Malaria in children

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The past decade has seen an unprecedented surge in political commitment and international funding for malaria control. Coverage with existing control methods (ie, vector control and artemisinin-based combination therapy) is increasing, and, in some Asian and African countries, childhood morbidity and mortality from malaria caused by *Plasmodium falciparum* are starting to decline. Consequently, there is now renewed interest in the possibility of malaria elimination. But the ability of the parasite to develop resistance to antimalarial drugs and increasing insecticide resistance of the vector threaten to reduce and even reverse current gains. *Plasmodium vivax*, with its dormant liver stage, will be particularly difficult to eliminate, and access to effective and affordable treatment at community level is a key challenge. New drugs and insecticides are needed urgently, while use of an effective vaccine as part of national malaria control programmes remains an elusive goal. This Seminar, which is aimed at clinicians who manage children with malaria, especially in resource-poor settings, discusses present knowledge and controversies in relation to the epidemiology, pathophysiology, diagnosis, treatment, and prevention of malaria in children.

Introduction

Despite substantial advances in treatment and prevention over the past decade, malaria still threatens the lives of millions of children in tropical countries. The symptoms of malaria are non-specific and parasitological diagnosis uncommon, making precise calculation of disease burden difficult and causing both overtreatment with antimalarial drugs and undertreatment of non-malarial causes of fever. Our understanding of the complex pathological mechanisms underlying uncomplicated and severe malaria in children is limited, and often derived from studies in adults. Once the disease becomes severe, therapeutic options are scarce and risk of mortality is high.

Over the past 5 years, increasing use of insecticide-treated nets, indoor residual spraying, and early treatment with artemisinin-based combination therapy (ACT) has led to real progress in reducing morbidity and mortality from malaria caused by *Plasmodium falciparum*, especially in Asia and some African countries. But the ability of the parasite to develop resistance to antimalarial drugs and increasing insecticide resistance of the vector threaten progress towards elimination. *Plasmodium vivax*, with its dormant liver stage, will be particularly difficult to control fully, while an effective and affordable vaccine against all species of malaria is still out of reach. In this Seminar, which is aimed at clinicians who manage children with malaria, especially in resource-poor settings, we discuss present knowledge and controversies in relation to the epidemiology, pathophysiology, diagnosis, treatment, and prevention of malaria in children.

Epidemiology and disease burden

Malaria is a protozoan infection of erythrocytes caused in human beings by five species of the genus *Plasmodium* (*P falciparum*, *P vivax*, *P ovale*, *P malariae*, and *P knowlesi*). In most cases, malaria is transmitted via the bite of an infected female anopheline mosquito, but congenital malaria and acquisition through infected blood transfusion are well described.[1,2] More than 40% of the world's population—approximately 3 billion people—are exposed to malaria in 108 endemic countries[3] (figure 1). Figures for disease burden vary widely, reflecting disparity in the data sources used to derive different estimates.[5] Estimates from WHO for 2008 suggested that 243 million cases (95% CI 190–311 million) of malaria (around 90% caused by *P falciparum*) resulted in 863 000 deaths (708 000–1 003 000), of which more than 80% occurred in children younger than 5 years of age in sub-Saharan Africa.[3] Mixed infections caused by more than one *Plasmodium* species are frequent but under recognised.

P falciparum is responsible for most malaria-related deaths worldwide and is the predominant *Plasmodium* species in sub-Saharan Africa. Transmission intensity and population at risk vary substantially between and within countries.[6] Of the 2·4 billion people at risk of falciparum malaria, 70% live in areas of unstable or low endemic risk. Almost all populations at medium and high levels of risk live in sub-Saharan Africa, where the burden of disease, death, and disability from falciparum malaria is high (figure 2).[7] In areas of high stable transmission, morbidity and mortality are highest in young children in whom acquired protective immunity is insufficient to protect against severe disease. Areas of low or unstable transmission are subject to malaria epidemics, and people of all ages are at risk of severe disease. There is substantial geographical overlap

Search strategy and selection criteria

We searched PubMed for publications in English using the terms "malaria and children", "malaria and infants", "malaria and epidemiology", "malaria and pathophysiology", "malaria and diagnosis", "malaria and therapy", "malaria and prevention". Our search focused on, but was not restricted to, publications in the past 5 years. We also searched the Cochrane Database of Systematic Reviews using the term "malaria" and our own database of references, as well as those of linked articles in the searched journals. When more than one article illustrated a specific point, the most representative article was chosen.

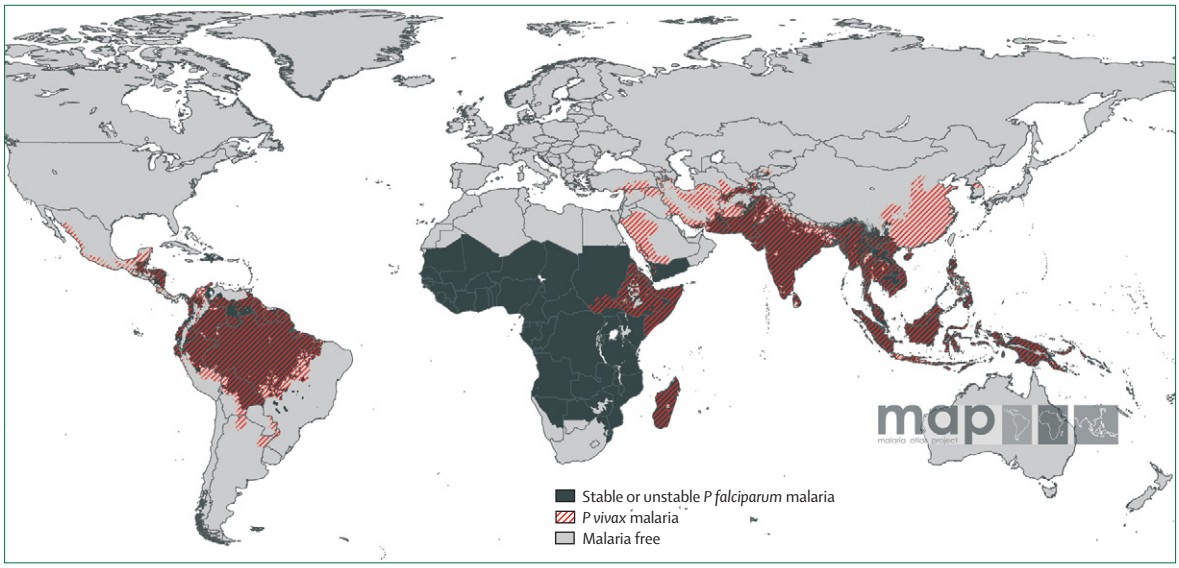

Figure 1: **Global spatial distribution of *Plasmodium falciparum* malaria in 2007 and preliminary global distribution of *Plasmodium vivax* malaria**
The distribution of *P falciparum* malaria was defined by use of reported case data, medical intelligence, and biological constraints of transmission to identify areas of stable and unstable transmission and malaria-free areas. The distribution of *P vivax* malaria shown here is preliminary and was defined by use of information contained in travel and health guidelines; work by the Malaria Atlas Project is looking into refining this distribution on the basis of similar methodologies to those used for the definitions of *P falciparum* (source: Malaria Atlas Project[4]).

