



REVIEW

## Malaria

Elizabeth Ashley<sup>a,b,c</sup>, Rose McGready<sup>a,b,c</sup>, Stephane Proux<sup>a</sup>,  
François Nosten<sup>a,b,c,\*</sup>

<sup>a</sup>Shoklo Malaria Research Unit, 68/30 Ban Toong Road, Mae Sot, Tak, 63110 Thailand

<sup>b</sup>Faculty of Tropical Medicine, Mahidol University, 420/6 Rajvithi Road, Bangkok, 10400, Thailand

<sup>c</sup>Centre for Clinical Vaccinology and Tropical Medicine Churchill Hospital, Old Road, Headington, Oxford, UK

Received 21 May 2005; accepted 21 June 2005

Available online 19 September 2005

### KEYWORDS

Malaria;  
Travellers;  
Artemisinin;  
Combination therapy

**Abstract** Malaria is increasing worldwide due to the emergence and spread of drug resistant strains. This poses major health and economic problems for the population living in endemic areas and increases the risk of infections in travelers. The diagnosis of malaria relies on a biological proof of infection by microscopy or with a rapid test. The treatment must be initiated without delay preferably with an artemisinin containing regimen. Uncomplicated malaria can be treated with oral drugs while severe infections will be hospitalized and treated with injectables. Special attention will be given to the most susceptible groups: children and pregnant women.

© 2005 Elsevier Ltd. All rights reserved.

### Introduction

Estimates of the population at risk from malaria have been revised recently using an approach where epidemiological, geographical and demographic data were combined.<sup>1</sup> The findings indicate that there were 515 (range 300–660) million episodes of clinical *Plasmodium falciparum* malaria in 2002. These estimates are substantially higher

than those reported by the World Health Organization (WHO) whose latest malaria report states that in 2003, 350–500 million people worldwide became ill with malaria.<sup>2</sup> The sources of the WHO data are reports from national malaria-control programmes, household surveys, drug efficacy monitoring at sentinel sites and health information systems. The largest discrepancy between the two methods of assessing incidence is in estimates in non-African countries.

In addition to the actual numbers affected by malaria being underestimated, malaria incidence has increased during the last decade despite efforts to control the disease. This is attributed mainly to

\*Corresponding author. Shoklo Malaria Research Unit, 732/6 Intharakiri Road, P.O. Box 46, Mae Sot, TAK 63110, Thailand. Tel.: +66 (55) 545 021; fax: +66 (55) 545 020.

E-mail address: SMRU@tropmedres.ac (F. Nosten).

the emergence of drug resistant organisms.<sup>3,4</sup> This massive burden of disease is borne by some of the poorest countries in the world and is in itself an obstacle to economic growth. However, as population migration, globalisation in business and commerce, and appetites for more adventurous travel increase, more people from non-endemic countries are being exposed to malaria. Approximately 25 000 travellers return from visiting endemic countries with malaria each year, of whom 100 will not survive the infection.<sup>5</sup> All of these deaths are potentially avoidable. The management of these patients presents a challenge to clinicians working in non-endemic countries for a number of reasons. Lack of familiarity with the disease may lead to a delay in considering the diagnosis, laboratory staff asked to make the diagnosis may be inexperienced and inappropriate drugs may be chosen to treat the disease.<sup>6</sup> Patterns of drug resistance are changing rapidly and it is difficult for physicians to keep pace, especially since it is a disease encountered relatively infrequently. Some of the most effective drugs used to treat resistant malaria are not registered internationally and are unavailable in countries with strict drug regulatory authorities compounding the problem. This review gives an overview of the epidemiology of malaria, the antimalarial drugs available, describes the signs and symptoms of the disease, methods of diagnosis and treatment, with emphasis on the newer treatments available, and finally outlines methods of prevention in travellers.

## Epidemiology of malaria

- Cause of malaria

Malaria is caused by the protozoan *Plasmodium*, four species of which infect humans. These are *P. falciparum*, *P. vivax*, *P. ovale* and *P. malariae*. Almost all deaths and severe disease are caused by *P. falciparum*. The vector responsible for malaria transmission is the female *Anopheles* mosquito. She injects approximately 15–20 sporozoites into the circulation. These reach the liver in a matter of minutes and start to reproduce, becoming hepatic schizonts which subsequently rupture. Hundreds of merozoites (approximately 32 per schizont) are released into the bloodstream and rapidly infect red blood cells. The time to hepatic schizont rupture is generally between 1 and 2 weeks. The young trophozoites consume haemoglobin in the red cells and develop into schizonts which rupture, releasing more merozoites to invade yet more

red blood cells causing the symptoms (fever) and the infective biomass to expand. This asexual life-cycle from the invasion of red blood cells by merozoites until schizont rupture takes 48 h for *falciparum*, *vivax* and *ovale* malarias and 72 h for *P. malariae*. Development of certain parasites into sexual forms starts after a number of asexual life-cycles have taken place. In *falciparum* malaria, gametocyte production takes approximately 10 days compared to only 4 days in *vivax* malaria. Ingestion of male and female gametocytes by a female *Anopheles* mosquito which fuse in the midgut to form a zygote, with the eventual development of new sporozoites, completes the life-cycle. In *vivax* and *ovale* malarias a number of the sporozoites arriving at the liver become dormant hypnozoites, capable of causing a relapse of malaria at a later date. *P. malariae* does not have the hypnozoite stage but may persist in the blood for many years if inadequately treated.<sup>7</sup>

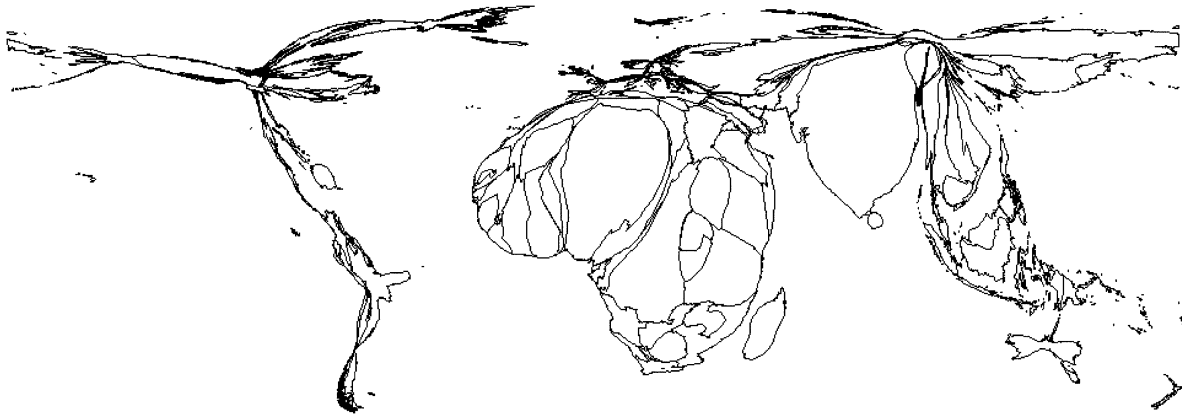
- Distribution of the disease

Malaria has a worldwide distribution, being found in tropical areas, throughout sub-Saharan Africa and to a lesser extent in South Africa, South East Asia, the Pacific islands, India and Central and South America (see Fig. 1).

