# Malaria

Nicholas J White, Sasithon Pukrittayakamee, Tran Tinh Hien, M Abul Faiz, Olugbenga A Mokuolu, Arjen M Dondorp

**Although global morbidity and mortality have decreased substantially, malaria, a parasite infection of red blood cells, still kills roughly 2000 people per day, most of whom are children in Africa. Two factors largely account for these decreases; increased deployment of insecticide-treated bednets and increased availability of highly effective artemisinin combination treatments. In large trials, parenteral artesunate (an artemisinin derivative) reduced severe malaria mortality by 22·5% in Africa and 34·7% in Asia compared with quinine, whereas adjunctive interventions have been uniformly unsuccessful. Rapid tests have been an important addition to microscopy for malaria diagnosis. Chemopreventive strategies have been increasingly deployed in Africa, notably intermittent sulfadoxine–pyrimethamine treatment in pregnancy, and monthly amodiaquine–sulfadoxine–pyrimethamine during the rainy season months in children aged between 3 months and 5 years across the sub-Sahel. Enthusiasm for malaria elimination has resurfaced. This ambitious but laudable goal faces many challenges, including the worldwide economic downturn, difficulties in elimination of vivax malaria, development of pyrethroid resistance in some anopheline mosquitoes, and the emergence of artemisinin resistance in *Plasmodium falciparum* in southeast Asia. We review the epidemiology, clinical features, pathology, prevention, and treatment of malaria.**

Published **Online**
August 15, 2013
http://dx.doi.org/10.1016/S0140-6736(13)60024-0

**This online publication has been corrected. The corrected version first appeared at thelancet.com on September 13, 2013**

**Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand** (Prof N J White FRS, Prof S Pukrittayakamee DPhil, Prof A M Dondorp MD); **Centre for Tropical Medicine, Nuffield Department of Clinical Medicine, Oxford, UK** (Prof N J White, Prof A M Dondorp); **Oxford University Clinical Research Unit, Hospital for Tropical Diseases, Ho Chi Minh City, Vietnam** (Prof T T Hien MD); **Department of Medicine, Dev Care Foundation, Dhaka, Bangladesh** (Prof M A Faiz PhD); **and University of Ilorin Teaching Hospital, Ilorin, Nigeria** (Prof O A Mokuolu FWACP)

Correspondence to:
Prof Nicholas J White, Mahidol Oxford Research Unit, Faculty of Tropical Medicine, Mahidol University, 420/6 Rajvithi Road, Bangkok 10400, Thailand
**nickw@tropmedres.ac**

See **Online** for appendix

## Introduction

Malaria is the most important parasitic disease of human beings. It is transmitted in 108 countries inhabited by roughly 3 billion people, and, in 2010, caused an estimated 216 million cases and 655 000 deaths.[1] More than 85% of malaria cases and 90% of malaria deaths occur in sub-Saharan Africa, mainly in young children (ie, those younger than 5 years). Malaria is a protozoan disease transmitted by *Anopheles* mosquitoes. Five species of the genus *Plasmodium* cause all malarial infections in human beings. Most cases are caused by either *Plasmodium falciparum* or *Plasmodium vivax*, but human infections can also be caused by *Plasmodium ovale*, *Plasmodium malariae*, and, in parts of southeast Asia, the monkey malaria *Plasmodium knowlesi*.[2] Almost all deaths are caused by falciparum malaria. Malaria in pregnancy (caused by both *P falciparum* and *P vivax*) causes indirect mortality from abortion and intrauterine growth retardation, which increases infant mortality. Malaria was once prevalent throughout much of the inhabited world, but has been eliminated from the USA and Canada, Europe, and Russia. Malaria prevalence resurged in tropical countries from the 1970s to the 1990s because of a combination of relaxation of control efforts, increasing antimalarial drug resistance, and insecticide resistance in the mosquito vectors. Since then, prevalence has fallen again as a result of substantial increases in donor funding, improved control, and increased enthusiasm for elimination and eradication.[3,4]

### Search strategy and selection criteria

We searched Medline and Embase with the terms "malaria" and "antimalarial drugs", in combination with the limiting term "human" for articles published in English and French between Jan 1, 2007, and Dec 31, 2011. We largely selected recent publications, but did not exclude commonly referenced and highly regarded older publications.

## Epidemiology

The main determinants of the transmission intensity of malaria are the density, longevity, biting habits, and efficiency of the mosquito vector. Only around 25 of the more than 400 anopheline species are good vectors.[5] The most effective vectors are long-lived and robust to environmental change, occur in high densities in tropical climates, breed readily, and preferentially bite humans—eg, the *Anopheles gambiae* complex in Africa. In most of Asia and South and Central America, where transmission is mainly low and seasonal, *P falciparum* and *P vivax* malaria have roughly equal prevalences.[6,7] In these areas, most people typically receive one or fewer infectious bites per year—the so-called entomological inoculation rate. Transmission intensities are much higher in much of sub-Saharan Africa, where *P falciparum* predominates, and parts of Oceania; entomological inoculation rates can be as high as 1000 per year in some areas (appendix).[6,7] In such settings, morbidity and mortality from malaria are pronounced during early childhood, but by adulthood most malaria infections are asymptomatic (figure 1).[9,10]

Constant, frequent, year-round infection is termed stable transmission. In the sub-Sahel region from Senegal to Sudan, transmission is intense but largely confined to the 3–4 month rainy season. In areas where transmission is low, erratic, or focal (often termed unstable transmission), full protective immunity from malaria is not acquired, and symptomatic disease can occur at all ages. In such areas, changes in environmental, economic, or social conditions—eg, heavy rains after drought, large population movements—together with a breakdown in malaria control and prevention services (often because of armed conflicts) can result in epidemics, with substantial mortality in all age groups.

## Biology

Female anopheline mosquitoes transmit malaria during a blood feed by inoculating microscopic motile *sporozoites*, which seek out and invade hepatocytes and then multiply.

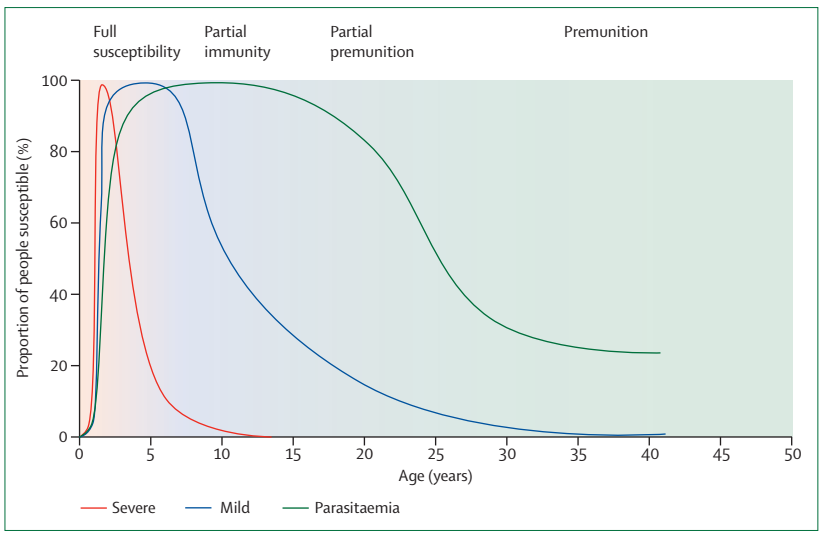


***Figure 1:*** **Relation between age and malaria severity in an area of moderate transmission intensity**
With repeated exposure protection is acquired, first against severe malaria, then against illness with malaria, and, much more slowly, against microscopy-detectable parasitaemia.[8]

A successful sporozoite can produce from 10 000 to more than 30 000 daughter merozoites in 5·5–8 days within a hepatocyte. When the hepatic schizont bursts, the liberated merozoites invade erythrocytes (figure 2). An asexual cycle in the blood takes roughly 48 h for *P falciparum*, *P vivax*, and *P ovale*, 72 h for *P malariae*, and 24 h only for *P knowlesi*.

The growing intraerythrocytic parasite consumes the red blood cell's contents, changes the cell membrane to facilitate importation of nutrients (inserting new parasite-derived proteins and exposing cryptic surface antigens), and disposes of the potentially toxic haem waste product through lipid-mediated crystallisation to biologically inert haemozoin (malaria pigment). In a susceptible individual, the parasite population expands by between six times and 20 times per cycle.[11] 6–8 days after emerging from the liver, when parasite densities have reached roughly 50/μL of blood (roughly 100 million parasites in the blood of an adult), they become detectable by microscopy or rapid diagnostic tests and the symptomatic stage of infection begins. The incubation period is therefore usually 12–14 days from the infecting bite. In *P vivax* and *P ovale* infections, some intrahepatic forms remain dormant as *hypnozoites* for between 2 weeks and more than a year (depending on geographic origin) before awakening to cause the relapses that characterise these infections.[12]

Parasites attach and enter erythrocytes via several pathways by different ligand–receptor interactions. For *P falciparum*, these interactions can be divided into two groups according to dependency on sialic acid residues (on glycophorins). Basigin, an Ok blood group antigen, has been identified as a strain transcending receptor for *PfRh5*, a parasite ligand essential for blood stage growth.[13] For *P vivax*, the predominant erythrocyte receptor is related to the Duffy blood group antigen $Fy^a$ or $Fy^b$. Most people who live or have origins in west Africa carry the Duffy-negative FyFy phenotype and are resistant to *P vivax* malaria.

The small ring forms of different malaria species look similar under light microscopy, but as the trophozoites mature within infected erythrocytes, species-specific characteristics become evident and dark malaria pigment becomes visible. By the end of the intra-erythrocytic lifecycle (figure 2), the parasite has consumed most of the red-cell contents and several nuclear divisions have taken place. The erythrocytic *schizont* then bursts and releases between six and 30 daughter merozoites, each of which can invade erythrocytes and repeat the cycle. Malarial disease is caused by the direct effects of red-cell parasitisation and destruction and the host reaction. Some blood-stage parasites develop into longer-lived sexual forms (*gametocytes*) that can transmit malaria to mosquitoes. In *P falciparum,* but not the other human malarias, this switch to gametocytogenesis is delayed, and the peak of gametocytaemia is 7–10 days after that of asexual parasitaemia. All multiplication within the human host is by mitosis. Meiosis (and thus genetic recombination) occurs only in the mosquito.

## Recurrent or persistent malaria

Blood-stage infection can persist for months or years (or decades in *P malariae* infections) when untreated. Waves of asexual parasitaemia and gametocytaemia result from antigenic variation. In tropical regions, *P vivax* relapses typically every 3–4 weeks (or every 6–8 weeks after treatment with slowly eliminated drugs, which suppress the first relapse). In temperate areas, *P vivax* can remain latent for 8–10 months between primary infection and first relapse.[12] Recurrent falciparum and vivax malaria have pronounced adverse effects in young children, and interfere with growth, development, and schooling.