between malaria and HIV, and co-infection is associated with increases in parasite density and case fatality.[8]

The epidemiology of falciparum malaria has been changing over the past 10 years, with declining numbers of clinical cases reported in different parts of the world. 38 countries (nine in Africa) documented reductions of more than 50% in the number of malaria cases during 2008 compared with 2000, although the number fell least in countries with the highest incidence rates.[3] In Asia, where most cases of malaria are confirmed by microscopy or rapid diagnostic test, the decline in cases of falciparum malaria is probably the combined result of economic development, increasing urbanisation, deforestation, early diagnosis, and use of ACTs.[9] In this region, *P vivax* is now emerging as the dominant *Plasmodium* species, with chloroquine resistance starting to spread.[10] Several African countries that have achieved high coverage with insecticide-treated nets, indoor residual spraying, and effective treatment programmes have recently reported a pronounced decline in malaria burden, accompanied, in some instances, by a sharp fall in all-cause mortality in children younger than 5 years of age.[11] Recent data from Kenya suggest that control of malaria could also have a major effect on invasive bacterial disease, specifically non-typhoidal salmonella (Scott A, Williams T, Kenya Medical Research Institute Centre for Geographic Medicine Research [Coast], Kilifi, Kenya, personal communication). Although the true burden of malaria in Africa might previously have been over-reported because of the paucity of parasitological confirmation of clinical cases,[12] use of ACTs and increased coverage with insecticide-treated nets and indoor residual spraying have undoubtedly contributed to the falling number of cases.

Enhanced optimism and a marked increase in funding for malaria control have prompted recent calls to revisit the possibility of malaria elimination in some countries and regions (panel 1). As a result of declining malaria transmission, areas previously regarded as highly endemic for the disease are now becoming intermediate or low risk. This improvement has been associated with a change in the observed age pattern of clinical malaria. In coastal Kenya, where parasite prevalence has been falling over the past 15 years, the mean age of children admitted to hospital with a positive malaria blood slide has increased from 3 years to 5 years.[13]

P vivax is the most prevalent of the five human malaria parasites outside Africa.[10] It is mostly absent from central and west Africa because a high proportion of the population have the Duffy-negative phenotype, which prevents erythrocyte invasion by the parasite. In other tropical regions of the world, *P vivax* coexists with other *Plasmodium* species and mixed infections are common. Because transmission rates are low in most regions where *P vivax* is prevalent, affected populations do not achieve high levels of immunity (or premunition) to this parasite and people of all ages are at risk of infection, although children are more often ill. Often termed benign malaria, there is increasing evidence that *P vivax* is responsible for substantial morbidity and mortality, especially in infants,[14] and the recent and rapid spread of chloroquine resistance is therefore concerning. Control is not straightforward because of the difficulty of achieving radical cure by

Roll Back Malaria Partnership

Figure 2: **Malaria remains a major impediment to child health, development, and survival**
Reproduced with permission from Roll Back Malaria Partnership.

Panel 1: **Definitions**

Malaria control
Reducing the disease burden to a level at which it is no longer a public health problem

Malaria elimination
Interrupting local mosquito-borne malaria transmission in a defined geographical area; imported cases will continue to occur

Malaria eradication
Permanent reduction to zero of the worldwide incidence of malaria

elimination of dormant liver stages (hypnozoites). The parasite is more easily transmissible than is *P falciparum* because the sexual forms (gametocytes) are produced earlier in the life cycle, often before treatment.

Infection with *P malariae* occurs in most malaria-endemic areas, but is much less common than is infection with *P falciparum* or *P vivax*. *P ovale* is rare outside Africa. *P knowlesi*, a zoonosis found throughout southeast Asia, is often misidentified as *P malariae*, although the clinical course is more severe and fatalities have been described.[15]

Clinical presentation

Children with uncomplicated malaria caused by all species of *Plasmodium* typically present with fever and vomiting. Headache, chills, muscle aches, and anorexia are common. Additionally, *P vivax* infections can be accompanied by intense rigors.[16] Vomiting, diarrhoea, and abdominal discomfort might be misinterpreted as gastroenteritis, whereas respiratory symptoms (tachypnoea, difficulty breathing, cough) might suggest pneumonia.[17] The severity and course of a clinical attack depend on the species and strain of the infecting plasmodium parasite, as well as the age, genetic constitution, malaria-specific immunity, and nutritional status[18] of the child, and previous exposure to antimalarial drugs. Children with high peripheral parasitaemia (>4–5% infected erythrocytes) are at increased risk of severe malaria and death.

There are no clinical features that reliably distinguish severe malaria from other severe infections in children. Impaired consciousness (prostration or coma), seizures, respiratory distress, severe anaemia, hypoglycaemia, metabolic acidosis, and hyperlactataemia, the most frequently reported clinical and laboratory features of severe falciparum malaria in children,[19,20] are also recognised features of severe sepsis.[21] 127 (6%) of 2048 children admitted to hospital in Kenya and Mozambique with severe falciparum malaria had concurrent positive blood cultures (an underestimate of bacteraemia), and case fatality is increased in parasitaemic children with invasive bacterial infection, HIV, or malnutrition.[8,22] At autopsy, seven of 31 Malawian children with a clinical diagnosis of cerebral malaria were found to have died from other causes.[23] Since severe malaria is a multisystem, multi-organ disease, children frequently present with more than one of the classic clinical phenotypes: cerebral malaria, respiratory distress, severe malarial anaemia, hypoglycaemia.

Cerebral malaria is defined by WHO as unrousable coma in a patient with *P falciparum* parasitaemia in whom other causes of encephalopathy have been excluded.[19] Although the term implies a distinct disease entity, the clinical syndrome is highly variable, with most cases falling into one of three main categories: coma with marked physiological derangement (severe anaemia, metabolic acidosis, respiratory distress, shock); coma with protracted or multiple seizures, where unconsciousness might be caused by a long (>1 h) postictal state or by subclinical or subtle seizure activity, characterised by conjugate eye deviation, nystagmus, salivation, and hypoventilation;[24] or a pure neurological syndrome of coma and abnormal motor posturing, which might be complicated by raised intracranial pressure and recurrent seizures.[25] All three categories fulfil WHO criteria for cerebral malaria, but pathophysiology and

prognosis vary in each case. Malarial retinopathy consists of a group of retinal abnormalities that are unique to severe malaria and common in children with cerebral malaria. A large, prospective autopsy study of children who died from cerebral malaria in Malawi showed that malarial retinopathy was better than any other clinical or laboratory feature for distinguishing malarial from non-malarial coma.[26] Although most children with cerebral malaria regain consciousness within 48 h and seem to make a full neurological recovery, approximately 20% die and 10% have persistent neurological sequelae.[27]

Respiratory distress (deep breathing, Kussmaul's respiration) is a clinical sign of metabolic acidosis,[28] and has emerged as a powerful independent predictor of fatal outcome in falciparum malaria.[20,29] It can be misinterpreted as cardiac failure and circulatory overload, especially if associated with severe tachycardia.