*Falciparum* is the predominant species in most endemic countries, exceptions being India and South America where *vivax* is more common. *P. ovale* is mainly found in West Africa. In South—East Asia, particularly along the borders of Thailand with Myanmar and Cambodia, *P. falciparum* is multidrug resistant with chloroquine, sulphadoxine-pyrimethamine (SP) and mefloquine monotherapies all ineffective and quinine slowly losing its potency. In sub-Saharan and South Africa chloroquine resistance to *falciparum* malaria is widespread and antifolate resistance is increasing rapidly. A degree of protective immunity develops in individuals infected repeatedly from birth in moderate to high transmission areas. This transient form of immunity is also known as premunition. It is lost rapidly if the host moves out of the endemic area. In all endemic areas, children and pregnant women are at higher risk of malaria and are more susceptible to severe disease.<sup>9</sup> Pregnant women are also more attractive to some malaria vectors and the non-immune pregnant traveller is at particular risk.<sup>10</sup>

- Control of malaria

Strategies include vector control with residual insecticide spraying, larva control and personal protection measures such as use of insecticide-treated bednets (ITNs), insect repellents and



**Figure 1** The gross national falciparum parasitemia (GNfP) cartogram 2002 showing the various continents as a function of the transmission intensity and the population exposed to the risk of malaria. Hay and Snow<sup>8</sup> with permission (Reprinted from *The Lancet, Infectious Diseases*, Vol. 4, Hay SI, et al. The global distribution and population at risk of malaria: past, present and future. Copyright June 2004, with permission from Elsevier.).

wearing appropriate clothing. Intermittent preventive treatment of certain population groups such as pregnant women and young children with SP has been used successfully.<sup>11,12</sup> In areas of multidrug resistance early diagnosis and treatment is relied upon. Research efforts to develop an effective malaria vaccine or a transgenic mosquito incapable of transmitting malaria continue, but neither is likely to be available for many years.

## The antimalarial drugs

The antimalarials in common use come from five classes of compound: the quinolines and arylaminoalcohols, the antifolates, the artemisinin derivatives, the hydroxynaphthaquinones and antibacterial agents.

- *Quinolines and arylaminoalcohols e.g. chloroquine, amodiaquine, quinine, quinidine, mefloquine, halofantrine, primaquine, tafenoquine, lumefantrine, piperaquine, pyronaridine.* *Chloroquine* is a 4-aminoquinoline that acts mainly on the large ring-form and mature trophozoite stages of the parasite. Resistance has been linked to a number of polymorphisms in the PfCRT gene on chromosome 7.<sup>13</sup> Side-effects include pruritis, rash, headache, gastrointestinal disturbance and rarely bone marrow suppression, hair loss and convulsions. Chloroquine is known to exacerbate psoriasis. It is highly toxic in overdose when it may cause fatal cardiac arrhythmias when given intravenously. Cumula-

tive doses of chloroquine (>5 years) are associated with retinal damage.<sup>14</sup>

*Amodiaquine* is a Mannich base 4-aminoquinoline. It is more active than chloroquine against resistant parasites. The side-effect profile is similar, except that prophylactic use has been associated with an unacceptably high incidence of serious toxicity with approximately 1 in 2000 patients developing agranulocytosis<sup>15</sup> and reports of significant hepatotoxicity.<sup>16</sup>

*Quinine* is an ancient drug derived from the bark of the cinchona tree. Side-effects are common and include tinnitus, hearing impairment, dizziness and vertigo. Quinine stimulates insulin production and may cause hypoglycaemia, a particular risk in pregnancy.<sup>17</sup> Rare adverse events include renal failure, intravascular coagulation and cardiotoxicity. ECG should be monitored in patients with known atrial fibrillation or other conduction defects. For treatment of falciparum malaria infections contracted in regions where sensitivity to quinine is reduced the drug is combined with an antibiotic such as tetracycline/doxycycline or clindamycin.<sup>18</sup> Intravenous or intramuscular quinine is used for the treatment of hyperparasitaemic infections and for severe malaria.

*Quinidine* is related to quinine but is more cardiotoxic. Intravenous quinidine is still used to treat severe malaria in the United States where quinine is not available.

*Mefloquine* is a quinoline methanol compound with a long terminal elimination half-life. Side-effects are frequent and include dizziness, nausea, vomiting, diarrhoea and abdominal pain. Neuropsychiatric side-effects such as seizures,

acute psychosis, anxiety neurosis, and major disturbances of sleep–wake rhythm are estimated to occur in 1 in 159 to 1 in 2089 patients following treatment doses.<sup>19,20</sup> The use of mefloquine is therefore contraindicated in patients with epilepsy, a history of neuropsychiatric disease or in patients recovering from cerebral malaria. It should not be given to treat patients who have already received the drug in the preceding 4 weeks or whose ability to work safely may be impeded by drug side-effects e.g. machine operators. As a treatment it should be combined with 3 days of artesunate.<sup>21</sup> A fixed co-formulation of the two medicines is under development. In Thailand, a retrospective study of 3587 pregnancies of which 208 were exposed to mefloquine treatment found that the drug was associated with an increased risk of stillbirth but not with abortion, low birthweight, or malformations of the fetus.<sup>22</sup> However a study in Malawi did not conclude there was an increased risk of stillbirth with mefloquine.<sup>23</sup>

*Primaquine* is an 8-aminoquinoline which eradicates hypnozoites of *P. vivax* and *P. ovale* in the liver. It has potent gametocytocidal properties. It is contraindicated in pregnancy or in individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency, as it may cause massive haemolysis.<sup>24</sup> Side-effects are usually gastrointestinal and dose-related.

*Tafenoquine* is a promising newer 8-aminoquinoline which has a much longer half-life than primaquine meaning shorter courses are effective to eradicate hypnozoites. It is also contraindicated in patients with G6PD deficiency. This drug is still in Phase III trials.

*Lumefantrine* is a racemic 2, 4, 7, 9-substituted fluorine derivative synthesised in China. It is manufactured as a fixed combination with artemether, one of the artemisinin derivatives. It is important to note that lumefantrine absorption varies widely between individuals and is dependent on co-administration with fat. Each dose should be taken at the same time as a fatty meal or a 200 ml carton of milk.<sup>25</sup>

*Piperaquine* is a bisquinoline compound related to chloroquine developed in the 1960s which was given as mass prophylaxis and treatment for falciparum malaria in China in the 1970s and 1980s when resistance began to develop. In recent years it has been co-formulated with dihydroartemisinin as a fixed dose combination that has been registered in a number of Asian countries. Experience with the drug so far suggests it is a highly effective and safe treatment for uncomplicated falciparum malaria.<sup>26</sup> It

will need to be registered internationally before it becomes widely available.

*Pyronaridine* is a Mannich base compound developed in China which has been combined with artesunate. In recent studies adverse events included headache, dizziness, nausea, vomiting, gastrointestinal disorders, palpitation, rash pruritus and transient electrocardiographic changes. All adverse events were mild and transient.<sup>27</sup> This new fixed combination is in Phase 2 clinical trials.

- *Antifols (folate biosynthesis inhibitors) e.g. pyrimethamine, proguanil, chlorproguanil, trimethoprim.*

*Pyrimethamine* acts by inhibiting plasmodial dihydrofolate reductase (DHFR) while the sulpha drugs, with which they are combined e.g. SP, inhibit dihydropteroate synthase (DHPS). There is marked synergy between the two compounds used in combination. Prolonged administration may cause dyserythropoiesis by interfering with folic acid metabolism, skin rashes and hypersensitivity have been described. Other side-effects include atrophic glossitis, abdominal pain and vomiting.