## Genetics

No infectious disease has shaped the human genome more than has malaria. The geographic distributions of sickle cell disease, haemoglobins C and E, ovalocytosis, thalassaemias, and glucose-6-phosphate dehydrogenase (G6PD) deficiency are roughly similar to that of malaria before the introduction of control measures, which suggests that these disorders confer a survival advantage in the presence of malaria. In the case of haemoglobin S [HbS], the heterozygote is protected against malaria, whereas the homozygote gets sickle cell disease—a so-called balanced polymorphism.[14] Malaria protective mechanisms include decreased parasite growth at low oxygen tensions (haemoglobin AS [HbAS], reduced cyto-adherence (haemoglobins AC [HbAC] and CC [HbCC], HbAS), reduced invasion (ovalocytosis), reduced parasite densities (G6PD deficiency), and reduced multiplication at high densities (haemoglobin AE [HbAE]).[15–17]

The immune response to malaria is incompletely understood. Non-specific host defence mechanisms


www.thelancet.com **Published online August 15, 2013 http://dx.doi.org/10.1016/S0140-6736(13)60024-0**

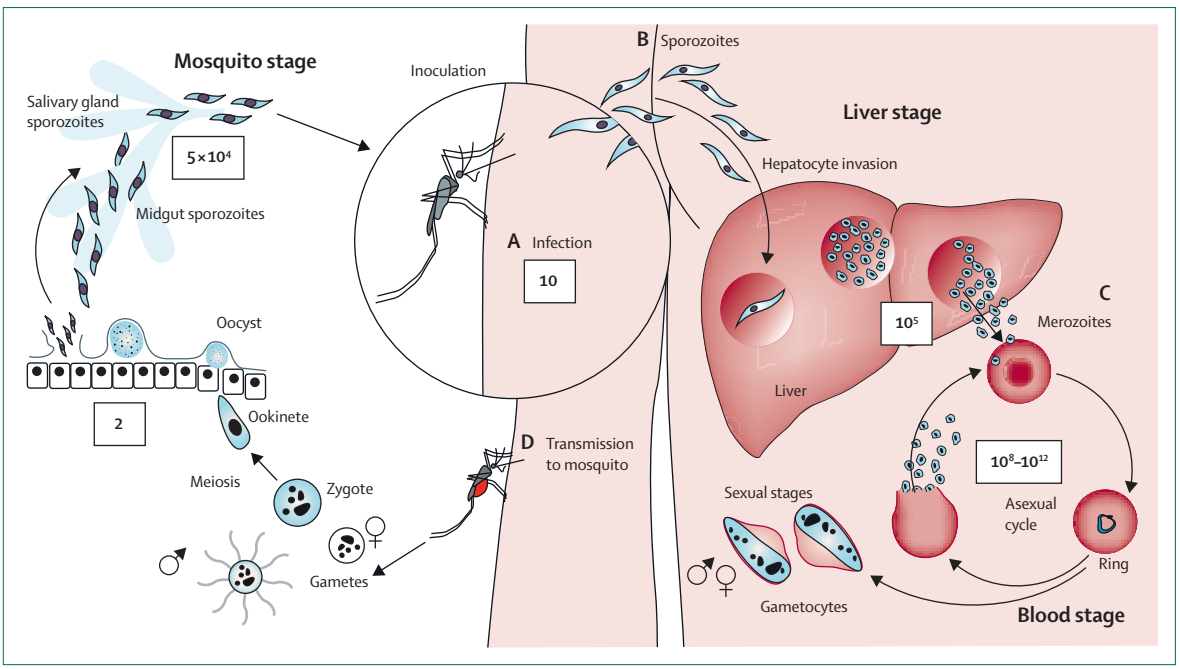


***Figure 2:*** **Lifecycle of *Plasmodium falciparum* in the human body and the anopheline mosquito**
The cycle begins with inoculation of motile sporozoites into the dermis (A; magnified), which then travel to the liver (B); each sporozoite invades a hepatocyte and then multiplies. After about a week, the liver schizonts burst, releasing into the bloodstream thousands of merozoites that invade red blood cells and begin the asexual cycle (C). Illness starts when total asexual parasite numbers in the circulation reach roughly 100 million. Some parasites develop into sexual forms (gametocytes). Gametocytes are taken up by a feeding anopheline mosquito (D) and reproduce sexually, forming an ookinete and then an oocyst in the mosquito gut. The oocyst bursts and liberates sporozoites, which migrate to the salivary glands to await inoculation at the next blood feed. The entire cycle can take roughly 1 month. Estimated numbers of parasites are shown in boxes—a total body parasite burden of $10^{12}$ corresponds to roughly 2% parasitaemia in an adult.

control the infection initially.[18] Subsequent strain-transcending and strain-specific immune responses then struggle against parasitic antigenic variation to eliminate the blood-stage infection. Both humoral and cellular immunity contribute to protection. Eventually, exposure to sufficient strains confers protection from illness, but not from infection (premunition; figure 1). Asymptomatic parasitaemia is common in adults and older children living high-transmission areas (figure 1).[8]

## Clinical features

In endemic areas malaria is often the most common cause of fever. The first symptoms of malaria are non-specific, and include a vague absence of wellbeing, headache, fatigue, muscle aches, and abdominal discomfort, which are followed by irregular fever. Nausea, vomiting, and orthostatic hypotension occur frequently. Generalised seizures are associated specifically with falciparum malaria and might be followed by coma (cerebral malaria). Most patients with uncomplicated infections have few abnormal physical findings other than fever, mild anaemia, and, after several days, a palpable spleen. The liver can become enlarged, especially in young children, whereas mild jaundice is more likely in adults. In young children living in regions in which transmission is stable, recurrent infections cause chronic anaemia and splenomegaly.

The manifestations of severe falciparum malaria, depend on age.[9] Severe anaemia and hypoglycaemia are more common in children, whereas acute pulmonary oedema, acute kidney injury, and jaundice are more common in adults; coma (cerebral malaria) and acidosis occur in all age groups (figure 3). Mortality rises when the proportion of infected erythrocytes (parasitaemia) exceeds 2%, although the relation between parasite density and prognosis in falciparum malaria is very variable. When treated promptly with effective anti-malarial drugs, uncomplicated falciparum malaria has a mortality of roughly 0·1%.

## Pathogenesis

In *P falciparum* malaria, protuberances or knobs emerge on the infected erythrocyte's surface 12–15 h after invasion. These protuberances extrude high-molecular-weight, antigenically variant, strain-specific adhesive proteins (*Pf*EMP1) that mediate cytoadherence—ie, attachment to endothelial surface receptors in veins and capillaries. Of the potential receptors identified, ICAM1 is probably the most important in the brain, chondroitin sulphate A in the placenta, and CD36 in most other organs.[19] Infected erythrocytes adhere to the vessel walls and sometimes to each other (platelet-mediated agglutination)[20] or uninfected erythrocytes (rosetting).[21] Adherence causes sequestration of red blood cells containing mature

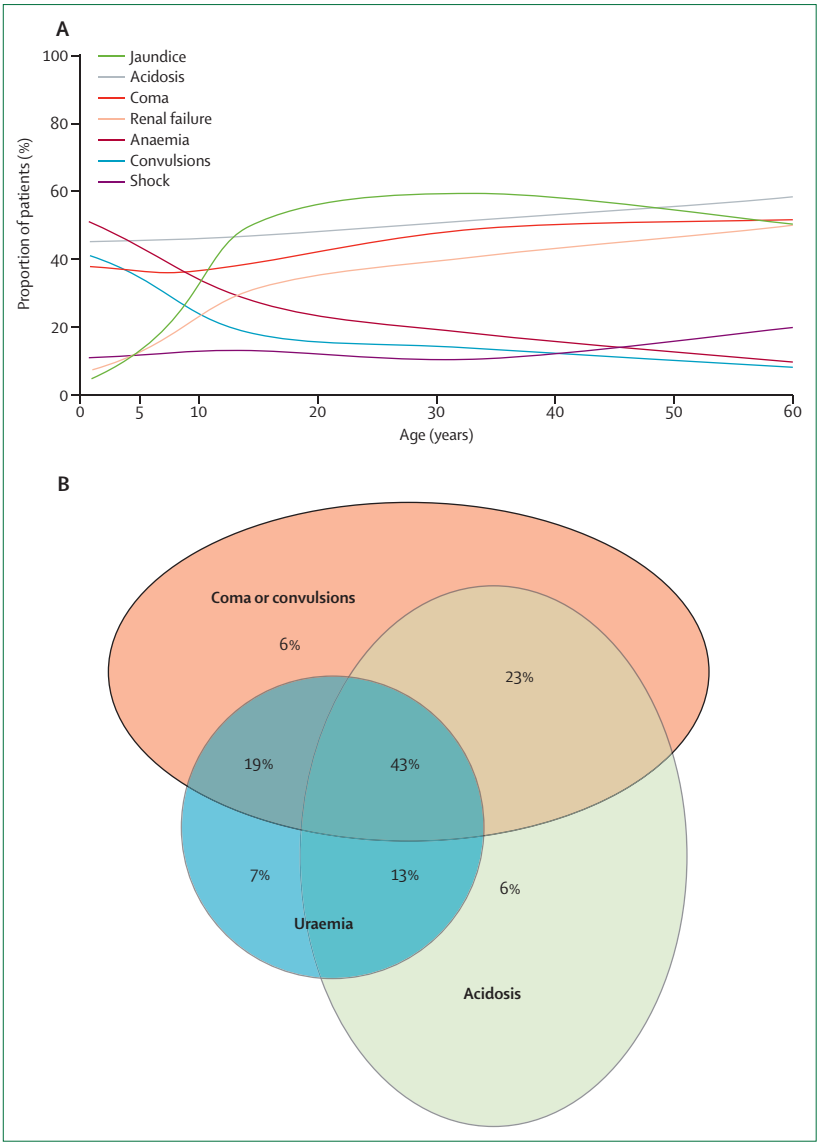


***Figure 3:*** **Manifestations of severe falciparum malaria by age (A) and mortality in children associated with CNS involvement, acidosis, and uraemia (B)**

Data from 3228 prospectively studied African children with severe falciparum malaria.[10] Uraemia here is defined as a blood urea nitrogen higher than 7.14 mmol/L. Surface areas denote the relative prevalence of the different severity signs, which frequently coexist. The percentages denote the observed mortality associated with the presenting signs.

parasites into vital organs (particularly the brain), where the sequestered parasites interfere with microcirculatory flow and metabolism and the functioning of vascular endothelium.[22] As a result, only the younger ring form *P falciparum* parasites circulate in falciparum malaria, and thus peripheral parasite counts underestimate the total number of parasites in the body. Other malarias are not sequestered substantially, so all developmental stages are noted in peripheral blood smears.