Severe malarial anaemia (figure 3; defined as haemoglobin concentration <50 g/L in the presence of *P falciparum* parasitaemia) is more common in children than in adults. Mortality of children with asymptomatic severe malarial anaemia is low (around 1%), but rises to more than 30% when anaemia is complicated by severe respiratory distress and metabolic acidosis.[20]

Hypoglycaemia (blood glucose concentration <2·2 mmol/L) is associated with a poor outcome in children with malaria[20,29] and other severe childhood infections.[30] Clinical evidence suggests that hypoglycaemia in African children with severe malaria results from impaired hepatic gluconeogenesis rather than from quinine-induced hyperinsulinaemia.[31]

Renal failure, caused by an acute tubular necrosis, a fairly frequent complication of severe malaria in adults, is rare in children.[19]

Severe anaemia, respiratory distress, and coma have been reported in infants and children with severe *P vivax* infection.[14] Detailed prospective studies are needed to document this further and to exclude the possibility of concurrent bacteraemia or *P falciparum* co-infection.

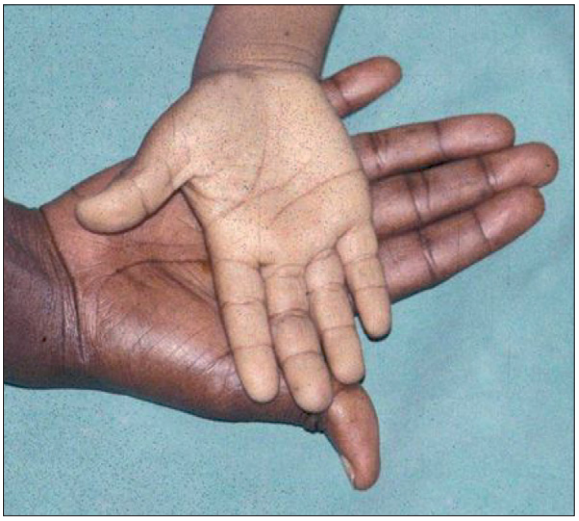

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Figure 3: **Malarial anaemia—pallor of child's palm with his mother's for comparison**

Pathophysiology

Although there is overwhelming evidence in falciparum malaria for sequestration of parasitised erythrocytes in the microcirculation and excessive release of proinflammatory cytokines, opinion is divided over which of these represents the main driving force leading to disease and death.[32–34] Clarification of this issue could have important implications for rational adjunctive therapy.

Sequestration of erythrocytes containing mature forms of *P falciparum* in the microvasculature of most vital organs is a well established feature of fatal falciparum malaria in adults;[35] by contrast, confirmation of its occurrence in children has been relatively recent.[23] Sequestration results from the interaction between parasite-derived molecules expressed on the surface of infected erythrocytes[36] and receptors expressed on the surface of the vascular endothelium, of which intercellular adhesion molecule 1 (ICAM1) is probably the most important within the brain.[37] Upregulation of ICAM1 and other endothelial receptors by the proinflammatory cytokine tumour necrosis factor (TNF) α is thought to promote cytoadherence of erythrocytes and platelet thrombi within the cerebral microvasculature.[37,38] Angiopoetin 2 sensitises vascular endothelium to the action of TNFα,[39] and increased concentrations in adults and children with severe malaria are associated with poor clinical outcome.[40] Raised concentrations of angiopoetin 2 might also compromise the integrity of the blood–brain barrier,[41] leading to leakage of plasma proteins, perivascular oedema, and neuronal injury, although cerebral oedema is not usually pronounced. Instead, brain swelling is probably caused by increased blood volume secondary to sequestration of infected erythrocytes and increased cerebral blood flow.[42] Evidence from autopsies in Malawian children with cerebral malaria suggests that there is dysregulation of the coagulation system,[43] with accumulation of thrombi, microhaemorrhages, and platelets in cerebral microvessels.[23,44] Reduced deformability of parasitised erythrocytes contributes to impaired microcirculatory flow and is a strong predictor of mortality in children and adults.[45] Direct in-vivo observation of microcirculatory flow in adults with severe malaria has shown extensive microvascular obstruction in proportion to disease severity.[46] Retinopathy in African children with cerebral malaria is associated with areas of capillary non-perfusion on fluorescein angiography[47] and, in fatal cases, histopathological evidence of sequestration in both the retinal[48] and cerebral microvasculature.[23]

Severe malaria has features in common with severe sepsis syndromes. The pathophysiology of both disorders might reflect a cytokine-driven systemic inflammatory response.[32] Clinical symptoms of malaria are associated with cyclic rupture of infected erythrocytes and the

release of erythrocyte and parasite debris, including malarial pigment (haemozoin) and glycosylphosphatidylinositol, the putative "malaria toxin".[49] The consequent activation of peripheral blood mononuclear cells stimulates the release of inflammatory cytokines,[50] and it has been suggested that the balance between proinflammatory and anti-inflammatory cytokines might be an important determinant of disease severity.

For more on **the FEAST trial** see http://www.feast-trial.org/

There is a large, somewhat contradictory, body of published work on the role of cytokines in malaria disease.[51,52] Many studies included small numbers of patients, and reported collated results for groups (severe malaria, cerebral malaria) that are clinically heterogeneous. Comorbidity, particularly with invasive bacterial disease, HIV, and malnutrition is increasingly reported, especially in children with severe falciparum malaria.[8] Indeed, incorrect diagnosis might explain many of the apparent differences between adult and childhood cerebral malaria, yet information about these important confounding factors is frequently absent. Variation in the geographical representation, age, and innate malarial immunity of patients and differences in the timing and frequency of blood sampling makes comparison between studies difficult. However, despite these shortcomings, several interesting and potentially important trends have emerged. Concentrations of the proinflammatory cytokines interleukin 1β, interleukin 6, and interleukin 8 are raised in patients with malaria,[53] and correlate with disease severity.[54] TNFα seems to be pivotal both in the early response to falciparum and vivax malaria,[55] and in late, severe manifestations.[32] The anti-inflammatory cytokines interleukin 10 and transforming growth factor (TGF) β might counteract the potentially harmful proinflammatory response to malaria antigens.[56] Low concentrations of interleukin 10 relative to TNFα have been found in patients with severe malarial anaemia,[57] and cytokine-induced dyserythropoiesis plus increased splenic removal of parasitised and non-parasitised erythrocytes[58] are thought to contribute to the pathogenesis of severe malarial anaemia.