*Proguanil* is a biguanide and, like chlorproguanil, acts as a prodrug for an active metabolite which also inhibits DHFR. It is a weak antimalarial and when used alone resistance developed quickly. Proguanil is well tolerated but can cause mild gastric intolerance, diarrhoea and aphthous ulceration. Doses must be reduced in patients with renal impairment.

*Chlorproguanil-dapsone (Lapdap<sup>®</sup>)* is the latest addition to this class. The fixed combination has been registered. It is thought to be more effective than SP against *P. falciparum* in Africa.<sup>28</sup> Haemolysis and methoglobinemia are the most frequent adverse effects reported with dapsone.

Antifolate resistance results from the sequential accumulation of point mutations in the DHFR gene. Acquisition of four DHFR mutations renders available antifols completely ineffective. Data from SE Asia, Southern Africa and South America indicate clonal spread of parasites carrying resistant DHFR alleles. There are five point mutations in DHPS conferring resistance to sulphonamides. The contribution of DHPS mutations to resistance to antifol–sulpha combinations is debated.

- *Artemisinin derivatives e.g. artemisinin, dihydroartemisinin, artemether, artesunate.* These drugs, known as quinghaosu in China, their country of origin are derived from *Artemisia annua*, the sweet wormwood plant. Use of this

plant in traditional Chinese medicine as a treatment for fever dates back to at least 300 AD.<sup>29–31</sup> These drugs have a very short terminal elimination half-life of a matter of hours. They form the mainstay of the modern treatment of malaria.<sup>32</sup> They act rapidly, have a broad stage-specificity of action and are extremely well tolerated. Evidence of their safety and efficacy comes from large randomised trials in tens of thousands of patients.<sup>33</sup> Mild gastrointestinal disturbance, dizziness, tinnitus and neutropenia have been reported but in general the artemisinin derivatives are very well tolerated. The only potentially serious adverse effect is a type 1 hypersensitivity reactions in approximately 1:3000 patients.<sup>34</sup> Artesunate is a water-soluble hemisuccinate derivative of dihydroartemisinin available as oral, suppository and intravenous preparations. Artemether is the methyl ether of dihydroartemisinin and exists in oral and intramuscular forms. Its use has been associated with an usual pattern of neuronal damage to certain brain stem nuclei in animals.<sup>35</sup> However this toxicity has not been found in humans.<sup>36</sup> The short half-life of these drugs means they are best suited to treating uncomplicated malaria combined with another drug rather than as monotherapy. If used alone a 7 day course must be prescribed. While artemisinin derivatives are not recommended for use in the first trimester of pregnancy since they cause fetal resorption in animal studies there has been no evidence of reproductive toxicity or teratogenicity from published data on their use for malaria treatment in hundreds of pregnant women.<sup>37</sup>

- *Hydroxynaphthaquinones e.g. atovaquone.* *Atovaquone* is used in a fixed combination with proguanil (Malarone™ GlaxoSmithKline) for malaria prophylaxis and treatment. Used alone atovaquone resistance develops at an alarmingly rapid rate.<sup>38</sup> The molecular basis is a single point mutation on the cytochrome *b* gene of *P. falciparum*. This combination is active on the ubiquinone metabolic pathway. Pharmacokinetic studies have shown absorption is also improved if taken with fat. Mild gastrointestinal side-effects have been described.
- *Antibacterial drugs with antimalarial activity e.g. clindamycin, tetracyclines.* These drugs are weak antimalarials and slow acting and should not be used as monotherapy to treat malaria. *Doxycycline* is used for chemoprophylaxis in travellers but photosensitivity may be a troublesome side-effect. Gastrointestinal effects such as nausea, vomiting and diarrhoea are common. Other adverse effects such as dry mouth,

glossitis, stomatitis, dysphagia and oesophageal ulceration are less common. Overgrowth of *Candida* and other bacteria may also occur. Pseudomembranous colitis, hepatotoxicity and pancreatitis have also been reported. Caution needs to be exercised in patients with renal impairment and hypersensitivity reactions may occur. Rashes, fixed drug reactions, drug fever, angioedema, urticaria, pericarditis and asthma have all been reported and, rarely, haemolytic anaemia, eosinophilia, neutropenia and thrombocytopenia.

The tetracyclines may be combined with quinine or one of the artemisinin derivatives to treat falciparum malaria but they are contraindicated in young children and pregnancy because they discolour developing bones and teeth<sup>39</sup> and can cause fatal hepatotoxicity.<sup>40</sup> *Clindamycin* is a good alternative in both these situations.

## Signs and symptoms of malaria

- **Uncomplicated malaria**  
The early signs and symptoms of malaria tend to be non-specific, characterised by fever, chills, headache, loss of appetite and body aches in adults or fever plus any other symptom in children. Characteristic fever patterns have been described with fever spikes every 2 days in falciparum, vivax or ovale malaria (tertian fever) or every 3 days in malariae infection (quartan fever). This periodicity is rarely seen and is most likely to occur if the infection is left untreated and becomes synchronous. Falciparum malaria may progress to severe disease, sometimes very rapidly. This is more likely in immigrants or asylum seekers with some acquired immunity. Hyper-reactive malarious splenomegaly may be the explanation for an enlarged spleen in individuals who have left an endemic area. Untreated malaria is associated with co-morbidity in the form of anaemia. *P. malariae* also causes quartan nephropathy, an immune-complex mediated focal segmental glomerulosclerosis which may present with a nephrotic syndrome.
- **Severe malaria**  
Manifestations of severe malaria cover a broad spectrum from prostration to unrousable coma. The WHO published a detailed case definition of severe falciparum malaria in 1990, later updated in 2000<sup>41</sup> (see Fig. 2). The mortality rate associated with treated cerebral malaria is 20% in non-pregnant adults

<p>Cerebral malaria: defined as unrousable coma not attributable to any other cause.          Generalized convulsions.          Severe normocytic anaemia (Haematocrit &lt;20% or haemoglobin &lt; 7 g/dl + 100,000 parasites/<math>\mu</math>L).          Hypoglycaemia (Plasma glucose &lt; 40 mg/dl).          Metabolic acidosis with respiratory distress (Plasma venous bicarbonate &lt;15 mmol/l).          Fluid and electrolyte disturbances.          Acute renal failure (Serumcreatinine &gt; 3 mg/dl and urine output &lt; 400 ml/24 hours).          Acute pulmonary oedema and adult respiratory distress syndrome (ARDS).          Circulatory collapse, shock, septicaemia          Abnormal bleeding.          Jaundice (Bilirubin &gt; 2.5 mg/dl + 100,000 parasites/<math>\mu</math>L)          Haemoglobinuria.          High fever.          Hyperparasitaemia (&gt;5% IRBC).          Prostration          Impairment of consciousness (Glasgow coma score &lt; 11)</p>
--

**Figure 2** WHO diagnostic criteria for severe malaria.

and 15% in children. Pregnancy puts a woman at much higher risk of developing severe disease.<sup>42</sup> Cerebral malaria in pregnancy carries a >50% mortality risk even with treatment.<sup>41</sup> Symptomatic pregnant women are also at risk of fever-induced contractions leading to abortion or premature delivery. Adults with cerebral malaria are typically comatose and may present with decorticate or decerebrate posturing. Cranial nerve abnormalities are uncommon. Tone may be increased, decreased or normal and reflexes brisk or depressed. The abdominal reflexes are invariably absent. Fixed jaw closure and teeth grinding (bruxism) may be observed. The jaw jerk is sometimes brisk and there is often a pout reflex. Retinal whitening, retinal haemorrhages, whitening of vessels, papilloedema or cotton wool spots may be visualised on direct fundoscopy. Seizures are common and may be focal or generalised. A severe metabolic acidosis is often present in severe malaria secondary to tissue hypoxia and is a major cause of death. Acute renal failure is more likely to occur in adults as is pulmonary oedema with Acute Respiratory Distress Syndrome (ARDS) which is also more common in pregnancy. Disseminated intravascular coagulation (DIC) has been described but is relatively rare.