*P vivax*, *P ovale*, and *P malariae* invade red blood cells selectively (eg, *P vivax* invades only young erythrocytes), and parasitaemias are usually less than 1%; *P falciparum* and *P knowlesi* are less selective and can reach very high parasite densities.[23] In *P vivax* malaria, the infected red blood cells enlarge and deform.[24] By contrast, as *P falciparum* matures, the infected red blood cell becomes more spherical and rigid. In severe falciparum malaria, uninfected erythrocytes also become less deformable, which compromises flow through the partially obstructed capillaries and venules and shortens their survival.[25]

The host responds to malaria by augmenting splenic immune function and filtrative clearance, accelerating removal of both parasitised and uninfected erythrocytes.[26,27] Schizont rupture releases parasite and host cellular material into the blood, which activates monocytes and macrophages and induces the release of proinflammatory cytokines, causing fever and other pathological effects.[28,29]

## Severe falciparum malaria

### Pathological changes

Severe falciparum malaria is caused mainly by extensive parasitised erythrocyte sequestration and consequent dysfunction of vital organs. Direct visualisation of the microcirculation and measurement of individual vessel flows in the retinal, buccal, and rectal circulations show reversible heterogeneous microvascular obstruction with patterns matching exactly those noted in tissues from fatal cases.[30,31] The extent of microvascular obstruction parallels clinical severity and established prognostic measures, such as plasma lactate and base deficit.[31] Local release of haemoglobin and haem depletes nitric oxide, causing endothelial dysfunction. Concentrations of L-arginine—a precursor of nitric oxide—are low and those of asymmetric dimethylarginine (an inhibitor of NO synthase) increased in patients with severe malaria.[32,33] Endothelial activation causes exocytosis of intracellular Weibel-Palade bodies, which contain bioactive molecules such as von Willebrand factor and angiopoietin 2.[34,35] Ultra-long multimers of von Willebrand factor can bind activated platelets expressing CD36 (the receptor for *PfEMP1*),[36] and thereby mediate cytoadherence. Concentrations of ADAMTS13, which cleaves and inactivates these multimers, are low in patients with severe malaria.[35]

### Cerebral malaria

In fatal cases of cerebral malaria, many cerebral capillaries and venules are packed tightly with parasitised erythrocytes, whereas other adjacent vessels are not obstructed (appendix).[22,37,38] A distinct and specific malarial retinopathy with haemorrhages and retinal and vessel whitening occurs both in children and in adults. Corresponding microvascular pathological changes have been recorded post mortem.[30,39,40] Organ-specific and systemic blood lactate–pyruvate ratios are increased in proportion to the severity of illness (a different profile to the hypermetabolism of sepsis).[41] All these findings suggest that extensive microvascular obstruction and impaired perfusion are the crucial pathophysiological

processes. Little histopathological evidence of inflammation is noted, although leucocytes are more prominent in the cerebral vessels of African children than in those of Asian adults who died from cerebral malaria.[42,43] A mild, generalised increase in systemic vascular permeability is noted. The blood–brain barrier is functionally intact,[44] although the results of autopsies of African children suggest some increase in permeability, with disruption of endothelial intercellular tight junctions.[45]

Imaging shows no evidence of cerebral oedema in most adults, whereas cerebral oedema is often present in African children, particularly in the agonal stages of disease.[46–48] Lumbar puncture opening pressures are usually normal in adults but increased in roughly 80% of children, although mean pressures (around 160 mm CSF) are similar.[49,50] Raised intracranial pressure probably results mainly from increased intracranial blood volume, which in turn is a result of sequestration of parasitised erythrocytes. In a study in India, adjunctive treatment with mannitol (to reduce brain swelling) prolonged coma duration and increased mortality.[51]

Coma can persist after the time by which cerebral parasite sequestration should have cleared. Transient disruption of axoplasmic transport[52] and persistent attachment of residual erythrocyte membranes and malaria pigment to vascular endothelium[22] stimulating continued activation provide a plausible explanation. Whereas adults rarely (ie, <3% of cases) have neurological sequelae, 3–15% of children who survive cerebral malaria—especially those with hypoglycaemia, severe anaemia, repeated protracted seizures, and deep coma—have residual neurological deficits, including hemiplegia, cerebral palsy, cortical blindness, deafness, and impaired cognition and learning (all of varying duration).[53–55] Roughly 10% of children have persistent language deficits, increased incidence of epilepsy, and decreased life expectancy.[56] The discrepancy between microvascular pathological changes in acute illness and the large vessel territory strokes that can follow cerebral malaria has not been explained satisfactorily.

### Severe anaemia

Severe anaemia is the main manifestation of severe malaria in young children (figure 3) in areas of high transmission,[57] and is usually the cumulative result of repeated infections. Accelerated splenic removal of mainly the unparasitised red blood cells and erythrocyte destruction at parasite schizogony are compounded by ineffective erythropoiesis.[27,58] Slight coagulation abnormalities are frequent, and thrombocytopenia is usual even in uncomplicated malaria (a normal platelet count should lead clinicians to question the diagnosis of malaria). Substantial bleeding from disseminated intravascular coagulation in severe malaria is rare. Haematemesis from stress ulceration or acute gastric erosions can occur.

### Acidosis and hypoglycaemia

An important cause of death associated with severe malaria (figure 3), acidosis results from accumulation of organic acids, including lactic acid,[41] and is often compounded by ketoacidosis in children and acute kidney injury in adults. Acidotic breathing is a sign of poor prognosis,[59,60] and is often followed by circulatory failure refractory to volume expansion and inotropic drugs, and ultimately respiratory arrest. Of the biochemical variables in severe malaria, plasma bicarbonate, base excess, or lactate concentrations have the highest predictive value for fatal outcomes.[10,59] Lactic acidosis results mainly from anaerobic glycolysis in tissues in which sequestered parasites obstruct microcirculatory flow, and is compounded by lactate production by malaria parasites and failures of hepatic and renal lactate clearance mechanisms. Although hypovolaemia can contribute to hyperlactataemia, its causative role in the acidosis of severe falciparum malaria is disputed.[61,62]

Hypoglycaemia is associated with lactic acidosis, and is especially problematic in children and pregnant women. It results from a failure of hepatic gluconeogenesis and an increase in tissue glucose consumption.[41,63] Hyperinsulinaemic hypoglycaemia is an important adverse effect of quinine (a powerful stimulant of pancreatic insulin secretion), and is particularly common in pregnant women, even in those with otherwise uncomplicated malaria.[64]

### Pulmonary oedema

Acute respiratory distress syndrome is a feared complication in adults with severe falciparum malaria (particularly in pregnant women), which can also occur in *P vivax* and *P knowlesi* infections.[65,66] Increased pulmonary capillary permeability develops in as much as 30% of adult patients and often manifests after the start of antimalarial treatment.[67,68] Pathogenesis is not fully understood, but inflammation-mediated endothelial damage might have an important role. The role of pulmonary vascular parasite sequestration is unclear. Careful fluid management is essential; rapid infusion of large volumes of intravenous fluid can be lethal.[69] In the absence of mechanical ventilation, the mortality of acute respiratory distress syndrome exceeds 80%. With mechanical ventilation, case fatality still exceeds 50% in falciparum malaria. Prognosis is better in vivax malaria.[67]

### Acute kidney injury

Acute kidney injury is common in adults with severe malaria (figure 3). It behaves clinically and pathologically like acute tubular necrosis. Pathogenesis remains unclear, but reduced microcirculatory flow probably contributes.[70] Acute kidney injury is frequently associated with dysfunction of several other vital organs (leading to high mortality) or can develop more slowly as other disease manifestations resolve. Acute kidney injury is oliguric in 60–70% of cases. In survivors, urine flow

resumes in a median of 4 days, and serum creatinine concentrations return to normal in a mean of 17 days.[71] Early haemofiltration or dialysis substantially improves outcomes, especially in acute hypercatabolic renal failure.[72] Oliguric renal failure is rare in children, although increased concentrations of blood urea are frequent and an independent risk factor for death in African children with severe malaria (figure 3B).[10]

### Jaundice

Severe jaundice results from a combination of haemolysis, hepatocyte injury, and cholestasis. Jaundice is more common in adults than in children (figure 3), and is often accompanied by renal impairment. Chronic carriage of hepatitis B virus might predispose to severe malaria in adults.[73]

### Interactions with other infections

Invasive bacterial infections, especially those caused by enteric bacteria, have been reported in 5–8% of African children with severe malaria.[74,75] In view of the low sensitivity of blood cultures, the true proportion could be much higher. Falciparum malaria is estimated to account for more than half of invasive bacterial disease in children living in malaria-endemic areas.[76] Increased translocation of gut bacteria across enteric epithelia is a likely source. Parasitic digestive vacuoles, containing malaria pigment, are phagocytosed rapidly by polymorphonuclear granulocytes and cause functional exhaustion, which blunts the microbicidal activity of the granulocytes and possibly increases susceptibility to invasive bacterial infections in severe malaria.[77] Neutrophil dysfunction might result from haemolysis-induced haeme oxygenase-1 induction.[78]

In endemic areas, severe malaria is frequently misdiagnosed in children with severe sepsis, pneumonia, meningitis, and other diseases associated with incidental malarial parasitaemia,[79] confounding clinical studies and pathological interpretations. Plasma *Pf*HRP2 concentrations can be used to distinguish severe malaria from other disorders.[80] HIV transmission and progression are accelerated by malaria.[81,82] The incidence of clinical malaria, severe malaria, and malaria-associated mortality is increased in adults with HIV infection and deteriorating immune status.[83–85] Concomitant HIV/AIDS increases the severity and mortality of severe falciparum malaria in children.[86,87]

## Severe vivax malaria

During the past 5 years, reports from Indonesia, Papua New Guinea, India, and the Amazon region describing severe and sometimes fatal disease in *P vivax* infections have become more frequent. Studies from Oceania and the Amazon show high prevalences of severe anaemia (19–89%) associated with vivax malaria, which is often ascribed to repeated frequent relapses or chronic infections as a result of chloroquine resistance.[88–90] Acute vivax malaria occasionally causes acute pulmonary oedema, but investigators of several series[91–95] have reported a high frequency of other severe manifestations, including coma (in 4–26% of severe cases), renal failure (4–45%), haemodynamic shock (0–54%), severe jaundice (0–59%), abnormal bleeding (0–11%; often with severe thrombocytopenia), and, in one series, frequent hypoglycaemia (13%). Case fatality in these series ranged from 0–25%. These reports contrast with those from other regions and historical observations that life threatening illness in vivax malaria is rare. In some reports, comorbidities have not been addressed adequately, and, in areas where prevalence is high (eg, New Guinea) the possibility that *P vivax* was incidental to a different disease process was not excluded. In a study done in the Indonesian province of Papua, where transmission of both *P vivax* and *P falciparum* is high, the risk of coma was estimated to be one in 29 486 (no deaths) in *P vivax* monoinfections and one in 1276 in *P falciparum* infections (18·5% mortality).[92] More detailed prospective clinical epidemiological studies are needed to establish whether the increase in the past 5 years of reports of severe manifestions of vivax malaria (other than severe anaemia and acute pulmonary oedema) are a result of multifocal emergence of virulent strains, previously underestimated severity, or over-reporting.