The rapid resolution of coma and subsequent recovery of most patients with cerebral malaria and the absence of autopsy evidence for microvasculature sequestration in all fatal cases are seen by some investigators as evidence that coma might be mainly a cytokine-induced metabolic encephalopathy, and not secondary to obstructed blood flow within the cerebral microvasculature.[59] Other experts argue that extensive intracerebral sequestration is the main pathological process and that consequent activation and dysfunction of the cerebral endothelium results in coma.[60] Their view is supported by the characteristic clinical syndrome, the fairly consistent pathological findings, and the good clinical prediction provided by retinal microvascular abnormalities.[47]

Metabolic acidosis is a consistent feature of severe malaria in children and adults[61,62] but differs fundamentally from that associated with sepsis. The relative importance of dehydration and hypovolaemia versus microvascular obstruction in the pathophysiology of acidosis is controversial.[63,64] The practical consequence is continuing uncertainty about the risks and benefits of vigorous intravenous volume expansion, especially with colloids, a question that is currently being addressed in a large randomised trial (the Fluid Expansion As a Supportive Therapy [FEAST] trial).

Diagnosis

Since the advent of chloroquine in the 1930s, treatment of fever with antimalarial drugs, without confirmatory diagnosis, has been the accepted standard of practice in many malaria-endemic areas, especially in Africa. However, the clinical presentation of malaria overlaps with other common illnesses, and attempts to develop clinical scoring systems of predictive value have proved unsuccessful.[65] Presumptive treatment has therefore resulted in overuse of antimalarial drugs, increasing drug resistance,[66] and, importantly, failure to treat alternative causes of fever.[12] WHO now recommends that parasitological confirmation by microscopy or rapid diagnostic test is obtained in all patients with suspected malaria before the start of treatment.[67]

Although malaria microscopy is the gold standard for confirmation of diagnosis, and has the added advantages of parasite quantification and species identification, its accuracy depends on the quality of the reagents and microscope and the experience of the microscopist. Microscopy has been used successfully in several countries in southeast Asia and the Americas, but much less so in African countries.

Simple immunochromatographic tests (rapid diagnostic tests) for malaria provide an alternative to microscopy at peripheral health facilities, and can facilitate diagnosis-guided treatment by village health workers. Use of rapid diagnostic tests at the community level is fairly widespread in parts of South America and Asia and, with funding from the Global Fund to Fight AIDS, Tuberculosis and Malaria, is now increasing in several African countries. The performance of malaria rapid diagnostic tests varies widely, with several being heat labile and of low sensitivity.[68] When used with ACTs, rapid diagnostic tests can be cost effective and potentially cost saving,[69] provided that health workers restrict antimalarial treatment to those with a positive test result.

Declining transmission intensity and the present interest in malaria elimination in some regions increases the importance of detection and treatment of low density parasitaemia. Field-friendly loop-mediated isothermal DNA amplification that detects submicroscopic parasitaemia with minimum sample processing, requires no sophisticated equipment, and can be read with the naked eye is being developed.[70]

Treatment of uncomplicated malaria

Treatment of uncomplicated falciparum malaria has three main objectives. The first is to cure the infection, since this prevents progression to severe disease and the additional

morbidity associated with treatment failure. The second is to prevent the development of antimalarial drug resistance, and the third is to reduce transmission. In all these respects, ACTs are much better than chloroquine, sulfadoxine-pyrimethamine, and quinine, still the most widely used antimalarial drugs. Artemisinin and its derivatives achieve the highest parasite killing rates and target asexual and sexual stages of parasite development in the blood with two important therapeutic consequences: prevention of clinical deterioration and interruption of transmission.[71] Combination of an artemisinin derivative with a longacting antimalarial drug reduces treatment duration from 7 days to 3 days. Artemisinins are generally well tolerated, and are recommended by WHO as first-line treatment for *P falciparum* and chloroquine-resistant *P vivax* infection.[67] The main ACTs are artesunate combined with either mefloquine or amodiaquine, artemether combined with lumefantrine, and dihydroartemisinin with piperaquine. Detailed information about drug dosing can be found in the second edition of the WHO guidelines for the treatment of malaria.[67]

Of the five *Plasmodium* species that affect human beings, only *P vivax* and *P ovale* form hypnozoites, parasite stages in the liver that can cause relapses weeks to months after the primary infection. The aim of treatment for vivax and ovale malaria is to cure the blood and liver stages of infection (radical cure), thereby preventing relapse and recrudescence. Chloroquine is recommended in countries where parasites are sensitive, with the addition of primaquine for 14 days to achieve radical cure.[67] Primaquine should not be given to children known to have severe glucose-6-phosphate dehydrogenase deficiency. Chloroquine is the recommended treatment for infections caused by *P malariae, P ovale*, and *P knowlesi*. Mefloquine, quinine, atovaquone-proguanil, artemether-lumefantrine, and dihydroartemisinin-piperaquine (but not sulfadoxine-pyrimethamine) retain excellent effectiveness against chloroquine-resistant parasites of all *Plasmodium* species.

Children with HIV infection who develop malaria should receive prompt, effective antimalarial treatment according to WHO guidelines.[67] Children receiving zidovudine[72] or efavirenz[73] should, if possible, avoid ACT regimens that contain amodiaquine.

Antimalarial drug resistance poses a major threat to malaria control efforts. Resistance to chloroquine and sulfadoxine-pyrimethamine originated on the Thai-Cambodian border and subsequently spread across Asia and Africa, causing millions of deaths,[74] and the recent finding in western Cambodia of reduced in-vivo susceptibility of *P falciparum* to artesunate monotherapy, characterised by slow parasite clearance without concomitant reduction of in-vitro susceptibility,[75] is therefore very worrying. Exposure of *P falciparum* to subtherapeutic concentrations of antimalarial drugs might arise from suboptimum dosing,[76] the use of ineffective, substandard, or counterfeit drugs,[77] or from failure to complete a full treatment course. Resistance of *P vivax* to chloroquine is well established in Indonesia, and is now emerging elsewhere in the Asia-Pacific region and in South America.[10]

As in many areas of paediatric medicine, treatment of malaria in children is hampered by a paucity of pharmacokinetic data and paediatric drug formulations. Most recommended doses are based on studies in adult patients, yet the disposition of many drugs is altered substantially in children and infants. Sulfadoxine-pyrimethamine has been in widespread use for decades, yet only recently has it been recognised that young children achieve suboptimum drug concentrations with currently recommended doses.[76] In children treated with dihydroartemisinin-piperaquine, one of the newer and most promising ACTs, low plasma concentrations of piperaquine on day 7 were associated with treatment failure.[78] There is an urgent need for dose optimisation studies in young children and infants and for pharmacokinetic data in high-risk groups, namely malnourished children and those co-infected with HIV.[79]

Key to reducing mortality and morbidity from malaria is the prompt delivery of effective drug treatment to sick children, yet few children aged under 5 years who have fever are treated with ACTs in Africa.[80] WHO is now promoting home management of malaria, the presumptive treatment of febrile children at or near home with antimalarial drugs distributed by trained members of the community, as a strategy for improving access to antimalarial drugs in Africa.[81] However, present guidelines recommend diagnosis-guided ACT for children with falciparum malaria[67] and experience from Asia suggests that rapid diagnostic tests and ACTs used by village health workers can substantially reduce morbidity and mortality.[9] Several research groups are now assessing whether a similar approach can be used in Africa.