- **Post-Malaria Neurological Syndrome**

A transient neurological syndrome may follow initial recovery from severe malaria. Symptoms include confusion, tremor and seizures. The risk of PMNS is increased by mefloquine treatment which should therefore be avoided in the follow-up oral treatment of severe malaria.<sup>43</sup>

## Diagnosis of malaria

The main reason for failure to diagnose malaria in non-endemic countries is failure to consider the disease. This and the delay before patients present are important factors contributing to malaria-related mortality in travellers.<sup>44</sup> As part of routine clinical practice all patients with fever should be asked about recent travel. Malaria in the absence of any history of travel is extremely unlikely but does occur and there have been a number of case-reports of nosocomial and airport malaria.<sup>45-47</sup> A low platelet count may be another clue from routine investigations that a patient has malaria. The gold standard for malaria diagnosis is microscopy of Giemsa stained thick and thin blood smears by a skilled microscopist and identification of asexual forms within red blood cells. Wright's or Field's stains may also be used. Clinical diagnoses of malaria have been shown repeatedly to be unreliable.<sup>48,49</sup> The quality of the blood smear is very important for the diagnosis to be made and takes practice to be done well. It is prudent to repeat the smear at least once if the first result is negative. There are newer malaria diagnostic techniques such as fluorescent microscopy or the detection of nucleic acid by polymerase chain reaction (PCR) but these are not routinely available. The QBC fluorescence method using Acridine Orange (AO) (Beckton-Dickinson) is non-specific as it stains nucleic acids from all cells types. The sensitivity of AO staining for detection of malaria parasites in infections with parasites levels of <100 parasites/ $\mu$ l (0.002% parasitaemia) has been reported to range from 41% to 93%. Non-falciparum infections can be misdiagnosed as falciparum

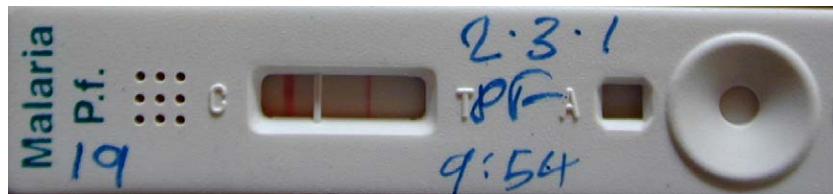


Figure 3 A Paracheck PF<sup>®</sup> Rapid Diagnostic Test positive for falciparum malaria (© SMRU).

infections, particularly in the early phase of the asexual cycle, when mostly ring forms are present. A number of rapid diagnostic immunochromatographic tests are also available. Assays are usually based on the detection either of the histidine-rich protein 2 (HRP-2) from *P. falciparum* or the parasite-specific lactate dehydrogenase (LDH) from the parasite glycolytic pathway found in all species.<sup>50</sup> A number of these rapid diagnostic tests have been evaluated in returned travellers with most tests now generating sensitivity and specificity values over 85–90% for *P. falciparum* species. However problems with poor detection of non-falciparum species and false negative results at lower parasitaemias still occur (Fig. 3).<sup>51</sup>

Rapid Diagnostic tests should not replace microscopy but may be a useful tool to exclude life-threatening falciparum infection before a smear result is available.<sup>52</sup> However it should be kept in mind that false negative results have been reported in severely ill patients with high parasitaemias (>20% of infected red blood cells [IRBC]). These false negative results are due to a prozone event that may occur at high antigen concentrations<sup>53</sup> as may happen with all immunological tests. If there is any doubt over species identification from a rapid test or slide result it is always safest to treat as falciparum malaria until proven otherwise.<sup>52,54</sup> It has been suggested that travellers be given rapid tests to diagnose their malaria.<sup>55</sup> A prospective study in a London clinic of 153 symptomatic patients presenting for a malaria test assessed their ability to perform self-diagnosis using the ICT malaria PF test card (ICT diagnostics, Sydney, NSW, Australia) with malaria blood film as the gold standard for diagnosis. Specificity was 97% (95% confidence intervals (CI) 93–99%) and sensitivity 95% (95% CI 74–99%). Nine per cent failed to perform a valid test.<sup>56</sup>

## Management of falciparum malaria

### ● General management

The strategy for treatment of malaria in travellers depends on the clinical condition of the patient, the parasitaemia, the area where the infection

occurred and the location where treatment is being sought. The potential for falciparum malaria to cause severe disease means that malaria parasites on a blood film (or a positive rapid test) must always be taken seriously and treated without delay. However in the context of an immune individual arriving febrile from a malaria-endemic country it is possible that the parasitaemia is an incidental finding and not the cause of the fever. If in doubt the patient should always be treated with effective drugs. Usually, uncomplicated malaria can be treated with oral drugs. The fever should be treated with antipyretics before giving anti-malarial treatment. If treatment is being given as an outpatient the first dose should be observed. If vomiting occurs within half an hour of the treatment the full dose should be repeated. If vomiting occurs between 30min and one hour after the treatment only half the dose should be repeated. Anti-emetics are sometimes useful to reduce vomiting. All malaria diagnoses made in non-endemic countries should be notified to the appropriate disease-control authority. If possible slides should be sent to a national reference laboratory for cross-checking. Patients should be advised to inform any travel companions they are being treated for malaria to avoid delays in diagnosis of other cases.

### ● Uncomplicated falciparum malaria

It is recommended that non-immune patients presenting with a parasitaemia  $\geq 2\%$  IRBC or with schizonts on the blood film should be admitted to hospital for treatment as should all pregnant women, young children or patients with any signs of complications. For many clinicians who see malaria infrequently, choosing the appropriate treatment can be difficult. We would suggest that the safest approach is to regard all imported falciparum malaria as chloroquine and SP resistant. The best treatment for uncomplicated disease with a parasitaemia  $< 4\%$  is an oral 3 day artemisinin-based combination treatment such as artemether-lumefantrine (Riamet<sup>®</sup>, Novartis, Basel, Switzerland) given with food containing fat. Not only are these new drugs highly efficacious, they are also more convenient than a course of intravenous or oral quinine.<sup>57</sup>

### The rationale for use of Artemisinin-based combination therapy

Artemisinin-based combination therapy is being deployed worldwide in order to combat the spread of antimalarial drug resistance. Drug resistant parasites occur naturally and are selected for. The use of two drugs with different mechanisms of action will dramatically reduce the likelihood of a resistant parasite surviving except in the rare event of infection with a doubly resistant mutant. The class of drugs best suited to provide one of the partners in a combination is the artemisinin derivatives. They are highly potent, capable of reducing the parasite biomass by a factor of  $10^4$  per asexual life-cycle. This will leave a much smaller number of parasites for the partner drug to kill while its concentration in plasma remains high. Another advantage of artemisinin derivatives is their ability to kill gametocytes thus interrupting malaria transmission making them the drugs of choice in epidemics. Brain stem neurotoxicity has been observed in animals, however these findings have never been reproduced in humans. Clinical resistance to these drugs has never been documented. Unfortunately most artemisinin-based combinations are unavailable in the West at the moment, although synthetic artemisinins are under development. An exception is artemether-lumefantrine (Riamet<sup>®</sup>, Coartem<sup>®</sup>, Novartis), now registered in 79 countries (including Switzerland, EU, Australia and Mexico). Returning travellers are not a group who contribute significantly to the spread of drug resistance worldwide, however these drugs are so well tolerated and of assured efficacy that they are the drugs of choice for this group of patients, particularly against multidrug resistant infections. Since 2001, 42 malaria-endemic countries, 23 of them in Africa, have adopted artemisinin-based combination therapies recommended by WHO. An additional 14 countries are in the process of changing their malaria treatment policy. If Western countries do not keep pace with changing treatment policies in endemic countries there is a risk that returning travellers may not be offered appropriate and effective treatment for their malaria.