## Malaria in pregnancy

In areas of high transmission, the risk of low birthweight (ie, <2·5 kg) roughly doubles when women have placental malaria; the effect is greatest during first pregnancies. This lower birthweight is associated with increased infant mortality.[96] Maternal anaemia is exacerbated, but most mothers remain asymptomatic despite intense accumulation of infected erythrocytes in the placental microcirculation. Congenital malaria occurs in roughly 5% of neonates but clears spontaneously in 62% of cases.[97] Maternal HIV infection predisposes pregnant women to malaria, predisposes to congenital malaria, and exacerbates reductions in birthweight.[98] In areas with unstable malaria transmission, pregnant women are at increased risk of developing severe falciparum malaria with a very high mortality rate (roughly 50%). High parasitaemias, severe anaemia, hypoglycaemia, and acute pulmonary oedema are all more frequent in pregnant than in non-pregnant women. In severe disease, fetal distress, premature labour, and stillbirth often occur.

In *P vivax* infections in pregnancy, severe malaria is very rare. No intense placental sequestration occurs yet the average reduction in birthweight is roughly 107 g (compared with 170 g in falciparum malaria).[99] Even oligosymptomatic, promptly treated *P falciparum* or *P vivax* infections increase the risks of having abortions and low birthweight (all gravida).[100,101] The risk of infant death is particularly high if maternal malaria occurs during late (ie, near-term) pregnancy.[102] Maternal death from haemorrhage at childbirth is correlated with malaria-induced anaemia.[100,101]

## Diagnosis and assessment

Thick and thin blood film microscopy examination remains the gold standard for diagnosis, but simple, sensitive, and specific antibody-based rapid diagnostic tests that detect *Pf*HRP2, pan-malaria or species-specific lactate dehydrogenase, or aldolase antigens in finger-prick blood are now used widely.[103] *Pf*HRP2-based tests might remain positive for weeks after acute infection, which limits usefulness in high-transmission areas, but can be used to diagnose severe malaria in patients who have taken artemisinin derivatives and cleared peripheral parasitaemia (tests remain strongly positive).

*Pf*HRP2-based rapid diagnostic tests are as good as is routine microscopy in the diagnosis of falciparum malaria. The new-generation tests based on detection of plasmodium lactate dehydrogenase are effective for diagnosis of both falciparum and vivax infections, although sensitivity is low at *P vivax* densities of less than 200/μL. Aldolase-based tests are less sensitive, especially for non-falciparum species.[103] Because of their simplicity and speed, rapid diagnostic tests are particularly valuable in epidemic investigations and surveys. However, they are expensive and do not quantify parasitaemia. The hidden sequestered biomass in severe malaria can be estimated from *Pf*HRP2 concentrations in plasma.[104]

## Prevention

### Vaccination

Much time, effort, and money have been spent on the development of malaria vaccines. The RTS,S subunit vaccine, which targets the circumsporozoite protein of *P falciparum* and is boosted with the potent ASO adjuvant, is the most advanced vaccine in development. The results of a large multicentre study[105] of RTS,S in infants aged 6–12 weeks at first immunisation (deployed as a monthly dose for three months in conjunction with an Expanded Programme of Immunisation vaccines) showed good safety but only moderate efficacy, with 30% protection against clinical malaria and 26% protection against severe malaria in the 12 months after the last dose. Previously reported results[106] in slightly older children (aged 5–17 months) were better, with 55% protection against all falciparum malaria and 35% protection against severe malaria during 14 months. Decisions about possible deployment are expected in 2014.

### Vector control

Vector control is an essential component of prevention. In areas of moderate or high transmission in Africa, deployment of pyrethroid-insecticide-treated mosquito nets reduced all-cause mortality by roughly 20% in children younger than 5 years.[107] Wide-scale deployment of such nets has contributed substantially to the fall in malaria morbidity and mortality. Long-lasting insecticide treated nets that retain activity for the natural life of the net without retreatment have been developed. In addition to protecting the user, insecticide-treated nets protect the community by killing anopheline mosquitoes (the so-called mass effect),[108,109] and should be deployed in all areas where malaria is endemic. They are usually very effective; however, in some parts of Asia, the main mosquito vectors bite outside early in the evening or morning and so the protective effect is small. Use of pyrethroids in agriculture and widespread deployment of insecticide-treated nets has put a tremendous selection pressure on anopheline mosquitoes and resistance has emerged.

Despite their extensive use for personal protection, remarkably few trials of widely used and very safe insect repellents (eg, diethyltoluamide) have been done. Indoor residual spraying with insecticides that persist and kill mosquitoes is an important component of malaria control.[110–112] Its efficacy strongly depends on the behaviour of the local *Anopheles* vectors (ie, whether the mosquitoes enter houses and rest there) and whether resistance has emerged. Dichlorodiphenyltrichloroethane (DDT) is still effective in parts of Asia and Africa and used for indoor residual spraying, which can result in high human exposure.[113] Only four general insecticide classes exist, and, in some areas, the development of resistance is undermining the efficacy of insecticide-based measures.[114] WHO has developed a global strategic framework for integrated vector management, which advocates an evidence-based, integrated approach for vector control and offers guidance for successful operationalisation of the different approaches.[115,116]

### Chemoprophylaxis and chemoprevention

Chemoprophylaxis is recommended for travellers during potential exposure to malaria.[117] For drugs that do not have activity against the pre-erythrocytic (liver) stage, chemoprophylaxis is given during exposure and for four weeks thereafter to catch any blood-stage infections that emerge from the liver. Recommendations for chemoprophylaxis depend on local patterns of susceptibility to antimalarials and the likelihood of acquisition of malaria. When uncertainty exists, drugs that effectively prevent infection with resistant *P falciparum* should be used—ie, atovaquone–proguanil, doxycycline, primaquine, or mefloquine. Chemoprophylaxis is never completely reliable, and malaria should always be a possible diagnosis in febrile patients who have travelled to endemic areas.

Previously, chemoprophylaxis was recommended for pregnant women in endemic areas, but in most areas resistance has developed against the drugs approved for this indication (ie, chloroquine, proguanil). In Africa, intermittent preventive treatment with sulfadoxine–pyrimethamine was given instead. A full course of sulfadoxine–pyrimethamine twice during later pregnancy provided partial protection.[118] A minimum of three doses of sulfadoxine–pyrimethamine are now recommended to provide continuous preventive effects. Resistance to sulfadoxine–pyrimethamine is increasing in Africa, and thus alternative drugs are being investigated for use in intermittent preventive treatment in pregnancy.[118]

All pregnant women in endemic areas should be encouraged to attend regular antenatal clinics (when available). Pregnant women travelling to endemic areas should be advised of the potential risks. Mefloquine is the only drug recommended for chemoprophylaxis in pregnant women travelling to areas with drug-resistant malaria, and is thought to be safe in the second and third trimesters of pregnancy; data for first-trimester exposures (although few) are reassuring.[119] The safety of other prophylactic antimalarials in pregnancy has not been established, although no harmful effects have been associated with atovaquone–proguanil.[120]

The intermittent treatment approach has been extended to infancy, where it can be delivered to all at-risk infants via the system in place for the expanded programme on immunisation. However, much malaria-related illness and death in Africa occurs in children aged 3–59 months in the Sahel sub-region during 4 months of the rainy season. WHO has recommended administration of monthly amodiaquine and sulfadoxine–pyrimethamine (maximum four doses) to all children aged 3–59 months in this region from the start of the yearly transmission season.[121] This seasonal malaria chemoprevention has superceded intermittent preventive treatment in infants. Intermittent preventive therapy is effective when delivered through schools or to adults at high risk of malaria.[122]

Since the 1930s, various approaches to treatment of whole populations have been taken. Mass drug administration to millions of people was effective in some settings but not in others and gained a poor reputation (perhaps undeservedly); thus this approach has been little used in recent years.[123]

***Panel 1:*** **Treatment of severe malaria in adults and children**

- Artesunate 2·4 mg/kg by intravenous or intramuscular* injection, followed by 2·4 mg/kg at 12 h and 24 h; continue injection once daily if necessary†
- Artemether 3·2 mg/kg by immediate intramuscular* injection, followed by 1·6 mg/kg daily
- Quinine dihydrochloride 20 mg salt per kg infused during 4 h, followed by maintenance of 10 mg salt per kg infused during 2–8 h every 8 h (can also be given by intramuscular injection* when diluted to 60–100 mg/mL)

Artesunate is the treatment of choice. Artemether should only be used if artesunate is unavailable. Quinine dihydrochloride should be given only when artesunate and artemether are unavailable. *Intramuscular injections should be given to the anterior thigh. †Young children with severe malaria have lower exposure to artesunate and its main biologically active metabolite dihydroartemisinin than do older children and adults. Revised dose regimens to ensure similar drug exposures have been suggested.[124]

## Treatment

### Severe disease

Severe falciparum malaria is a medical emergency, and necessitates intensive nursing care and careful management (panel 1). In Asia, parenteral artesunate significantly reduced mortality from 22·4% to 14·7% compared with quinine (figure 4) (appendix).[54] In the largest study[53] so far of children hospitalised with severe falciparum malaria in Africa, artesunate significantly reduced mortality from 10·9% to 8·5% compared with quinine. Intravenous or intramuscular artesunate is thus the treatment of choice for severe malaria worldwide[120] (including in patients with severe vivax and knowlesi malaria[125]). Artesunate has no important local or systemic adverse effects, although high cumulative doses (≥6 mg/kg per day) can temporarily suppress bone marrow. Delayed haemolysis starting a week after artesunate treatment for severe malaria has been noted in travellers (particularly those initially presenting with high parasitaemias) returning to hospitals in non-endemic countries.[126] This haemolysis is probably partly caused by the loss of once-infected erythrocytes, which results from splenic pitting of parasites killed by artesunate.