Many patients in malaria-endemic countries seek treatment through the private sector, where access to ACTs is limited by their high cost (presently ten to 20 times that of chloroquine or sulfadoxine-pyrimethamine). The high cost encourages use of sub-optimum therapies and creates a market for substandard artemisinin drugs, thereby accelerating the development of resistance. The Affordable Medicines Facility—Malaria (panel 2) was devised to address these difficulties through a global ACT subsidy.[85]

The role of iron supplementation in the prevention and treatment of anaemia in malaria-endemic regions has been much debated. Iron deficiency has an adverse effect on child health, development, and survival,[86] and WHO guidelines recommend routine iron supplementation for children aged 6 months to 24 months living in areas where anaemia prevalence is 40% or more.[87] Alterations of iron metabolism in the human host are, however, thought to increase resistance to infection by restricting the availability of iron to microorganisms,[88] and the effect

Panel 2: The Affordable Medicines Facility—Malaria

For more on the **Affordable Medicines Facility—Malaria** see http://www.theglobalfund.org/documents/amfm/AMFmFAQs_en.pdf

The Affordable Medicines Facility—Malaria (AMFm) aims to increase access to good quality artemisinin-based combination therapies (ACTs) by subsidising producer prices worldwide and saturating the market, thereby driving out monotherapy and poor quality or inappropriate drugs.[82] AMFm was first proposed in 2004 and is hosted by the Global Fund to Fight AIDS, Tuberculosis and Malaria. Phase 1 rollout in 11 countries, with concurrent operational research, monitoring and evaluation, will take place over 2 years from mid 2010. So far, pilot ACT subsidies in four countries have yielded variable results,[83] suggesting that strategies for increasing ACT access must be tailored to individual country settings. Several concerns have been raised in relation to this largely untested initiative.[84] Improved availability of over-the-counter ACTs might undermine current treatment guidelines which advocate parasitological diagnosis,[67] and increase the use of ACT for non-malarial illness. Additionally, there are concerns that the subsidy might not be passed on from provider to consumer. Assessment of the phase 1 rollout is central to establishing whether this innovative approach will fulfil its potential to increase access to good quality ACTs.

of iron supplementation on malaria and other infectious diseases has been the subject of several recent reviews and meta-analyses.[89,90] With effective malaria control, iron supplementation should not be withheld from children with anaemia in endemic areas.

Treatment of severe malaria

For more on the **Africa Quinine versus Artesunate in Severe Malaria Trial** see http://www.controlled-trials.com/mrct/trial/441379/malaria+and+artesunate

Untreated falciparum malaria in a non-immune individual can progress within hours to life-threatening illness, and, in rural settings, most malaria deaths occur outside hospital. Prompt oral treatment with effective antimalarial drugs is essential, but for those unable to tolerate oral treatment, time to parenteral treatment is a crucial determinant of outcome. For some people, it can take several hours to reach a health facility, and rectal administration of artesunate at home can be life saving.[91]

More than 50% of deaths from severe childhood illnesses, including malaria, occur within 24 h of hospital admission,[92] and early identification and treatment of children at highest risk of death are therefore of great importance. Respiratory distress and impaired consciousness (prostration or coma) are simple, well established clinical signs that suggest a poor prognosis,[93] and should be used to rapidly identify those in need of immediate treatment.

There has been surprisingly little progress towards reducing current mortality rates (15–30%) for children admitted to hospital with severe malaria and other life-threatening infections. Antimalarial drugs and antibiotics have formed the mainstay of treatment, with far less emphasis being placed on adjunctive supportive care. Two examples of the clinical presentation of cerebral malaria are shown in panel 3. The following management strategies assume that no facilities are available for assisted ventilation, since this is the reality in most hospitals in resource-poor countries.

Airway patency should be checked, and oxygen given via face mask or rebreathing bag. Intravenous access should be rapidly established and seizures lasting more than 5 min treated with intravenous diazepam. Although the threshold for treatment of hypoglycaemia is blood glucose concentration less than 2·2 mmol/L, recent data suggest that use of a higher treatment threshold (around 4·0 mmol/L) might be more appropriate.[94] In practice, since rapid bedside measurement of blood glucose is unavailable in many hospitals in resource-poor settings, guidelines recommend pragmatic treatment of all children with impaired consciousness with 5 mL per kg intravenous 10% glucose.[30] Blood for transfusion should be urgently requested for the first child described in panel 3.

Therapeutic concentrations of an effective antimalarial drug need to be achieved as soon as possible. Quinine is often the only available treatment and should be given by slow rate-controlled infusion after a loading dose.[67] Quinine can be given by intramuscular[95] or rectal (Quinimax, Sanofi-Winthrop, Gentilly, France)[96] routes if intravenous administration is not possible. Once the child is able to tolerate oral treatment, quinine plus clindamycin should be continued for 7 days or a full course of oral ACT prescribed.[67]

Artemisinin derivatives (mainly artesunate and artemether) are a potential alternative to quinine. Absorption of intramuscular artemether can be erratic in patients with severe malaria.[97] On the basis of data from the large South East Asian Quinine Artesunate Malaria Trial, intravenous artesunate reduces mortality by 35% compared with quinine.[98] At US$140 per death averted, artesunate is highly cost effective.[99] In Asia, intravenous artesunate is now the drug of choice for treatment of severe malaria. A large multicentre trial is currently underway to assess whether the drug is also effective in African children.