If artemether-lumefantrine is not available alternative treatments would be a 3 day course of atovaquone-proguanil or a 7 day course of quinine plus either a tetracycline or clindamycin. Atovaquone-proguanil should not be given if it has been

used as prophylaxis. Drug dosages are listed in Table 1.

- Uncomplicated hyperparasitemic falciparum malaria:
 

Hyperparasitaemia is defined by the WHO handbook for the management of severe malaria as a 5% IRBC parasitaemia or higher. It must be remembered that parasitaemia does not correlate well with disease severity. Research from low transmission areas suggests parasitaemias  $\geq 4\%$  IRBC in non-immune individuals require a longer course of treatment (preferably with an artemisinin) to ensure complete cure without later recurrence. A 3 day treatment is not sufficient and is associated with an unacceptably high relapse rate. A 7 day treatment should be used following the severe malaria guidelines.
- Severe malaria:
 

There is no specific treatment for severe malaria other than parenteral antimalarial drugs given at the correct dose, combined with appropriate supportive care. For the majority of returning travellers this drug will be intravenous quinine. Parenteral artesunate (2.4 mg/kg at H0, 12, 24 and then daily) is the preferred treatment<sup>78</sup> but is not widely available as the manufacturing process is not recognised as meeting Good Manufacturing Practices (GMP) standards. Quinine is much less rapid at clearing parasites and has a high rate of complications, such as hypoglycaemia and a higher incidence of black-water fever.<sup>58</sup> Synthetic trioxane compounds for parenteral administration, related to the artemisinin derivatives are in the development process. Quinine should never be given by bolus intravenous injection. A loading dose (20 mg/kg) should be given over 4h.<sup>59</sup> Routine monitoring for hypoglycaemia is required which may be refractory to treatment in pregnant women. The assessment of fluid balance is critical in severe malaria. Many patients will require blood transfusion. Convulsions should be treated promptly with intravenous or rectal diazepam. The use of phenobarbitone as primary prophylaxis for convulsions was associated with increased mortality in a study of Kenyan children with cerebral malaria but in ventilated patients this risk should be obviated.<sup>60</sup> There is no role for steroids in the management of cerebral malaria. A lumbar puncture should be performed to exclude the possibility of concomitant bacterial meningitis and concomitant septicaemia should be considered in the presence of persisting fever or neurological deterioration despite adequate antimalarial therapy. Jaundice in malaria is due

**Table 1** Antimalarial treatment.

Uncomplicated falciparum malaria or mixed infection. Parasitaemia <4% IRBC	<p>Artemether–lumefantrine*            One dose twice a day for 3 days, according to weight:            &lt; 15 kg: 1 tablet per dose            16–25: 2 tablets per dose            26–35: 3 tablets per dose            &gt; 35: 4 tablets per dose            OR            Atovaquone 20 mg/kg/day, proguanil 8 mg/kg/day for 3 days.†            OR            Quinine 10 mg/kg three times a day for 7 days            +            Tetracycline 16 mg/kg/day for 7 days given as 3 or 4 divided doses or Doxycycline 4 mg/kg/day for 7 days or Clindamycin 5 mg/kg three times per day for 7 days.‡            OR            Artesunate 4 mg/kg/day for 3 days+            Mefloquine 25 mg/kg given as 15 mg/kg and 10 mg/kg on the 2nd and 3rd days of treatment.§</p>
Severe malaria or uncomplicated falciparum malaria with parasitaemia ≥4% IRBC	<p>Artesunate i.v.            2.4 mg/kg at hour 0 and hour 12 followed by 2.4 mg/kg daily until oral medication is tolerated. Continue oral drug 2 mg/kg daily until day 7, adding a second agent as for quinine (below).            OR            Quinine i.v.            Loading dose (LD) 20 mg/kg given over four hours, then 10 mg/kg given 8 h after the LD was started, followed by 10 mg/kg every 8 h for 7d. Once the patient has recovered sufficiently to tolerate oral medication a second drug should be added e.g. doxycycline 4 mg/kg/day for 7 days, clindamycin 5 mg/kg three times daily for 7 days or atovaquone 20 mg/kg/day+ proguanil 8 mg/kg/day for 3 days.            OR            Quinidine gluconate¶ in normal saline 10 mg/kg i.v. over 1 h, then 0.02 mg/kg/minute. Monitor ECG for 72 h.            OR 15 mg/kg i.v. over 4 h, then 7.5 mg/kg i.v. over 4 h q8 h × 72 h or until tolerates oral therapy.</p>
Non-falciparum malaria	<p>Chloroquine phosphate (1 tablet contains 250 mg salt, equivalent to 155.3 mg base). Dose is 10 mg/kg base once a day for 2 days followed by 5 mg/kg base on third day.            Plus            Primaquine** 0.3 mg base/kg daily (maximum dose 15 mg) for 14 days.</p>

\*Each dose of artemether–lumefantrine must be given with food containing some fat e.g. a 200 ml carton of milk. No data on use in pregnancy.

†Malarone®.

‡Tetracyclines are contraindicated in pregnant women and children less than 8 years.

§Contraindications to mefloquine treatment include treatment with the drug in the previous 63 days, epilepsy or neuropsychiatric disorder, history of allergy, machine operator.

¶Not recommended. Used in United States only.

\*\**P. vivax* and *P. ovale* only. Contraindicated in pregnancy or G6PD deficiency.

to intravascular haemolysis of parasitised red cells and hepatic dysfunction. If haemolysis is massive haemoglobinuria may occur. Exchange transfusion has been advocated for treatment of severe malaria with >10% IRBC parasitaemia although this is not an absolute indication for blood exchange, for example in a patient who is clinically well. This procedure should only be

attempted in a specialised unit. Erythrocytapheresis, a current-generated cell-separating technique has been used as an adjunctive therapy to treat a small number of patients with severe falciparum malaria with promising results.<sup>61</sup> Once a patient with severe malaria is well enough to tolerate oral medication treatment route may be changed and a second agent

such as doxycycline or clindamycin should be added.

- **Non-falciparum malaria**  
Most non-falciparum infections are chloroquine sensitive, however there have been reports of chloroquine resistant *P. vivax* from Papua New Guinea, Indonesia and South America.<sup>62,63</sup> Chloroquine will eradicate the asexual blood stages of the parasite but not any hypnozoites in the liver following vivax or ovale infection. Radical cure requires treatment with primaquine if pregnancy and G6PD deficiency have been excluded (see Table 1). Some guidelines advocate giving intermittent therapy with reduced dose primaquine to eradicate hypnozoites of patients with less severe forms of G6PD deficiency.