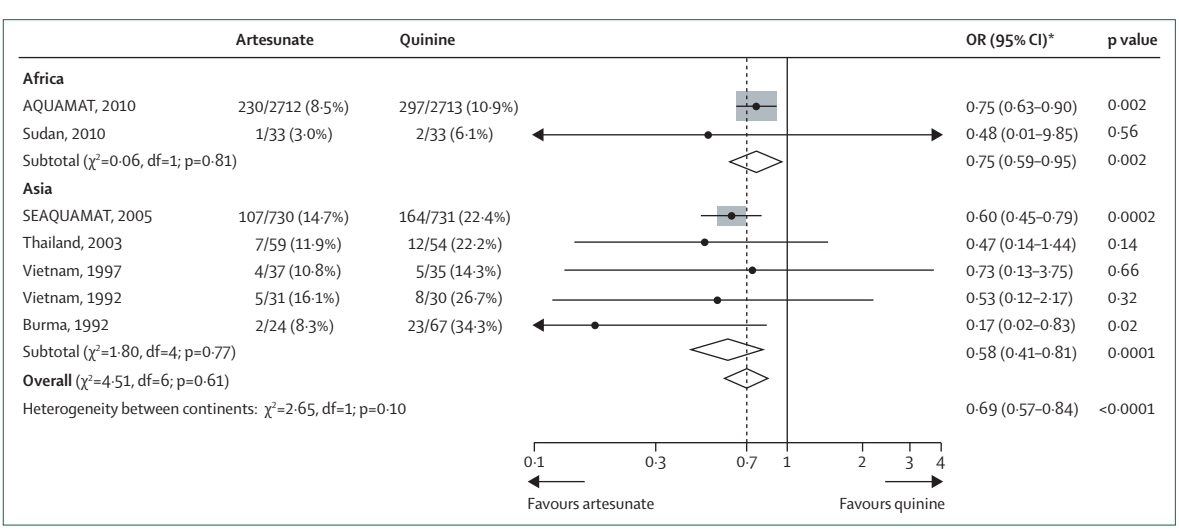


***Figure 4:*** **Meta-analysis of all randomised controlled trials of parenteral artesunate versus parenteral quinine in severe malaria**
Reproduced from Dondorp and colleagues.[53] The solid vertical line represents equality of the two groups; the dashed line is the overall treatment difference. The size of the squares is proportional to the size, and therefore weight, of the trial. OR=odds ratio. *99% CIs for totals.

Artemether and artemotil (arteether) are oil-based formulations given by intramuscular injection that are absorbed erratically and confer a smaller survival benefit than does artesunate.[127,128] In a large placebo-controlled trial,[129] community-based pre-referral treatment with a rectal formulation of artesunate for patients unable to take oral medications decreased malaria mortality in severely ill children by 25%.

In acute renal failure or severe metabolic acidosis, haemofiltration or hemodialysis should be started early.[72] Dose reduction of artemisinin derivatives is unnecessary, even in renal failure. Prophylactic anticonvulsants are potentially dangerous; high-dose phenobarbital (20 mg/kg) doubled mortality in children with cerebral malaria—patients died mainly from respiratory arrest.[130]

In unconscious patients, blood glucose should be measured every 4–6 h and dextrose continuously infused to maintain concentrations higher than 4 mmol/L. Hypoglycaemia (<2·2 mmol/L) should be treated immediately with bolus glucose. Parasite counts and haematocrit concentrations should be measured every 6–12 h. Anaemia develops rapidly in severe malaria; if haematocrit falls to less than 20% (haemoglobin <70 g/L), then packed cells or whole (preferably fresh) blood should be transfused carefully. The transfusion threshold for children in Africa (where anaemia is very common and safe blood for transfusion is scarce) is a haematocrit concentration of 15% or less (haemoglobin concentrations less than 50 g/L). Renal function should be checked daily. Management of fluids is difficult, especially in adults, because the risks of overhydration (pulmonary oedema) have to be balanced against those of underhydration (exacerbation of renal impairment and tissue hypoperfusion). Large fluid boluses are harmful at all ages.[68,69] Early enteral feeding in non-intubated comatose adults can cause aspiration pneumonia, so feeding should not start until the third day of the coma.[131] When the patient can take tablets reliably, a full course of artemisinin combination treatment should be given.[120]

Intravenous antimicrobials should be given to all children with suspected severe malaria in areas of moderate or high transmission.[132] Convulsions should be treated with intravenous or rectal benzodiazepines and respiratory support provided when necessary. Aspiration pneumonia should be suspected in any unconscious child or adult patient with convulsions, particularly when persistent hyperventilation is noted. Hypoglycaemia or septicaemia should be suspected after sudden deterioration for no obvious reason during treatment. Patients who bleed spontaneously should be given packed red blood cells with fresh frozen plasma or, when unavailable, fresh blood and parenteral vitamin K.

## Uncomplicated falciparum malaria

Artemisinin combination treatment is the recommended first-line therapy for uncomplicated falciparum malaria in all endemic areas, and is highly efficacious against the other human malarias. The artemisinin component (artesunate, artemether, or dihydroartemisinin) is given for 3 days with a slowly eliminated antimalarial, preferably in a fixed-dose combination (table). Artemisinin combination treatment is rapidly and reliably effective, associated with few adverse effects,[133] and curative in more than 90% of cases (except in foci of artemisinin resistance). The price of such treatment has dropped substantially, making it more generally affordable. Unfortunately, fake or substandard antimalarials are widespread in many Asian and African countries, which compromises effectiveness, selects for resistance, and diminishes confidence in the health sector. Atovaquone–proguanil is highly effective everywhere, but seldom used in endemic areas because of the cost and propensity for high-grade resistance to emerge from single mutations in the *cyt b* gene. The duration of post-treatment prophylaxis after artemisinin combination treatment varies. Slowly eliminated partner drugs, such as mefloquine and piperaquine, provide 4–6 weeks' prophylaxis, whereas reinfections after treatment with artemether–lumefantrine often emerge within a month. In low transmission areas, a single gametocytocidal dose of primaquine (0·25 mg base per kg) should be added to all artemisinin combination treatments for falciparum malaria (except for those in infants and pregnant women, in whom primaquine is not recommended) to sterilise the infection and prevent onward transmission.[134] Testing for G6PD deficiency is not necessary with this dose.

Patients should be monitored for vomiting for 1 h after any oral antimalarial dosing. If the patient vomits, another dose should be given. Minor adverse effects (eg, nausea, abdominal discomfort, headache, dizziness) occur frequently in malaria, and often result from the illness rather than the treatment. 3 day artemisinin combination regimens are well tolerated, although

| | Regimens |
|---|---|
| All *Plasmodium falciparum* malaria | Artemether–lumefantrine 1·5 mg/kg–9 mg/kg twice daily for 3 days with food or milk<br>Artesunate 4mg/kg daily for 3 days and mefloquine 25 mg base per kg (8 mg/kg/daily for 3 days*)†<br>Dihydroartemisinin–piperaquine 2·5 mg/kg–20 mg/kg daily for 3 days |
| Sensitive *P falciparum* malaria | Artesunate 4mg/kg daily for 3 days and a single dose of sulfadoxine–pyrimethamine 25 mg/kg–1·25 mg/kg<br>Artesunate 4 mg/kg and amodiaquine* 10 mg base per kg daily for 3 days |
| Chloroquine-sensitive *Plasmodium vivax*‡, *Plasmodium malariae*‡, *Plasmodium ovale*‡, *Plasmodium knowlesi*‡ | Chloroquine 10 mg base per kg immediately, followed by 10 mg/kg at 24 h and 5 mg/kg at 48 h |

*WHO prequalified fixed dose formulations are preferable to loose tablets. A taste masked dispersible paediatric tablet formulation of artemether-lumefantrine is available. †High failure rates with artesunate–mefloquine have been reported on the Thailand–Myanmar border. ‡Any of the artemisinin combination treatments can be given except for artesunate–sulfadoxine–pyrimethamine where *P vivax* is resistant. Patients with *P vivax* or *P ovale* infections should also be given a 14 day course of primaquine to eradicate hypnozoites (radical cure). However, severe G6PD deficiency is a contraindication because a 14 day course of primaquine can cause severe haemolytic anaemia in this group.

***Table:*** **Treatment of uncomplicated malaria**

**Panel 2: Second line treatments and new drugs**

- Artesunate 2 mg/kg daily plus tetracycline* 4 mg/kg four times daily, doxycycline* 3 mg/kg daily, or clindamycin 10 mg/kg twice daily for 7 days
- Quinine 10 mg salt per kg three times daily plus tetracycline* 4 mg/kg four times daily, doxycycline* 3 mg/kg daily, or clindamycin 10 mg/kg twice daily for 7 days
- Atovaquone–proguanil 20 mg/kg–8 mg/kg daily for three days (with food)
- Artesunate–pyronaridine 4 mg/kg–12 mg/kg daily for three days[135,136]

*Not suitable for pregnant women or children younger than 8 years.

mefloquine is associated with increased rates of vomiting and dizziness. The frequency of serious adverse neuropsychiatric reactions to mefloquine is around one per 1000 patients treated in Asia but as high as one per 200 in African and white patients. All the antimalarial quinolines (ie, chloroquine, mefloquine, and quinine) exacerbate orthostatic hypotension, and are tolerated better by children than by adults (panel 2).

## Resistance

Western Cambodia and the Thailand–Myanmar border, where artemisinin-resistant *P falciparum* has emerged,[137,138] are the regions of greatest concern. Resistance to both chloroquine and sulfadoxine–pyrimethamine emerged prreviously in this area, and in both cases the resistance genes spread to Africa and caused millions of deaths. Artemisinin-resistant parasites are cleared slowly from the blood after artemisinin combination treatment. Parasite clearance times exceed 3 days, and treatment failure occurs more often. Resistance to amodiaquine, sulfadoxine–pyrimethamine, and, to a lesser extent, mefloquine, limits deployment of artemisinin combinations containing these drugs in several areas. Up-to-date information about antimalarial drug resistance is available from the Worldwide Antimalarial Resistance Network.

For the **Worldwide Antimalarial Resistance Network** see http://www.wwarn.org

### *P vivax* and other malarias

Despite increasing resistance in *P vivax*, chloroquine is widely used to treat non-falciparum malarias, except in Indonesia and Papua New Guinea, where highly resistant *P vivax* is widespread.[139] In Asia, *P vivax* and *P falciparum* often co-infect, and, in parts of southeast Asia, subsequent *P vivax* infection occurs in as much as 50% of patients treated for falciparum malaria.[140] In view of the increasing resistance to chloroquine in *P vivax*, the potential for misdiagnosis and subsequent inadvertent use of chloroquine to treat falciparum malaria, and operational advantages, artemisinin combination treatment seems a good first-line treatment for all human malarias.

