimalarials used now were developed more than 30 years ago and have fallen to resistance Fast-spreading multidrug resistance Rate at which antimalarial drug resistance is developing is outpacing the development of new antimalarial drugs Little pharmaceutical industry interest in antimalarials Few effective drugs available to treat malaria	Short term: Use antimalarials in combination to avoid or delay resistance Active development and deployment of combination antimalarial drugs that do not share the same resistance mechanisms (artemisinin combinations) Ensure that affordable combination drugs are readily available to all who need them Monitor resistance on isolates from patients treated under controlled conditions Conduct studies of the rational use of antimalarial drugs in the community Research on the formulation, packaging, and deployment of new drugs Study the effects of deploying artemisinin combinations in high-transmission areas on resistance Study the relation between deployment and adherence (coverage) and the emergence of resistance Medium term: Identify the three most important potential new drugs (oral drugs in combination with artemisinin derivatives to avoid emergence of resistance and gain years of drug development) and facilitate rapid development (new parenteral artesunate formulation, DHA-piperaquine, artesunate-pyronaridine) Develop prospective studies on the medium-term consequences of the use of one or the other treatment in various pilot locations Research and advocate for antimalarials for pregnant women Develop truly new, affordable, and easy-to-use compounds

ITN=insecticide-treated mosquito nets.

presentation, and distribution of the existing combinations, and speed up the implementation of new treatment protocols. It takes years, much suffering, and many lost lives before failing first-line drugs are replaced by more effective medications. Policy-makers are not informed adequately even when the needed knowledge is available.

Nearly all of the antimalarial drugs we use today were developed more than 30 years ago.[105] The history of this past 30 years of research on neglected tropical diseases now leaves little doubt that little will happen if we rely only on the private sector.[106] Nevertheless, the drug development pipeline for malaria is not as poor as that for other, more neglected tropical diseases.[107,108] Research and development on malaria drugs has received some public-sector input from the Walter Reed Army Institute for Research, WHO/TDR, the Multilateral Initiative for Malaria, the National Institutes of Health, and the Medicines for Malaria Venture. To date, however, public-sector engagement has proved to be insufficient.

Mathematical modelling predicts that existing drugs should be used in combination if their effectiveness is to be safeguarded.[7,72] This prediction has been confirmed in southeast Asia. The precise choice of combinations and formulations requires an immediate research effort. The formulation, packaging, deployment, and adherence to these new drugs should be studied. Such studies require only a small investment compared with the costs of developing new drugs. Ensuring access to these treatments will necessitate specific financial efforts. However, no one can predict how long the present combinations will remain effective, so truly new, affordable, and easy-to-use compounds to treat malaria must be developed as well. As new drugs are developed, they should also be included in combinations. More research is needed, but this should not be an excuse for delayed action. Unless a radically different treatment strategy is adopted now, with available effective combinations of antimalarial drugs, malaria rates will continue to increase and drug resistance will worsen.

Conclusions

Combating malaria is possible, but increased funding is needed to mobilise and optimise existing tools (table 2). In the longer term, support will be needed to channel the results from fundamental research into truly new control tools (eg, new drugs, diagnosis, insecticides, and vaccines). A small part of funds presently devoted to control measures needs to be committed to continuous assessment of their true effect. Efficacious antimalarial-combination treatments are available now that will reduce transmission rates and disease incidence in low-transmission areas. Urgent research is needed to optimise formulation, delivery, and use of these existing tools.

New infectious diseases such as HIV/AIDS, the recrudescence of tuberculosis and malaria, together with ecological degradation, ethnic conflict, poverty, and famine are signs of an unstable world despite major economic progress in the more developed regions. Modern communication, transport, and the emergence of new infectious diseases have created common global risks, and it is increasingly impossible to ignore the plight of billions of people who live impoverished lives.[109] Modern society cannot ignore the strategic and moral imperative of alleviating the suffering of a significant number of the world's people.

Acknowledgments

This article stems from work developed by the Drugs for Neglected Diseases (DND) Working Group, an independent interdisciplinary working group (from academics, international and national institutions, and the pharmaceutical industry) established by Médecins Sans Frontières in the framework of the Campaign for Access to Essential Medicines. We thank J P Guthmann, M Nacher, and members of the DND working group for their comments.

The opinions expressed in this paper are those of the authors and may not reflect the position of the employing organisation.

Conflict of interest

We declare no conflict of interest.

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