## Treatment in special circumstances

- **Pregnancy.**  
The recommended first-line treatment for uncomplicated falciparum malaria in pregnancy is quinine and clindamycin.<sup>64</sup> Severe malaria treatment is the same as for non-pregnant adults although extra vigilance is needed to avoid hypoglycaemia. Non-falciparum malaria is treated with chloroquine but primaquine may not be used to eliminate *P. vivax* hypnozoites so there is a risk of relapse, unless weekly chloroquine prophylaxis is used (McGready, pers. comm.). Specialist advice should be sought in more complicated treatment scenarios. Approximately 100 pregnant women in the second and third trimester have been treated with the triple combination of artesunate–atovaquone and proguanil with excellent efficacy and tolerability and no adverse effects for the fetus.<sup>65</sup> Trials of artemether–lumefantrine treatment of malaria in pregnancy are in the early stages. Artemisinin derivatives can be used in the second and third trimesters<sup>66</sup> and should not be withheld in any trimester if there is a life-saving situation or if no other treatment is suitable. As with lumefantrine, atovaquone, proguanil and probably other antimalarials, artesunate pharmacokinetics are altered during pregnancy<sup>67,68</sup> and the dosages recommended for non-pregnant adults may be insufficient.
- **Children**  
In most situations children with malaria should be admitted to hospital for observed treatment. There is a lack of paediatric formulations available although some are under development e.g. artemether–lumefantrine. Artemether–lumefantrine is recommended for treatment of children aged 12 years or more and weighing at least 35 kg. However it has been used to treat large numbers of young children weighing as little as 5 kg successfully in trials.<sup>69</sup> There are paediatric tablets of atovaquone–proguanil to treat children weighing over 11 kg. Mefloquine has been used to treat children weighing 5 kg and above<sup>70</sup> but should be prescribed with artesunate.
- **Congenital malaria**  
Congenital malaria should always be suspected in unwell infants of women who have lived in a malaria-endemic country during their pregnancy. Clinical signs are non-specific e.g. fever, irritability, feeding problems, hepatosplenomegaly, anaemia and jaundice. The differential diagnosis includes bacterial, cytomegalovirus, herpes simplex, rubella, toxoplasma or syphilis infections. All neonates born to women who have had malaria in the week prior to delivery should have a malaria smear soon after birth. A positive malaria smear should always be treated, initially parenterally with intramuscular or intravenous quinine or artesunate, followed by oral treatment once the infant becomes malaria smear negative (Table 1). Care should be taken with intramuscular quinine which should be diluted by 50% with sterile water to reduce the risk of abscess formation.
- **Stand-by emergency treatment**  
There are situations in which provision of stand-by self-treatment for patients may be considered.<sup>71</sup> Suitable indications would include travel to an area of multidrug resistant malaria for which no appropriate chemoprophylaxis recommendations can be made e.g. border areas of Thailand or where access to diagnosis and good quality effective drugs cannot be guaranteed. Counterfeit antimalarials have been found throughout South East Asia and a number of antimalarial formulations in African and Asian countries have been found to be of poor quality or containing no active drug.<sup>72</sup> Artemether–lumefantrine (Riamet<sup>®</sup>, Coartem<sup>®</sup>) has been registered in Switzerland for use as stand-by emergency treatment (SBET) for travellers. Some national health authorities recommend atovaquone–proguanil as SBET in areas of multidrug resistance although it is not licensed for this purpose and should not be prescribed if the drug is being used as prophylaxis. It must be stressed that the purpose of SBET is as a holding measure until expert opinion and treatment can be sought and is not a substitute for confirmed diagnosis and medical advice.<sup>73</sup> As stated previously clinical diagnoses of malaria are

unreliable and it is important to know the species and parasitaemia to treat the infection adequately.

- Management of treatment failures:

Treatment failure in malaria is usually a result of drug resistance, a short treatment course being prescribed to treat a high parasite biomass, non-adherence to a full course of treatment, e.g. 7 days of quinine due to the high rate of side-effects, or pharmacokinetic factors, e.g. inadequate dose or absorption of artemether-lumefantrine when given without food containing fat. A history of previous treatment should always be taken as the first episode of imported malaria diagnosed may be a treatment failure itself or, in the case of vivax or ovale malarias, a relapse of an infection previously treated with a blood schizonticide only. In these situations symptoms and presentation to a clinic may be very delayed. In the event of falciparum treatment failure an alternative to the first treatment should be given if available and should be supervised (see Table 1). A relapse of non-falciparum malaria needs treatment with chloroquine plus primaquine. If chloroquine resistance is suspected artemether-lumefantrine or quinine may be used at the doses recommended for falciparum malaria.

## Prevention of malaria in travellers

(see Table 2)

Prevention of malaria in travellers to malaria-endemic areas relies on taking personal protection measures to avoid biting by the vector and chemoprophylaxis. An antimalarial vaccine targeting the pre-erythrocytic stage of the parasite would be needed to protect travellers and there has been some promising work in this direction. A risk assessment should take into account the purpose of travel, activities planned, nature of accommodation, drug allergies and concomitant diseases. Before prescribing antimalarial prophylaxis it must be explained that it is not 100% effective and any febrile illness could still be malaria. The drugs used may be divided into those which are able to inhibit parasite development in the pre-erythrocytic stage in the liver such as atovaquone-proguanil and those which inhibit asexual blood stage development e.g. chloroquine, mefloquine, doxycycline, primaquine. Primaquine is sometimes given as terminal prophylaxis as a 2 week course on return from an endemic area. The long-acting 8-aminoquinoline tafenoquine may be a convenient alternative prophylactic

agent in the future. Increasing drug resistance means many prophylactic drug regimens used previously e.g. chloroquine+proguanil can no longer be relied upon in the majority of malaria-endemic countries. The artemisinin derivatives, quinine, SP and amodiaquine should not be given as prophylaxis. There are a number of websites giving up-to-date recommendations for choice of drug by country of travel e.g. WHO (<http://www.who.int.ith>), the UK-based National Travel Health Network and Centre (NaTHNaC) (<http://www.nathnac.org/index.htm>) and the website of Centers for Disease Control (<http://www.cdc.gov/travel/>). It is a good idea to start chemoprophylaxis a week before travel to enable therapeutic drug concentrations to be reached and to ensure the drug is tolerated. Since atovaquone-proguanil targets the parasite pre-erythrocytic stage it needs only to be started 1 or 2 days before travel. Concerns about potential significant neuropsychiatric reactions to mefloquine following prophylactic doses which have been reported to occur at frequencies of up to 0.7% of travellers mean it is advisable to start this even earlier.<sup>74</sup> Adherence to a chemoprophylactic regimen for a prolonged period of time is difficult and the cost of the drugs, particularly when multiplied for a family travelling together may be prohibitive. Travellers must be advised to seek medical attention as soon as possible should they develop a febrile illness, whether they have been taking their prophylaxis or not. Some physicians may choose to prescribe a SBET discussed in the treatment section. Travellers who take SBET or prescribed malaria treatment while travelling should resume their chemoprophylaxis. However if the treatment was with quinine and the prophylactic drug is mefloquine it should be delayed for at least 24 h since concurrent use of the two drugs has been associated with an increased incidence of seizures and electrocardiogram abnormalities.