To prevent relapses of tropical *P vivax* malaria, a full course of primaquine (0·5 mg base per kg daily for 14 days—so-called radical treatment) should be given (table).[120] For *Plasmodium ovale* and temperate strains of *P vivax*, the primaquine dose is 0·25 mg base per kg per day. Testing for G6PD deficiency is necessary because daily primaquine causes potentially dangerous haemolysis in G6PD-deficient patients. In patients with mild variants of G6PD deficiency, weekly primaquine (0·75 mg base per kg) for 8 weeks is safer than, and probably as effective as, daily treatment. Pregnant women with vivax or ovale malaria should be given suppressive prophylaxis with chloroquine (5 mg base per kg per week) until delivery, at which point radical treatment with primaquine can be given.

## Control and elimination

Where malaria has been reduced substantially, acquisition of immunity slows and symptomatic disease extends to older children and then to adults. Occasional epidemics can occur. This pattern, which is now noted in some parts of Africa, is similar to that reported previously in Asia and southern Europe. In areas of low seasonal transmission—eg, much of Asia, Central and South America, strengthening of control measures usually has a greater effect on *P falciparum* than on *P vivax*. Some countries—eg, Turkmenistan (2006), United Arab Emirates (2007), Morocco (2010), Armenia (2011)—have achieved elimination in the past 10 years. Others, where local transmission no longer occurs, await WHO certification—eg, Egypt (1998), Mauritius (1998), Oman (2000), Algeria (2005), Syria (2005). In some areas, despite substantial financial investment in malaria control, commensurate reductions in case numbers have not been noted. Possibly, the epidemiology of malaria in these areas was underestimated. Often, small foci of stable transmission within low transmission areas act as transmission reservoirs, and asymptomatic malaria has been underestimated substantially.

Counterfeit and substandard drugs are a major threat to malaria control, and more active counter measures, stronger legislation, and better surveillance are needed.[141,142]

Artemisinin resistance poses the greatest threat to global malaria control, and more vigorous containment and elimination measures than have been instituted in the past 6 years are needed. Radical measures to eliminate resistance foci, such as mass drug administration, might be needed. The value of active case detection is uncertain. Greater use of primaquine to prevent relapse of vivax malaria and as a gametocytocide in falciparum malaria would help with control and elimination in areas with low transmission.[143]

**Contributors**

NJW and AMD wrote the first draft, all authors then reviewed and edited subsequent drafts.

**Conflicts of interest**

We declare that we have no conflicts of interest.

**Acknowledgments**

NJW and AMD are supported by the Wellcome Trust as part of the Wellcome Trust–Mahidol University–Oxford Tropical Medicine Research Programme.

**References**

1 WHO. World Malaria Report 2011. Geneva, World Health Organization, 2011.

2 Kantele A, Jokiranta TS. Review of cases with the emerging fifth human malaria parasite, *Plasmodium knowlesi*. *Clin Infect Dis* 2011; **52:** 1356–62.

3 Feachem RGA, Phillips AA, Targett GA, Snow RW. Call to action: priorities for malaria elimination. *Lancet* 2010; **376:** 1517–21.

4 Alonso PL, Brown G, Arevalo-Herrera M, et al. A research agenda to underpin malaria eradication. *PLoS Med* 2011; **8:** e1000406.

5 Sinka ME, Bangs MJ, Manguin S, et al. A global map of dominant malaria vectors. *Parasit Vectors* 2012; **5:** 69.

6 Gething PW, Patil AP, Smith DL, et al. A new world malaria map: *Plasmodium falciparum* endemicity in 2010. *Malar J* 2011; **10:** 378.

7 Gething PW, Elyazar IR, Moyes CL, et al. A long neglected world malaria map: *Plasmodium vivax* endemicity in 2010. *PLoS Negl Trop Dis* 2012; **6:** e1814.

8 Sarda V, Kaslow DC, Williamson KC. Approaches to malaria vaccine development using the retrospectroscope. *Infect Immun* 2009; **77:** 3130–40.

9 Dondorp AM, Lee SJ, Faiz MA, et al. The relationship between age and the manifestations of and mortality associated with severe malaria. *Clin Infect Dis* 2008; **47:** 151–57.

10 von Seidlein L, Olaosebikan R, Hendriksen IC, et al. Predicting the clinical outcome of severe falciparum malaria in african children: findings from a large randomized trial. *Clin Infect Dis* 2012; **54:** 1080–90.

11 Simpson JA, Aarons L, Collins WE, Jeffery GM, White NJ. Population dynamics of untreated *Plasmodium falciparum* malaria within the adult human host during the expansion phase of the infection. *Parasitology* 2002; **124:** 247–63.

12 White NJ. Determinants of relapse periodicity in *Plasmodium vivax* malaria. *Malar J* 2011; **10:** e297.

13 Crosnier C, Bustamante LY, Bartholdson SJ, et al. Basigin is a receptor essential for erythrocyte invasion by *Plasmodium falciparum*. *Nature* 2011; **480:** 534–37.

14 Williams TN. Balancing act: haemoglobinopathies and malaria. *Lancet Infect Dis* 2012; **12:** 427–28.

15 Cholera R, Brittain NJ, Gillrie MR, et al. Impaired cytoadherence of *Plasmodium falciparum*-infected erythrocytes containing sickle hemoglobin. *Proc Natl Acad Sci USA* 2008; **105:** 991–96.

16 Taylor SM, Parobek CM, Fairhurst RM. Haemoglobinopathies and the clinical epidemiology of malaria: a systematic review and meta-analysis. *Lancet Infect Dis* 2012; **12:** 457–68.

17 Cyrklaff M, Sanchez CP, Kilian N, et al. Hemoglobins S and C interfere with actin remodeling in *Plasmodium falciparum*-infected erythrocytes. *Science* 2011; **334:** 1283–86.

18 Cordery DV, Urban BC. Immune recognition of *Plasmodium*-infected erythrocytes. *Adv Exp Med Biol* 2009; **653:** 175–84.

19 Cooke B, Coppel R, Wahlgren M. Falciparum malaria: sticking up, standing out and out-standing. *Parasitol Today* 2000; **16:** 416–20.

20 Pain A, Ferguson DJ, Kai O, et al. Platelet-mediated clumping of *Plasmodium falciparum*-infected erythrocytes is a common adhesive phenotype and is associated with severe malaria. *Proc Natl Acad Sci USA* 2001; **98:** 1805–10.

21 Doumbo OK, Thera MA, Kone AK, et al. High levels of *Plasmodium falciparum* rosetting in all clinical forms of severe malaria in African children. *Am J Trop Med Hyg* 2009; **81:** 987–93.

22 Pongponratn E, Turner GD, Day NP, et al. An ultrastructural study of the brain in fatal *Plasmodium falciparum* malaria. *Am J Trop Med Hyg* 2003; **69:** 345–59.

23 Simpson JA, Silamut K, Chotivanich K, Pukrittayakamee S, White NJ. Red cell selectivity in malaria: a study of multiple-infected erythrocytes. *Trans R Soc Trop Med Hyg* 1999; **93:** 165–68.

24 Suwanarusk R, Cooke BM, Dondorp AM, et al. The deformability of red blood cells parasitized by *Plasmodium falciparum* and *P. vivax*. *J Infect Dis* 2004; **189:** 190–94.

25 Dondorp AM, Nyanoti M, Kager PA, Mithwani S, Vreeken J, Marsh K. The role of reduced red cell deformability in the pathogenesis of severe falciparum malaria and its restoration by blood transfusion. *Trans R Soc Trop Med Hyg* 2002; **96:** 282–86.

26 Looareesuwan S, Ho M, Wattanagoon Y, et al. Dynamic alteration in splenic function during acute falciparum malaria. *N Engl J Med* 1987; **317:** 675–79.

27 Buffet PA, Safeukui I, Deplaine G, et al. The pathogenesis of *Plasmodium falciparum* malaria in humans: insights from splenic physiology. *Blood* 2011; **117:** 381–92.

28 Karunaweera ND, Grau GE, Gamage P, Carter R, Mendis KN. Dynamics of fever and serum levels of tumor necrosis factor are closely associated during clinical paroxysms in *Plasmodium vivax* malaria. *Proc Natl Acad Sci USA* 1992; **89:** 3200–03.

29 Ayimba E, Hegewald J, Segbena AY, et al. Proinflammatory and regulatory cytokines and chemokines in infants with uncomplicated and severe *Plasmodium falciparum* malaria. *Clin Exp Immunol* 2011; **166:** 218–26.

30 Beare NA, Taylor TE, Harding SP, Lewallen S, Molyneux ME. Malarial retinopathy: a newly established diagnostic sign in severe malaria. *Am J Trop Med Hyg* 2006; **75:** 790–97.

31 Dondorp AM, Ince C, Charunwatthana P, et al. Direct in vivo assessment of microcirculatory dysfunction in severe falciparum malaria. *J Infect Dis* 2008; **197:** 79–84.

32 Yeo TW, Lampah DA, Tjitra E, et al. Relationship of cell-free hemoglobin to impaired endothelial nitric oxide bioavailability and perfusion in severe falciparum malaria. *J Infect Dis* 2009; **200:** 1522–29.

33 Yeo TW, Lampah DA, Tjitra E, et al. Increased asymmetric dimethylarginine in severe falciparum malaria: association with impaired nitric oxide bioavailability and fatal outcome. *PLoS Pathog* 2010; **6:** e1000868.

34 Yeo TW, Lampah DA, Gitawati R, et al. Angiopoietin-2 is associated with decreased endothelial nitric oxide and poor clinical outcome in severe falciparum malaria. *Proc Natl Acad Sci USA* 2008; **105:** 17097–102.

35 de Mast Q, Groot E, Asih PB, et al. ADAMTS13 deficiency with elevated levels of ultra-large and active von Willebrand factor in *P falciparum* and *P vivax* malaria. *Am J Trop Med Hyg* 2009; **80:** 492–98.

36 Bridges DJ, Bunn J, van Mourik JA, et al. Rapid activation of endothelial cells enables *Plasmodium falciparum* adhesion to platelet-decorated von Willebrand factor strings. *Blood* 2010; **115:** 1472–74.

37 Silamut K, Phu NH, Whitty C, et al. A quantitative analysis of the microvascular sequestration of malaria parasites in the human brain. *Am J Pathol* 1999; **155:** 395–410.

38 White NJ, Turner GD, Day NP, Dondorp AM. Lethal malaria: Marchiafava and Bignami were right. *J Infect Dis* 2013; published online April 12. DOI:10.1093/infdis/jit116.

39 Beare NA, Harding SP, Taylor TE, Lewallen S, Molyneux ME. Perfusion abnormalities in children with cerebral malaria and malarial retinopathy. *J Infect Dis* 2009; **199:** 263–71.