Prostration with respiratory distress, lactic acidosis, delayed capillary refill, and severe tachycardia (see child 1 in panel 3) are clinical features of severe falciparum malaria that are indistinguishable from severe sepsis.[100] Children with severe malaria should, when possible, have blood cultures taken at the time of admission, with lumbar puncture done on all children with impaired consciousness. Empirical antibiotic treatment should be given when clinical condition prevents or delays lumbar puncture. Although there is continuing debate about the need for routine antibiotic treatment of children with severe malaria, the consequences of failing to treat life-threatening illness are sufficiently serious to merit empirical parenteral antibiotic treatment for any seriously ill child with malaria, especially those who are young[101] or who have severe anaemia.[102] Recent reports suggest that

malaria and bacterial co-infection mainly occur with multidrug-resistant gram-negative bacteria, particularly non-typhoidal salmonellae,[102] and the best choice of antibiotic would therefore be a quinolone or third-generation cephalosporin.[103]

Although mortality of children with asymptomatic severe malarial anaemia is low (around 1%), it rises to 30–40% for children in whom anaemia is complicated by severe respiratory distress and metabolic acidosis (eg, child 1 in panel 3).[20] Rapid blood transfusion can be life saving, but blood banking facilities are inadequate in many rural hospitals, and transfusion might be delayed until a donor is found. Consequently, most deaths occur before a transfusion can be given,[104] and clinical management during the pretransfusion period could affect outcome. A small trial in children aged 1–4 years suggests that intravenous infusion of 20 mL per kg saline or albumin during the pretransfusion period is safe.[105] The effect of intravascular volume expansion on mortality of children with malaria and other severe febrile illnesses is being assessed in the FEAST trial, as previously mentioned; results are expected in 2011.

For many years, it has been widely assumed that respiratory distress in children with severe malarial anaemia represents congestive cardiac failure, and that blood should be transfused very slowly with concomitant use of diuretics.[106] Recent work has shown, however, that the haemodynamic characteristics of this group of children are more characteristic of hypovolaemia than of cardiac failure and that rapid blood transfusion is well tolerated, although the optimum volume and speed of transfusion are unknown.[28,107]

Abnormal motor posturing (see child 2 in panel 3) can be associated with intracranial hypertension,[25] but evidence from randomised trials does not support the use of single-dose mannitol as an adjunctive treatment.[108]

Seizures are a common presenting feature of falciparum malaria in young children, and, when protracted or multiple, are associated with an increased risk of neurological sequelae, cognitive deficiency,[109] and epilepsy.[110] The burden of long-term neurological and cognitive impairments in children with malaria has been underestimated,[111] and long-term neurocognitive impairments were reported in 24% of 308 children surviving cerebral malaria or malaria with multiple seizures,[112] but more data are needed to support this finding. In a large, randomised, controlled study in unventilated Kenyan children aged 9 months to 13 years with cerebral malaria, a single intramuscular dose of phenobarbital 20 mg/kg on admission was associated with substantially decreased frequency of seizures but increased mortality, possibly from respiratory depression.[113] Whether a lower dose of phenobarbital could reduce frequency of seizures without a concomitant rise in mortality is unknown. This approach would not benefit children who have had protracted or multiple seizures before admission,[113] and electrographic studies suggest that, in some cases, seizures might be the result, and not the cause, of neuronal injury.[24] So far, no studies have been adequately powered to assess the effect of seizure prophylaxis on neurological sequelae.[114]

Over the past 25 years, various adjunctive supportive treatments, each based on prevailing hypotheses of the pathophysiology of severe malaria, have been assessed in clinical trials. The results, without exception, have been very disappointing.[115] Many studies of potential adjunctive treatments have been done in murine models of malaria, but none have shown any practical relevance to the disease in human beings.[116]

The clinical status of children with severe malaria can deteriorate rapidly, and regular observation of vital signs is essential. Blood glucose should be monitored every 4 h and haemoglobin and parasite count every 12–24 h, with additional measurement prompted by any deterioration in conscious level. Current evidence does not preclude routine use of antipyretic drugs, including non-steroidal anti-inflammatory drugs such as ibuprofen, in children with malaria.[117] Little attention has been paid to the

Panel 3: Clinical presentation of two African children with cerebral malaria

Child 1: aged 12 months

- 3 day history of fever, pallor, and rapid breathing; now drowsy and unable to feed
- Examination: temperature 38·8°C; pale conjunctivae; respiratory rate 50 breaths per min; deep breathing and subcostal recession (respiratory distress); pulse 160 beats per min; blood pressure 85/50 mm Hg; capillary refill time 4 s;* Blantyre coma score 2†
- Investigations: haemoglobin 35 g/L; blood glucose 2·2 mmol/L; sodium 132 mmol/L; potassium 5·0 mmol/L; creatinine 90 μmol/L; lactate 7 mmol/L; base deficit 18 mmol/L
- Malaria thin film: 8% *Plasmodium falciparum* parasitaemia

Child 2: aged 36 months

- 2 day history of fever, vomiting, and diarrhoea
- Unconscious since protracted generalised seizure 12 h before admission
- Examination: temperature 39°C; respiratory rate 28 breaths per min; pulse 110 beats per min, blood pressure 90/50 mm Hg; capillary refill time 2 s;* Blantyre coma score 2;† intermittent extensor (opisthotonic) posturing
- Investigations: haemoglobin 108 g/L; blood glucose 4·5 mmol/L; sodium 134 mmol/L; potassium 3·6 mmol/L; creatinine 80 μmol/L; lactate 2 mmol/L; base deficit 4 mmol/L
- Malaria thick film: scanty *P falciparum* parasitaemia

*Normal capillary refill time less than 3 s. †Blantyre coma score assesses child's response to painful stimulus; maximum score 5 (fully conscious), minimum score 0 (deep coma); score ≤2 comatose.

Panel 4: **Benefits of insecticide-treated nets**[130–132]

Community randomised trials in Africa have shown that full coverage with insecticide-treated nets can halve the number of episodes of clinical malaria and reduce all-cause mortality in children younger than 5 years of age. Initial fears that reducing malaria transmission might paradoxically increase child mortality through delayed acquisition of malarial immunity have not been realised. When used by pregnant women, insecticide-treated nets can lead to substantial reductions in low birthweight, placental parasitaemia, stillbirths, and miscarriages. By reducing the vector population, insecticide-treated nets provide protection for all people in a community, including those who do not sleep under a net themselves.

nutritional requirements of children with severe malaria, yet many are poorly nourished, which might adversely affect outcome.[18]

Children with severe infections caused by *P vivax* or *P knowlesi* need prompt effective treatment, supportive care, and close observation as do children with severe falciparum malaria.[67] Such treatment is particularly needed for young infants, who can have a rapid drop in haemoglobin concentration. Severe vivax and knowlesi malaria should be treated initially with intravenous artesunate, changing to an oral ACT once the child is able to drink.

Prevention of malaria with antimalarial drugs

Children visiting malaria-endemic countries, either as tourists or as returning immigrants from non-endemic countries, are non-immune and at increased risk of malaria. The geographical risk of malaria varies widely, and parents should seek specific advice on the areas they plan to visit with their children. Children should be protected from vectors between dusk and dawn. Chemoprophylaxis should be given according to international recommendations.

