

Malaria

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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-Saharan. 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.

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-Saharan 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.

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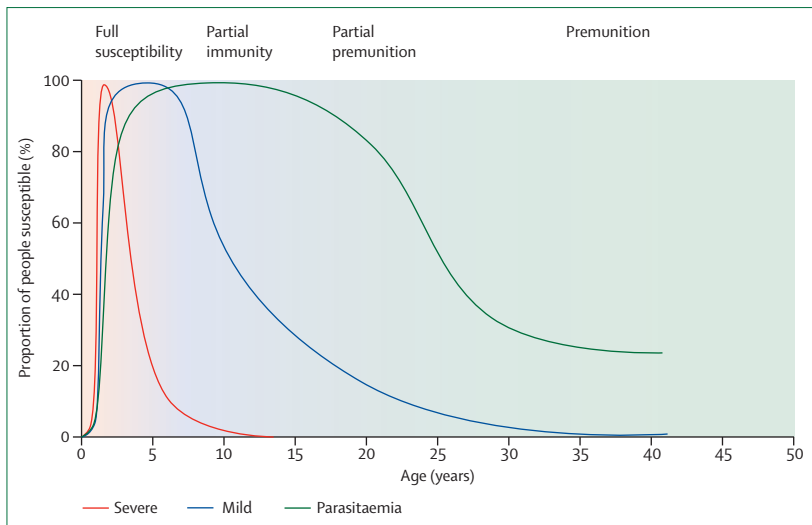


Figure 1: Relation between age and malaria severity in an area of moderate transmission intensity
 With repeated exposure protection is acquired, first against severe malaria, then against illness with malaria, and, much more slowly, against microscopy-detectable parasitaemia.⁸

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 glycoporphins). Basigin, an Ok blood group antigen, has been identified as a strain transcending receptor for *PfPrh5*, 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 malarial species, 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 cytoadherence (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

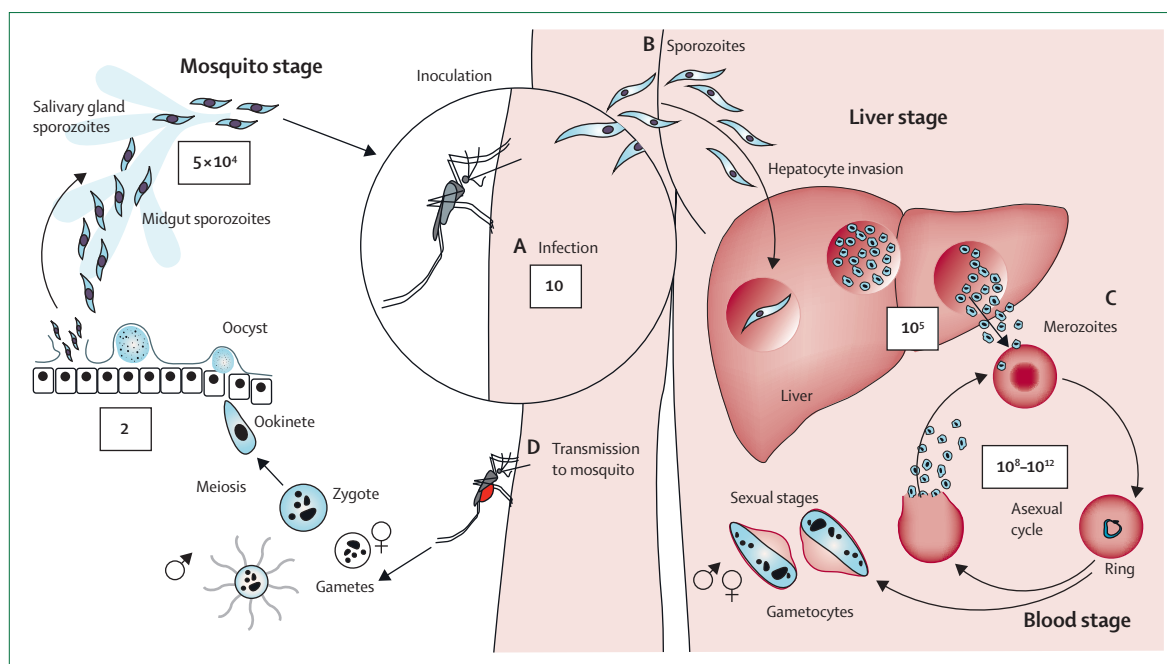


Figure 2: Lifecycle of *Plasmodium falciparum* in the human body and the anopheline mosquito

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 (PfEMP1) 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