40 Maude RJ, Beare NA, Abu Sayeed A, et al. The spectrum of retinopathy in adults with *Plasmodium falciparum* malaria. *Trans R Soc Trop Med Hyg* 2009; **103:** 665–71.

41 Day NP, Phu NH, Mai NT, et al. The pathophysiologic and prognostic significance of acidosis in severe adult malaria. *Crit Care Med* 2000; **28:** 1833–40.

42 MacPherson GG, Warrell MJ, White NJ, Looareesuwan S, Warrell DA. Human cerebral malaria. A quantitative ultrastructural analysis of parasitized erythrocyte sequestration. *Am J Pathol* 1985; **119:** 385–401.

43 Medana IM, Turner GD. *Plasmodium falciparum* and the blood-brain barrier—contacts and consequences. *J Infect Dis* 2007; **195:** 921–23.

44 Warrell DA, Looareesuwan S, Phillips RE, et al. Function of the blood-cerebrospinal fluid barrier in human cerebral malaria: rejection of the permeability hypothesis. *Am J Trop Med Hyg* 1986; **35:** 882–89.

45 Dorovini-Zis K, Schmidt K, Huynh H, et al. The neuropathology of fatal cerebral malaria in malawian children. *Am J Pathol* 2011; **178:** 2146–58.

46 Potchen MJ, Kampondeni SD, Seydel KB, et al. Acute brain MRI findings in 120 Malawian children with cerebral malaria: new insights into an ancient disease. *Am J Neuroradiol* 2012; **33:** 1740–46.

47 Idro R, Jenkins NE, Newton CRJC. Pathogenesis, clinical features, and neurological outcome of cerebral malaria. *Lancet Neurol* 2005; **4:** 827–40.

48 Medana IM, Day NP, Sachanonta N, et al. Coma in fatal adult human malaria is not caused by cerebral oedema. *Malar J* 2011; **10:** e267.

49 Waller D, Crawley J, Nosten F, et al. Intracranial pressure in childhood cerebral malaria. *Trans R Soc Trop Med Hyg* 1991; **85:** 362–64.

50 Newton CRJC, Winstanley PA, Peshu N, et al. Intracranial pressure in African children with cerebral malaria. *Lancet* 1991; **337:** 573–76.

51 Mohanty S, Mishra SK, Patnaik R, et al. Brain swelling and mannitol therapy in adult cerebral malaria: a randomized trial. *Clin Infect Dis* 2011; **53:** 349–55.

52 Medana IM, Day NP, Hien TT, et al. Axonal injury in cerebral malaria. *Am J Pathol* 2002; **160:** 655–66.

53 Dondorp AM, Fanello CI, Hendriksen ICE, et al. Artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): an open-label, randomised trial. *Lancet* 2010; **376:** 1647–57.

54 South East Asian Quinine Artesunate Malaria Trial (SEAQUAMAT) group. Artesunate versus quinine for treatment of severe falciparum malaria: a randomised trial. *Lancet* 2005; **366:** 717–25.

55 Idro R, Ndiritu M, Ogutu B, et al. Burden, features, and outcome of neurological involvement in acute falciparum malaria in Kenyan children. *JAMA* 2007; **297:** 2232–40.

56 Birbeck GL, Molyneux ME, Kaplan PW, et al. Blantyre Malaria Project Epilepsy Study (BMPES) of neurological outcomes in retinopathy-positive paediatric cerebral malaria survivors: a prospective cohort study. *Lancet Neurol* 2010; **9:** 1173–81.

57 Calis JC, Phiri KS, Faragher EB, et al. Severe anemia in Malawian children. *N Engl J Med* 2008; **358:** 888–99.

58 Price RN, Simpson JA, Nosten F, et al. Factors contributing to anemia after uncomplicated falciparum malaria. *Am J Trop Med Hyg* 2001; **65:** 614–22.

59 Hanson J, Lee SJ, Mohanty S, et al. A simple score to predict the outcome of severe malaria in adults. *Clin Infect Dis* 2010; **50:** 679–85.

60 Marsh K, Forster D, Waruiru C, et al. Indicators of life-threatening malaria in African children. *N Engl J Med* 1995; **332:** 1399–404.

61 Jarvis JN, Planche T, Bicanic T, et al. Lactic acidosis in Gabonese children with severe malaria is unrelated to dehydration. *Clin Infect Dis* 2006; **42:** 1719–25.

62 Hanson J, Lam SW, Mahanta KC, et al. Relative contributions of macrovascular and microvascular dysfunction to disease severity in falciparum malaria. *J Infect Dis* 2012; **206:** 571–79.

63 Krishna S, Waller DW, ter Kuile F, et al. Lactic acidosis and hypoglycaemia in children with severe malaria: pathophysiological and prognostic significance. *Trans R Soc Trop Med Hyg* 1994; **88:** 67–73.

64 White NJ, Warrell DA, Chanthavanich P, et al. Severe hypoglycemia and hyperinsulinemia in falciparum malaria. *N Engl J Med* 1983; **309:** 61–66.

65 Anstey NM, Handojo T, Pain MC, et al. Lung injury in vivax malaria: pathophysiological evidence for pulmonary vascular sequestration and posttreatment alveolar-capillary inflammation. *J Infect Dis* 2007; **195:** 589–96.

66 Daneshvar C, Davis TM, Cox-Singh J, et al. Clinical and laboratory features of human *Plasmodium knowlesi* infection. *Clin Infect Dis* 2009; **49:** 852–60.

67 Taylor WR, Hanson J, Turner GD, White NJ, Dondorp AM. Respiratory manifestations of malaria. *Chest* 2012; **142:** 492–505.

68 Hanson J, Lam SWK, Mohanty S, et al. Fluid resuscitation of adults with severe falciparum malaria: effects on acid-base status, renal function, and extravascular lung water. *Crit Care Med* 2013; **41:** 972–81.

69 Maitland K, Kiguli S, Opoka RO, et al. Mortality after fluid bolus in African children with severe infection. *N Engl J Med* 2011; **364:** 2483–95.

70 Nguansangiam S, Day NP, Hien TT, et al. A quantitative ultrastructural study of renal pathology in fatal *Plasmodium falciparum* malaria. *Trop Med Int Health* 2007; **12:** 1037–50.

71 Trang TT, Phu NH, Vinh H, et al. Acute renal failure in patients with severe falciparum malaria. *Clin Infect Dis* 1992; **15:** 874–80.

72 Phu NH, Hien TT, Mai NT, et al. Hemofiltration and peritoneal dialysis in infection-associated acute renal failure in Vietnam. *N Engl J Med* 2002; **347:** 895–902.

73 Barcus MJ, Hien TT, White NJ, et al. Short report: hepatitis b infection and severe *Plasmodium falciparum* malaria in Vietnamese adults. *Am J Trop Med Hyg* 2002; **66:** 140–42.

74 Berkley JA, Lowe BS, Mwangi I, et al. Bacteremia among children admitted to a rural hospital in Kenya. *N Engl J Med* 2005; **352:** 39–47.

75 Bronzan RN, Taylor TE, Mwenechanya J, et al. Bacteremia in Malawian children with severe malaria: prevalence, etiology, HIV coinfection, and outcome. *J Infect Dis* 2007; **195:** 895–904.

76 Scott JAG, Berkley JA, Mwangi I, et al. Relation between falciparum malaria and bacteraemia in Kenyan children: a population-based, case-control study and a longitudinal study. *Lancet* 2011; **378:** 1316–23.

77 Dasari P, Reiss K, Lingelbach K, et al. Digestive vacuoles of *Plasmodium falciparum* are selectively phagocytosed by and impair killing function of polymorphonuclear leukocytes. *Blood* 2011; **118:** 4946–56.

78 Cunnington AJ, de Souza JB, Walther M, Riley EM. Malaria impairs resistance to Salmonella through heme- and heme oxygenase-dependent dysfunctional granulocyte mobilization. *Nat Med* 2012; **18:** 120–27.

79 Reyburn H, Mbatia R, Drakeley C, et al. Overdiagnosis of malaria in patients with severe febrile illness in Tanzania: a prospective study. *BMJ* 2004; **329:** 1212.

80 Hendriksen IC, Mwanga-Amumpaire J, von Seidlein L, et al. Diagnosing severe falciparum malaria in parasitaemic African children: a prospective evaluation of plasma *Pf*HRP2 measurement. *PLoS Med* 2012; **9:** e1001297.

81 Abu-Raddad LJ, Patnaik P, Kublin JG. Dual infection with HIV and malaria fuels the spread of both diseases in sub-Saharan Africa. *Science* 2006; **314:** 1603–06.

82 Kublin JG, Patnaik P, Jere CS, et al. Effect of *Plasmodium falciparum* malaria on concentration of HIV-1-RNA in the blood of adults in rural Malawi: a prospective cohort study. *Lancet* 2005; **365:** 233–40.

83 Whitworth J, Morgan D, Quigley M, et al. Effect of HIV-1 and increasing immunosuppression on malaria parasitaemia and clinical episodes in adults in rural Uganda: a cohort study. *Lancet* 2000; **356:** 1051–56.

84 Chalwe V, van Geertruyden JP, Mukwamataba D, et al. Increased risk for severe malaria in HIV-1-infected adults, Zambia. *Emerg Infect Dis* 2009; **15:** 749.

85 Patnaik P, Jere CS, Miller WC, et al. Effects of HIV-1 serostatus, HIV-1 RNA concentration, and CD4 cell count on the incidence of malaria infection in a cohort of adults in rural Malawi. *J Infect Dis* 2005; **192:** 984–91.

86 Berkley JA, Bejon P, Mwangi T, et al. HIV infection, malnutrition, and invasive bacterial infection among children with severe malaria. *Clin Infect Dis* 2009; **49:** 336–43.

87 Hendriksen IC, Ferro J, Montoya P, et al. Diagnosis, clinical presentation, and in-hospital mortality of severe malaria in HIV-coinfected children and adults in Mozambique. *Clin Infect Dis* 2012; **55:** 1144–53.

88 Tjitra E, Anstey NM, Sugiarto P, et al. Multidrug-resistant *Plasmodium vivax* associated with severe and fatal malaria: a prospective study in Papua, Indonesia. *PLoS Med* 2008; **5:** e128.

89 Genton B, d'Acremont V, Rare L, et al. *Plasmodium vivax* and mixed infections are associated with severe malaria in children: a prospective cohort study from Papua New Guinea. *PLoS Med* 2008; **5:** e127.

90 Alexandre MA, Ferreira CO, Siqueira AM, et al. Severe *Plasmodium vivax* malaria, Brazilian Amazon. *Emerg Infect Dis* 2010; **16:** 1611–14.