For more on **malaria vaccination requirements and recommendations for travellers** see http://apps.who.int/tools/geoserver/www/ith/index.html

For more on **international recommendations for chemoprophylaxis** see http://wwwnc.cdc.gov/travel/yellowbook/2010/chapter-2/malaria.aspx

Intermittent preventive treatment (IPT) is the administration of a full therapeutic dose of an antimalarial drug (or a combination of drugs) at specified timepoints, whether or not parasites are present.[118] To be fully preventive (and not only presumptive), the drug(s) need to protect against recurrence of an existing infection and against new infections, ideally until the next dose is given. This requirement calls for slowly eliminated drugs to be given at the right dose and the right time.[119] The most studied drug for IPT is sulfadoxine-pyrimethamine. A recent analysis of pooled efficacy data from six randomised trials of sulfadoxine-pyrimethamine given to infants (IPTi) showed that compared with placebo, the intervention had a protective efficacy of 30·3% against clinical malaria, 21·3% against anaemia (haemoglobin <80 g/L or packed-cell volume <25%), and 38·1% against hospital admissions associated with malaria parasitaemia, but no effect on mortality.[120] IPT with sulfadoxine-pyrimethamine should not be given to HIV-infected infants who are receiving routine prophylaxis with co-trimoxazole or other sulfa-containing drugs.[121] WHO has recommended IPTi with sulfadoxine-pyrimethamine in areas of Africa with moderate to high malaria transmission and low resistance to this drug combination.[122] However, the spread of sulfadoxine-pyrimethamine resistance is rapidly compromising its future effectiveness[123] and new drugs are needed.

In children aged 2 months to 10 years, randomised trials have shown that a full treatment course of sulfadoxine-pyrimethamine or amodiaquine (with or without artesunate), given at 1–2 monthly intervals to asymptomatic children during the transmission season, can reduce rates of clinical malaria by between 67·5% and 85% or more compared with placebo over a 3–4 month period of follow-up.[124–127] Piperaquine has shown promising results when given once a month to children,[128] but data for its pharmacokinetics are still insufficient and its use as monotherapy should be avoided. In schoolchildren (aged 5–18 years) a treatment course of sulfadoxine-pyrimethamine and amodiaquine at 4 monthly intervals over 1 year reduced the prevalence of anaemia and improved school performance.[129] However, since none of these trials reported measurements of drug concentrations, the main determinants of efficacy (dose and frequency) cannot be fully assessed.

Vector control

Despite compelling evidence of benefit in areas of high malaria transmission (panel 4),[130–132] coverage with insecticide-treated nets has, until recently, remained low. However, ambitious global targets for reducing malaria burden and child mortality[133] can only be achieved by rapidly increasing coverage with effective methods of malaria control. Instead of targeting protection at young African children and pregnant women, WHO now recommends coverage of insecticide-treated nets for all individuals at risk of malaria.[134] The proportion of households in Africa estimated to own at least one insecticide-treated net rose from 17% in 2006 to 31% in 2008, with 24% of children younger than 5 years of age using an insecticide-treated net during 2008.[3]

Indoor residual spraying, the application of longacting chemicals on the walls and roofs of all houses and domestic animal shelters in a given area to kill local mosquito vectors, formed the basis of the Malaria Eradication Programme (1955–69) and contributed to a substantial reduction in malaria burden worldwide, particularly in Asia, Latin America, and southern Africa.[135] Although indoor residual spraying was never taken to scale in large parts of sub-Saharan Africa, consistent use of the intervention over time has altered vector distribution and malaria epidemiology in much of southern Africa. Success depends on high, sustained coverage, correct timing of spraying (which should occur