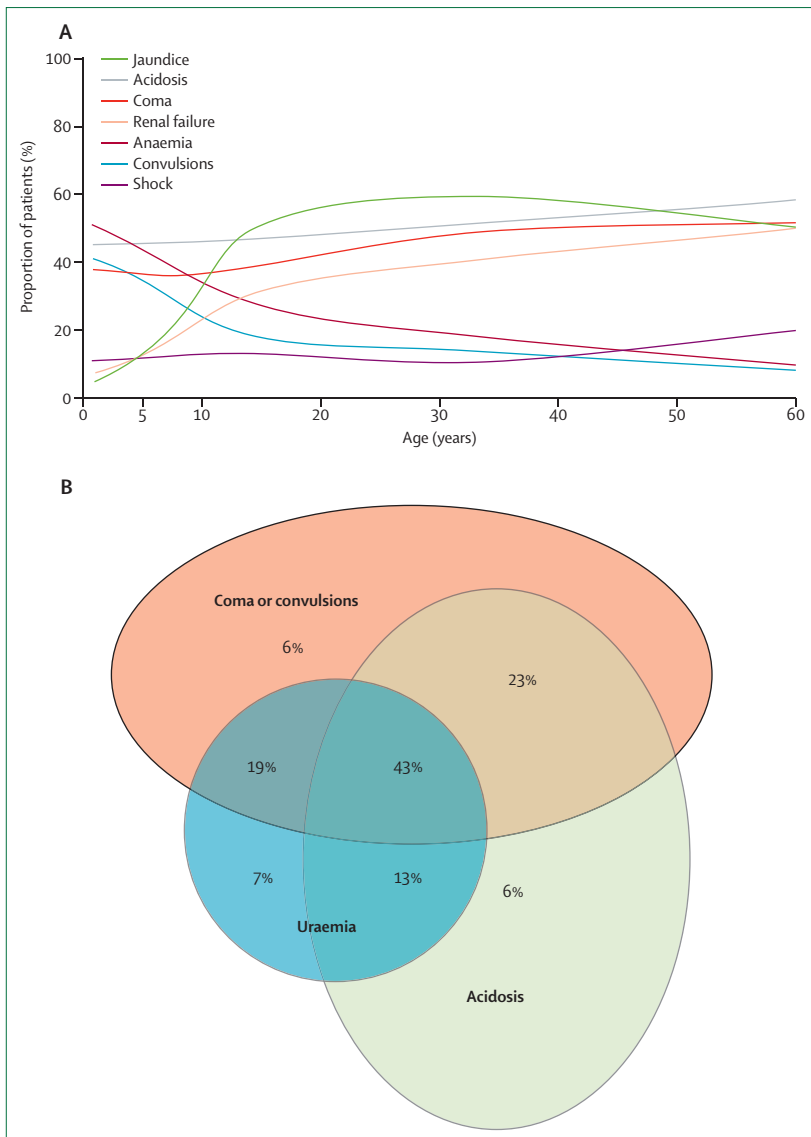


Figure 3: Manifestations of severe falciparum malaria by age (A) and mortality in children associated with CNS involvement, acidosis, and uraemia (B)

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 angiotensin 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 transport⁵² and persistent attachment of residual erythrocyte membranes and malaria pigment to vascular endothelium²² 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 PfHRP2 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 29486 (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 manifestations 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 *PfHRP2*, pan-malaria or species-specific lactate dehydrogenase, or aldolase antigens in finger-prick blood are now used widely.¹⁰³ *PfHRP2*-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).

PfHRP2-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 *PfHRP2* 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 study¹⁰⁵ 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 results¹⁰⁶ 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 superseded 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

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 study⁵³ 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 worldwide¹²⁰ (including in patients with severe vivax and knowlesi malaria¹²⁵). 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.

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

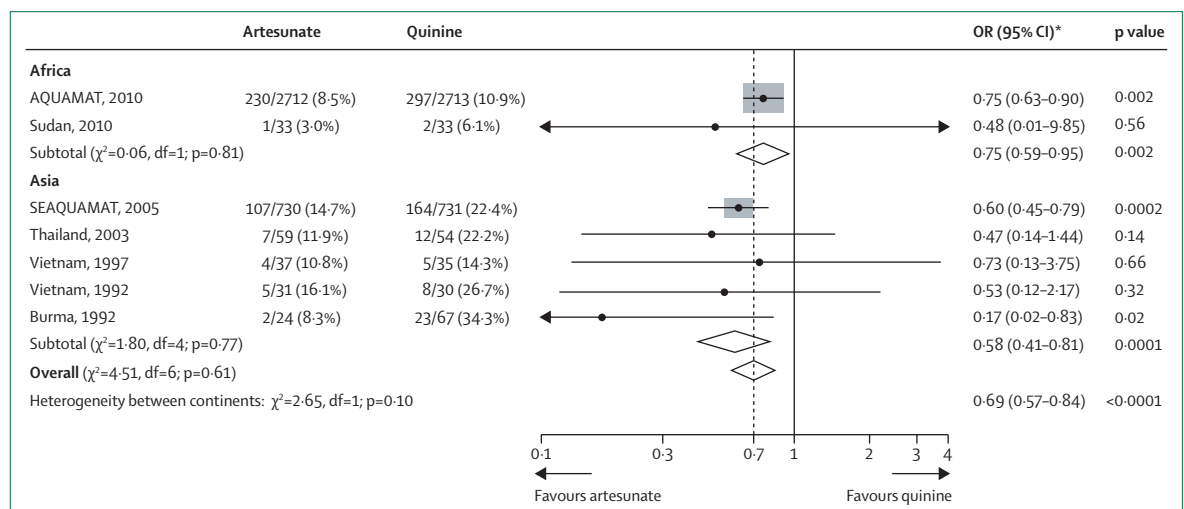


Figure 4: Meta-analysis of all randomised controlled trials of parenteral artesunate versus parenteral quinine in severe malaria

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 piperazine, 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 <i>Plasmodium falciparum</i> malaria	Artemether-lumefantrine 1.5 mg/kg–9 mg/kg twice daily for 3 days with food or milk Artesunate 4 mg/kg daily for 3 days and mefloquine 25 mg base per kg (8 mg/kg/daily for 3 days)*† Dihydroartemisinin-piperazine 2.5 mg/kg–20 mg/kg daily for 3 days
Sensitive <i>P falciparum</i> malaria	Artesunate 4 mg/kg daily for 3 days and a single dose of sulfadoxine-pyrimethamine 25 mg/kg–1.25 mg/kg Artesunate 4 mg/kg and amodiaquine* 10 mg base per kg daily for 3 days
Chloroquine-sensitive <i>Plasmodium vivax</i> ‡, <i>Plasmodium malariae</i> ‡, <i>Plasmodium ovale</i> ‡, <i>Plasmodium knowlesi</i> ‡	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 previously 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.

***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.

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