91 Barcus MJ, Basri H, Picarima H, et al. Demographic risk factors for severe and fatal vivax and falciparum malaria among hospital admissions in northeastern Indonesian Papua. *Am J Trop Med Hyg* 2007; **77:** 984–91.

92 Lampah DA, Yeo TW, Hardianto SO, et al. Coma associated with microscopy-diagnosed *Plasmodium vivax*: a prospective study in Papua, Indonesia. *PLoS Negl Trop Dis* 2011; **5:** e1032.

93 Manning L, Laman M, Law I, et al. Features and prognosis of severe malaria caused by *Plasmodium falciparum*, *Plasmodium vivax* and mixed Plasmodium species in Papua New Guinean children. *PLoS One* 2011; **6:** e29203.

94 Kochar DK, Das A, Kochar SK, et al. Severe *Plasmodium vivax* malaria: a report on serial cases from Bikaner in northwestern India. *Am J Trop Med Hyg* 2009; **80:** 194–98.

95 Shaikh S, Memon H, Iohano B, Shaikh A, Ahmed I, Baird JK. Severe disease in children hospitalized with a diagnosis of *Plasmodium vivax* in south-eastern Pakistan. *Malar J* 2012; **11:** 144.

96 Desai M, ter Kuile FO, Nosten F, et al. Epidemiology and burden of malaria in pregnancy. *Lancet Infect Dis* 2007; **7:** 93–104.

97 Falade C, Mokuolu O, Okafor H, et al. Epidemiology of congenital malaria in Nigeria: a multi-centre study. *Trop Med Int Health* 2007; **12:** 1279–87.

98 Steketee RW, Nahlen BL, Parise ME, Menendez C. The burden of malaria in pregnancy in malaria-endemic areas. *Am J Trop Med Hyg* 2001; **64** (suppl): 28–35.

99 Nosten F, McGready R, Simpson JA, et al. Effects of *Plasmodium vivax* malaria in pregnancy. *Lancet* 1999; **354:** 546–49.

100 Rijken MJ, McGready R, Boel ME, et al. Malaria in pregnancy in the Asia-Pacific region. *Lancet Infect Dis* 2012; **12:** 75–88.

101 McGready R, Lee SJ, Wiladphaingern J, et al. Adverse effects of falciparum and vivax malaria and the safety of antimalarial treatment in early pregnancy: a population-based study. *Lancet Infect Dis* 2012; **12:** 388–96.

102 Bardaji A, Sigauque B, Sanz S, et al. Impact of malaria at the end of pregnancy on infant mortality and morbidity. *J Infect Dis* 2011; **203:** 691–99.

103 WHO. Malaria rapid diagnostic test performance —results of WHO product testing of malaria RDTs: round 3 (2010–2011). Geneva: World Health Organization, 2011.

104 Dondorp AM, Desakorn V, Pongtavornpinyo W, et al. Estimation of the total parasite biomass in acute falciparum malaria from plasma *Pf*HRP2. *PLoS Med* 2005; **2:** e204.

105 RTS,S Clinical Trials Partnership. A phase 3 trial of RTS,S/AS01 malaria vaccine in African infants. *N Engl J Med* 2012; **367:** 2284–95.

106 Agnandji ST, Lell B, Soulanoudjingar SS, et al. First results of phase 3 trial of RTS,S/AS01 malaria vaccine in African children. *N Engl J Med* 2011; **365:** 1863–75.

107 Phillips-Howard PA, Nahlen BL, Kolczak MS, et al. Efficacy of permethrin-treated bed nets in the prevention of mortality in young children in an area of high perennial malaria transmission in western Kenya. *Am J Trop Med Hyg* 2003; **68** (suppl): 23–29.

108 Moonen B, Cohen JM, Snow RW, et al. Operational strategies to achieve and maintain malaria elimination. *Lancet* 2010; **376:** 1592–603.

109 Godfray HC. Mosquito ecology and control of malaria. *J Anim Ecol* 2013; **82:** 15–25.

110 Barnes KI, Durrheim DN, Little F, et al. Effect of artemether-lumefantrine policy and improved vector control on malaria burden in KwaZulu-Natal, South Africa. *PLoS Med* 2005; **2:** e330.

111 Enayati A, Hemingway J. Malaria management: past, present, and future. *Annu Rev Entomol* 2010; **55:** 569–91.

112 Pluess B, Tanser FC, Lengeler C, Sharp BL. Indoor residual spraying for preventing malaria. *Cochrane Database Syst Rev* 2010; **4:** CD006657.

113 Aneck-Hahn NH, Schulenburg GW, Bornman MS, Farias P, de Jager C. Impaired semen quality associated with environmental DDT exposure in young men living in a malaria area in the Limpopo Province, South Africa. *J Androl* 2007; **28:** 423–34.

114 van den Berg H. Global status of DDT and its alternatives for use in vector control to prevent disease. *Environ Health Perspect* 2009; **117:** 1656–63.

115 WHO. Global strategic framework for integrated vector management. Geneva: World Health Organization, 2004.

116 Beier JC, Keating J, Githure JI, Macdonald MB, Impoinvil DE, Novak RJ. Integrated vector management for malaria control. *Malar J* 2008; **7** (suppl): S4.

117 Chen LH, Wilson ME, Schlagenhauf P. Prevention of malaria in long-term travelers. *JAMA* 2006; **296:** 2234–44.

118 Malaria Policy Advisory Committee to the WHO: conclusions and recommendations of September 2012 meeting. *Malar J* 2012; **11:** e424.

119 Schlagenhauf P, Blumentals WA, Suter P, et al. Pregnancy and fetal outcomes after exposure to mefloquine in the pre- and periconception period and during pregnancy. *Clin Infect Dis* 2012; **54:** e124–31.

120 WHO. Guidelines for the treatment of malaria, 2nd edn. Geneva: WHO Press, 2010.

121 WHO. WHO policy recommendation: seasonal malaria chemoprevention (SMC) for *Plasmodium falciparum* malaria control in highly seasonal transmission areas of the Sahel sub-region in Africa. Geneva: World Health Organization, 2012.

122 Clarke SE, Jukes MCH, Njagi JK, et al. Effect of intermittent preventive treatment of malaria on health and education in schoolchildren: a cluster-randomised, double-blind, placebo-controlled trial. *Lancet* 2008; **372:** 127–38.

123 von Seidlein L, Greenwood BM. Mass administrations of antimalarial drugs. *Trends Parasitol* 2003; **19:** 452–60.

124 Hendriksen I, Mtove G, Kent A, et al. Population pharmacokinetics of intramuscular artesunate in African children with severe malaria: implications for a practical dosing regimen. *Clin Pharmacol Ther* 2013; **93:** 443–50.

125 Barber BE, William T, Grigg MJ, et al. A prospective comparative study of knowlesi, falciparum and vivax malaria in Sabah, Malaysia: high proportion with severe disease from *Plasmodium knowlesi* and *P vivax* but no mortality with early referral and artesunate therapy. *Clin Infect Dis* 2013; **56:** 383–97.

126 Kreeftmeijer-Vegter AR, van Genderen PJ, Visser LG, et al. Treatment outcome of intravenous artesunate in patients with severe malaria in the Netherlands and Belgium. *Malar J* 2012; **11:** e102.

127 Tran TH, Day NP, Nguyen HP, et al. A controlled trial of artemether or quinine in Vietnamese adults with severe falciparum malaria. *N Engl J Med* 1996; **335:** 76–83.

128 van Hensbroek MB, Onyiorah E, Jaffar S, et al. A trial of artemether or quinine in children with cerebral malaria. *N Engl J Med* 1996; **335:** 69–75.

129 Gomes MF, Faiz MA, Gyapong JO, et al. Pre-referral rectal artesunate to prevent death and disability in severe malaria: a placebo-controlled trial. *Lancet* 2009; **373:** 557–66.

130 Crawley J, Waruiru C, Mithwani S, et al. Effect of phenobarbital on seizure frequency and mortality in childhood cerebral malaria: a randomised, controlled intervention study. *Lancet* 2000; **355:** 701–06.

131 Maude RJ, Hoque G, Hasan MU, et al. Timing of enteral feeding in cerebral malaria in resource-poor settings: a randomized trial. *PLoS One* 2011; **6:** e27273.

132 Farnert A, Gwer S, Berkley JA. Clinical considerations for antibiotic choices in the treatment of severe malaria. *Trends Parasitol* 2010; **26:** 465–66.

133 International Artemisinin Study Group. Artesunate combinations for treatment of malaria: meta-analysis. *Lancet* 2004; **363:** 9–17.

134 WHO Global Malaria Programme. Single dose primaquine as a gametocytocide in *Plasmodium falciparum* malaria. http://www.who.int/malaria/diagnosis_treatment/treatment/who_pq_policy_recommendation/en/ (accessed Dec 20, 2012).

135 Rueangweerayut R, Phyo AP, Uthaisin C, et al. Pyronaridine-artesunate versus mefloquine plus artesunate for malaria. *N Engl J Med* 2012; **366:** 1298–309.

136 Tshefu AK, Gaye O, Kayentao K, et al. Efficacy and safety of a fixed-dose oral combination of pyronaridine-artesunate compared with artemether-lumefantrine in children and adults with uncomplicated *Plasmodium falciparum* malaria: a randomised non-inferiority trial. *Lancet* 2010; **375:** 1457–67.

137 Dondorp AM, Nosten F, Yi P, et al. Artemisinin resistance in *Plasmodium falciparum* malaria. *N Engl J Med* 2009; **361:** 455–67.

138 Phyo AP, Nkhoma S, Stepniewska K, et al. Emergence of artemisinin-resistant malaria on the western border of Thailand: a longitudinal study. *Lancet* 2012; **379:** 1960–66.

139 Douglas NM, Anstey NM, Angus BJ, Nosten F, Price RN. Artemisinin combination therapy for vivax malaria. *Lancet Infect Dis* 2010; **10:** 405–16.

140 Smithuis F, Kyaw MK, Phe O, et al. Effectiveness of five artemisinin combination regimens with or without primaquine in uncomplicated falciparum malaria: an open-label randomised trial. *Lancet Infect Dis* 2010; **10:** 673–81.

141 Newton PN, Fernandez FM, Plancon A, et al. A collaborative epidemiological investigation into the criminal fake artesunate trade in South East Asia. *PLoS Med* 2008; **5:** e32.

142 Nayyar GML, Breman JG, Newton PN, Herrington J. Poor-quality antimalarial drugs in southeast Asia and sub-Saharan Africa. *Lancet Infect Dis* 2012; **12:** 488–96.

143 White NJ. Primaquine to prevent transmission of falciparum malaria. *Lancet Infect Dis* 2013; **13:** 175–81.