- Chemoprophylaxis for pregnant travellers

The safest advice for pregnant would-be travellers is not to travel. If a pregnant woman decides to travel there is a limited choice of drugs not contraindicated for use in pregnancy. Chloroquine is safe in those few areas where it is still effective; mefloquine is considered by some authorities to be safe after the first trimester, although treatment doses have been associated with stillbirth.

- Children

Chloroquine, like many antimalarials, has a very bitter taste and may be used in children if they are travelling to a chloroquine sensitive area and if they can be persuaded to take it. There is a

**Table 2** Antimalarial drugs for prophylaxis in travellers.

DRUG	DOSE	Notes
Atovaquone-proguanil 1. Paediatric tablets (62.5 mg atovaquone and 25 mg proguanil hydrochloride)	Children $\geq$ 11 kg body weight: 11–20 kg: 1 paediatric tablet daily 21–30 kg: 2 paediatric tablets daily 31–40 kg: 3 paediatric tablets daily	Start: 2 days before travel. Stop: 1 week after leaving malarious area. Not recommended in pregnancy.
2. Adult tablets (250 mg atovaquone/100 mg proguanil)	Adults or children $\geq$ 41 kg body weight: 1 adult tablet daily	
Mefloquine: 250 mg mefloquine hydrochloride tablets (= 228 mg base)	Children $\geq$ 10 kg: 10–19 kg: $\frac{1}{4}$ tablet once/week 20–30 kg: $\frac{1}{2}$ tablet, once/week 31–45 kg: $\frac{3}{4}$ tablet once/week Adults or children $\geq$ 46 kg: 1 tablet weekly	Start: 2–4 weeks before travel Stop: 4 weeks after leaving malarious area.
Doxycycline	Children $\geq$ 8 years: 2 mg/kg daily Adults: 100 mg daily	Start: 2 days before travel Stop: 4 weeks after leaving malarious area. Contraindicated in children < 8 years and pregnancy.
Primaquine: Primaquine phosphate 7.5 or 15 mg tablets.	Children: 0.5 mg/kg base (1.0 mg/kg salt) up to adult dose, orally, daily Adults: 30 mg daily As terminal prophylaxis: Give the same daily dose for 14 days after leaving malarious area.	Start: 1 week before travel. Stop: 1 week after leaving malarious area (unless using as terminal prophylaxis) Contraindicated in pregnancy or G6PD deficiency.
Chloroquine Chloroquine phosphate 500 mg tablets (= 300 mg base) and Proguanil	Children: once weekly dose INFANT < 12 weeks, BW < 6 kg: 37.5 mg 12 wks–11 months 6–10 kg: 75 mg CHILD > 1 year 10–16 kg: 112.5 mg 16–25 kg: 150 mg 25–45 kg: 225 mg With proguanil 3 mg/kg daily. Adults: 300 mg chloroquine base (500 mg salt) weekly with proguanil 200 mg daily	Not recommended; ensure travel is to an area where chloroquine remains sensitive. Start: 2–4 weeks before travel Stop: 4 weeks after leaving malarious area.

paediatric tablet of atovaquone–proguanil for children weighing more than 11 kg. Mefloquine has been given to infants weighing more than 5 kg as treatment but is only recommended as prophylaxis in children weighing more than 15 kg. Doxycycline is contraindicated in children less than 8 years old.

- Long-term travellers

A high proportion of exposed travellers are people travelling for longer periods to visit friends and relatives, particularly to sub-Saharan Africa.<sup>75</sup> Manufacturers' recommendations for long-term use of antimalarial drugs are conser-

vative due to lack of safety data. Chloroquine has been taken safely for periods of many years at doses used for malaria chemoprophylaxis. Retinal toxicity has been described in people prescribed long-term chloroquine for rheumatological disorders, however at doses in excess of those used for antimalarial prophylaxis.<sup>14,76</sup> Periodic ophthalmological examination is recommended. Proguanil is thought to be safe if taken continuously for several years. Mefloquine is licensed for use for up to 1 year although there are reports of continuous use for 2 years or more. There is no evidence of cumulative

toxicity.<sup>77</sup> Doxycycline is licensed for up to 2 years or more in the treatment of acne in the same dose as is used for malaria prophylaxis. Atovaquone-proguanil (Malarone™) is not licensed for long-term use since it is a relatively new combination; however there is experience of both constituent drugs being used continuously for longer periods.

## Conclusion

The spread of drug resistance is having a disastrous impact on poorer countries with mortality from malaria increasing and a delay in changing treatment policies to effective drugs as they are considered unaffordable. For returning travellers the problem in accessing effective treatment may be lack of availability rather than cost. Highly effective antimalarials which are easily available and life-saving in endemic countries are considered unsafe for use in the West. This situation is likely to change as newer artemisinin compounds whose manufacturing processes will satisfy international drug regulatory authorities are being developed with support from agencies like the Drugs for Neglected Diseases Initiative (<http://www.dndi.org>) and Medicines for Malaria Venture (<http://www.mmv.org>). Increasing international travel and the spread of drug resistance which limits chemoprophylaxis options for travellers plus a rise in the number of asylum seekers means malaria is likely to be encountered more frequently by general practitioners in non-endemic countries. Falciparum malaria may be a lethal infection but if it is diagnosed early it is a very treatable one, providing an effective treatment is administered. Increasingly this will be an artemisinin-based combination therapy. Physicians should familiarise themselves with these new drugs.