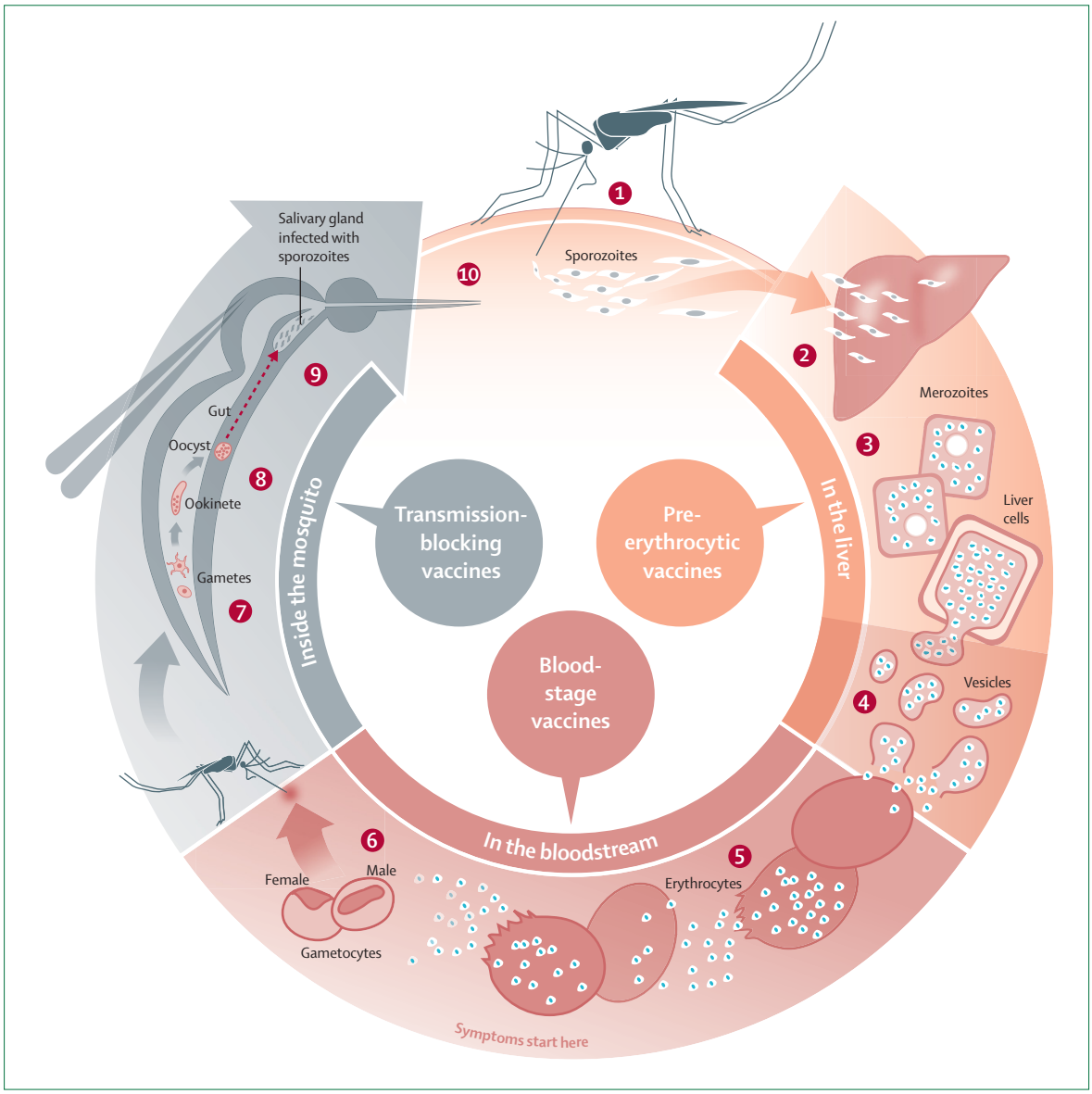

Figure 4: **Sites in the malaria life cycle that could be interrupted by vaccines**
(1) Malaria infection begins when an infected female anopheles mosquito bites a person, injecting *Plasmodium* spp parasites, in the form of sporozoites, into the bloodstream. (2) The sporozoites pass quickly into the human liver. (3) The sporozoites multiply asexually in the liver cells over the next 7–10 days, causing no symptoms. (4) In an animal model, the parasites, in the form of merozoites, burst from the liver cells in vesicles, journey through the heart, and arrive in the lungs, where they settle within lung capillaries. The vesicles eventually disintegrate, freeing the merozoites to enter the blood phase of their development.[139] (5) In the bloodstream, the merozoites invade erythrocytes and multiply again until the cells burst. Then they invade more erythrocytes. This cycle is repeated, causing fever each time parasites break free and invade blood cells. (6) Some of the infected blood cells leave the cycle of asexual multiplication. Instead of replicating, the merozoites in these cells develop into sexual forms of the parasite, called gametocytes, that circulate in the bloodstream. (7) When a mosquito bites an infected human, it ingests the gametocytes, which develop further into mature sex cells called gametes. (8) The gametes develop into actively moving ookinetes that burrow through the mosquito's midgut wall and form oocysts. (9) Inside the oocyst, thousands of active sporozoites develop. The oocyst eventually bursts, releasing sporozoites that travel to the mosquito salivary glands. (10) The cycle of human infection begins again when the mosquito bites another person. Reproduced with permission from Breaking the Cycle with Vaccines; PATH Malaria Vaccine Initiative.[140]

before the start of the transmission season), and continued vector susceptibility to the insecticide used.[136] Rising insecticide resistance of malaria vectors, particularly to pyrethroids, the insecticide used to treat netting material, poses a serious threat to indoor residual spraying and insecticide-treated net programmes, while cross-resistance between the four classes of insecticide recommended for indoor residual spraying is well recognised. The development of insecticides belonging to new or different classes is a public health priority.

Malaria vaccines

The quest for a malaria vaccine continues unabated. More than 30 years after the first demonstration of

vaccination against malaria in human beings,[137] use of an effective vaccine as part of national malaria control programmes remains an elusive goal. Until recently, vaccine development strategies focused on the prevention of clinical disease. The substantial reduction in malaria burden reported in several endemic countries suggests, however, that greater emphasis should now be placed on the development of vaccines that interrupt transmission.[138]

Pre-erythrocytic (liver stage) vaccines block the entry of sporozoites into hepatocytes or destroy infected hepatocytes (figure 4), thereby preventing clinical disease. This process was initially achieved in animal models of malaria by vaccination with radiation-attenuated sporozoites, an approach that is now generating a substantial amount of renewed interest with the first trial in human beings of a whole sporozoite vaccine. RTS,S is the most developed and promising synthetic pre-erythrocytic vaccine candidate, although protection is modest and transient;[141–143] a large phase 3 trial is underway in Africa.

For more on **vaccination with radiation-attenuated sporozoites** see http://www.malariavaccine.org/files/MVI factsheet_Sanaria_091026.pdf

For more on **the phase 3 trial of RTS,S in Africa** see http://www.malariavaccine.org/files/1122009_RTSSP3_FactSheet_PATH_FINAL.pdf

Vaccines against the pathogenic asexual blood stages of plasmodium parasites are designed with the main objective of preventing clinical disease (figure 4). Antibodies to region II of the *P vivax* Duffy binding protein are associated with strain-specific immunity,[144] supporting further research into this potential vaccine target. Polymorphism of the surface proteins of *P falciparum* and variability in the parasite invasion pathways mean, however, that production of a blood-stage vaccine against this species is much more challenging.

Transmission-blocking vaccines are not designed to protect the vaccinated individual from contracting malaria, but instead to reduce the number of infectious vectors and the circulating parasite population. Research on transmission-blocking vaccines has traditionally targeted surface proteins of mosquito stages of *P falciparum* and *P vivax* (figure 4); phase 1 vaccine trials have shown immunogenicity of these vaccines in human beings.[145] More recent work has targeted antigens in the mosquito midgut or saliva that facilitate parasite invasion of the vector and host, respectively (figure 4).[146]

Interest in the development of a multi-antigen, multistage vaccine that targets different stages in the parasite's life cycle is now increasing.[147] This approach might confer better protection than do vaccines based on single antigens, and avoid vaccine failure caused by polymorphic variation in parasite populations.[148]

Conclusions

We are facing a pivotal period in the history of malaria control. Increasing intervention coverage combined with measurable evidence of effect from several countries and regions have strengthened political resolve to control the disease. There has been an unprecedented increase in international funding commitments, which rose from $0·3 billion in 2003 to $1·7 billion in 2009.[3] Rapid scale-up of insecticide-treated nets and ACTs has halved childhood morbidity and mortality from malaria in some countries in Africa with stable, high transmission, reawakening interest in the prospect of malaria elimination and, in the long term, eradication. Of the 108 countries in which malaria is endemic, those with lower transmission intensities in southern Africa and Asia have reduced the burden of the disease to such an extent that it has ceased to be a major public health problem, whereas a few low burden countries in the WHO Eastern Mediterranean and European regions have completely eliminated the disease.[3] In 16 endemic countries, malaria risk is restricted to *P vivax*, control of which will require the development of safer and more effective antihypnozoite drugs than are currently available.

The harmful consequences of relaxing intensive control efforts have already been reported,[135] and highlight the need to control malaria in a step-wise fashion, starting with low transmission countries, while maintaining good control elsewhere.[149] Limited access to effective and affordable treatment at community level is a challenge that needs to be overcome. Resistance to artemisinin derivatives and pyrethroid insecticides is a major concern, and its spread now threatens to undermine and even reverse gains in malaria control. Without the rapid development of safe and effective alternatives for treatment and prevention, malaria elimination will become increasingly difficult and eradication impossible. The effect will be felt most by the millions of children that have this preventable, but deadly, disease.

Contributors

All authors contributed to the literature search and writing of this Seminar under the coordination of the corresponding author.

Conflicts of interest

We declare that we have no conflicts of interest.

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