## References

1. Snow RW, Guerra CA, Noor AM, Myint HY, Hay SI. The global distribution of clinical episodes of *Plasmodium falciparum* malaria. *Nature* 2005;434(7030):214–7.
2. Korenromp E, Miller J, Nahlen B, Wardlaw T, Young M. *World malaria report*. Geneva: Roll Back Malaria Partnership, World Health Organisation and United Nations Children's Fund (UNICEF); 2005.
3. Snow R, Trape JF, Marsh K. The past, present and future of childhood malaria mortality in Africa. *Trends Parasitol* 2001;17(12):593–7.
4. White NJ, Nosten F, Looareesuwan S, Watkins WM, Marsh K, Snow RW, et al. Averting a malaria disaster. *Lancet* 1999; 353(9168):1965–7.
5. Wellems TE, Miller LH. Two worlds of malaria. *N Engl J Med* 2003;349(16):1496–8.
6. Milne LM, Kyi MS, Chiodini PL, Warhurst DC. Accuracy of routine laboratory diagnosis of malaria in the United Kingdom. *J Clin Pathol* 1994;47(8):740–2.
7. White N. Malaria. In: Zumla GCA, editor. *Manson's tropical diseases*. 21 ed. Edinburgh: W.B. Saunders; 2003. p. 1205–96.
8. Hay SI, Guerra CA, Tatem AJ, Noor AM, Snow RW. The global distribution and population at risk of malaria: past, present, and future. *Lancet Infect Dis* 2004;4:327–36.
9. Luxemburger C, Ricci F, Nosten F, Raimond D, Bathet S, White NJ. The epidemiology of severe malaria in an area of low transmission in Thailand. *Trans R Soc Trop Med Hyg* 1997;91(3):256–62.
10. McGready R, Ashley EA, Nosten F. Malaria and the pregnant traveller. *Travel Med Infect Dis* 2004;2:127–42.
11. Kayentao K, Kodio M, Newman RD, Maïga H, Doumtable D, Ongoïba A, et al. Comparison of intermittent preventive treatment with chemoprophylaxis for the prevention of malaria during pregnancy in Mali. *J Infect Dis* 2005;191(1): 109–16.
12. Schellenberg D, Menendez C, Aponte JJ, Kahigwa E, Tanner M, Mshinda H, et al. Intermittent preventive antimalarial treatment for Tanzanian infants: follow-up to age 2 years of a randomised, placebo-controlled trial. *Lancet* 2005; 365(9469):1481–3.
13. Su X, Kirkman LA, Fujioka H, Wellems TE. Complex polymorphisms in an approximately 330 kDa protein are linked to chloroquine-resistant *P. falciparum* in Southeast Asia and Africa. *Cell* 1997;91(5):593–603.
14. Finbloom DS, Silver K, Newsome DA, Gunkel R. Comparison of hydroxychloroquine and chloroquine use and the development of retinal toxicity. *J Rheumatol* 1985;12(4): 692–4.
15. Hatton CS, Peto TE, Bunch C, Pasvol G, Russell SJ, Singer CR, et al. Frequency of severe neutropenia associated with amodiaquine prophylaxis against malaria. *Lancet* 1986; 1(8478):411–4.
16. Sturchler D, Schar M, Gyr N. Leucopenia and abnormal liver function in travellers on malaria chemoprophylaxis. *J Trop Med Hyg* 1987;90(5):239–43.
17. Looareesuwan S, Phillips RE, White NJ, Kietinun S, Karbwang J, Rackow C, et al. Quinine and severe falciparum malaria in late pregnancy. *Lancet* 1985;2(8445):4–8.
18. Kremsner PG, Winkler S, Brandts C, Neifer S, Bienzle U, Graninger W. Clindamycin in combination with chloroquine or quinine is an effective therapy for uncomplicated *Plasmodium falciparum* malaria in children from Gabon. *J Infect Dis* 1994;169(2):467–70.
19. Weinke T, Trautmann M, Held T, Weber G, Eichenlaub D, Fleischer K, et al. Neuropsychiatric side effects after the use of mefloquine. *Am J Trop Med Hyg* 1991;45(1):86–91.
20. Nosten F, van Vugt M. Neuropsychiatric adverse effects of Mefloquine: what do we know and what should we do? *CNS Drugs* 1999;11:1–8.
21. Nosten F, Luxemburger C, ter Kuile FO, Woodrow C, Eh JP, Chongsuphajaisiddhi T, et al. Treatment of multidrug-resistant *Plasmodium falciparum* malaria with 3-day artesunate-mefloquine combination. *J Infect Dis* 1994;170(4): 971–7.
22. Nosten F, Vincenti M, Simpson J, Yei P, Thwai KL, de Vries A, et al. The effects of mefloquine treatment in pregnancy. *Clin Infect Dis* 1999;28(4):808–15.
23. Steketee RW, Wirima JJ, Slutsker L, Khoromana CO, Heymann DL, Breman JG. Malaria treatment and prevention in pregnancy: indications for use and adverse events associated with use of chloroquine or mefloquine. *Am J Trop Med Hyg* 1996;55(1):50–6.

24. Clyde DF. Clinical problems associated with the use of primaquine as a tissue schizontocidal and gametocytocidal drug. *Bull World Health Organ* 1981;59(3):391–5.
25. Ezzet F, van Vugt M, Nosten F, Looareesuwan S, White NJ. Pharmacokinetics and pharmacodynamics of lumefantrine (benflumetol) in acute falciparum malaria. *Antimicrob Agents Chemother* 2000;44(3):697–704.
26. Ashley EA, Krudsood S, Phaiphun L, Srivilairit S, McGready R, Leowattana W, et al. Randomized, controlled dose-optimization studies of dihydroartemisinin-piperaquine for the treatment of uncomplicated multidrug-resistant falciparum malaria in Thailand. *J Infect Dis* 2004;190(10):1773–82.
27. Ringwald P, Bickii J, Basco L. Randomised trial of pyronaridine versus chloroquine for acute uncomplicated falciparum malaria in Africa. *Lancet* 1996;347(8993):24–8.
28. Winstanley P. Chlorproguanil-dapsone (LAPDAP) for uncomplicated falciparum malaria. *Trop Med Int Health* 2001;6(11):952–4.
29. China Cooperative Research Group. Chemical studies on qinghaosu (artemisinin). China Cooperative Research Group on qinghaosu and its derivatives as antimalarials. *J Tradit Chin Med* 1982;2(1):3–8.
30. Li GQ, Guo XB, Jin R, Wang ZC, Jian HX, Li ZY. *Clinical trials on qinghaosu and its derivatives*. China: Guangzhou College of Traditional Chinese Medicine; 1990.
31. Li GQ, Arnold K, Guo XB, Jian HX, Fu LC. Randomised comparative study of mefloquine, qinghaosu, and pyrimethamine-sulfadoxine in patients with falciparum malaria. *Lancet* 1984;2(8416):1360–1.
32. Artesunate combinations for treatment of malaria: meta-analysis. *Lancet* 2004;363(9402):9–17.
33. Price R, van Vugt M, Phaiphun L, Luxemburger C, Simpson J, McGready R, et al. Adverse effects in patients with acute falciparum malaria treated with artemisinin derivatives. *Am J Trop Med Hyg* 1999;60(4):547–55.
34. Leonardi E, Gilvary G, White NJ, Nosten F. Severe allergic reactions to oral artesunate: a report of two cases. *Trans R Soc Trop Med Hyg* 2001;95(2):182–3.
35. Brewer TG, Peggins JO, Grate SJ, Petras JM, Levine BS, Weina PJ, et al. Neurotoxicity in animals due to arteether and artemether. *Trans R Soc Trop Med Hyg* 1994;88 (Suppl 1):S33–6.
36. Hien TT, Davis TM, Chuong LV, Ilett KF, Sinh DX, Phu NH, et al. Comparative pharmacokinetics of intramuscular artesunate and artemether in patients with severe falciparum malaria. *Antimicrob Agents Chemother* 2004;48(11):4234–9.
37. McGready R, Cho T, Keo NK, Thwai KL, Villegas L, Looareesuwan S, et al. Artemisinin antimalarials in pregnancy: a prospective treatment study of 539 episodes of multidrug-resistant *Plasmodium falciparum*. *Clin Infect Dis* 2001;33(12):2009–16.
38. Looareesuwan SVC, Webster HK, Kyle DE, Hutchinson DB, Canfield CJ. Clinical studies of atovaquone, alone or in combination with other antimalarial drugs, for treatment of acute uncomplicated malaria in Thailand. *Am J Trop Med Hyg* 1996;54(1):62–6.
39. Manson JD. Tetracyclines and the teeth. *Lancet* 1966;1(7446):1104.
40. [No authors listed] Na. Tetracyclines and the liver in pregnancy. *Lancet* 1966;1(7433):357–8.
41. World Health Organisation. Severe falciparum malaria. *Trans R Soc Trop Med Hyg* 2000;94(Suppl).
42. Luxemburger C, McGready R, Kham A, Morison L, Cho T, Chongsuphajaisiddhi T, et al. Effects of malaria during pregnancy on infant mortality in an area of low malaria transmission. *Am J Epidemiol* 2001;154(5):459–65.
43. Nguyen TH, Day NP, Ly VC, Waller D, Nguyen HP, Bethell DB, et al. Post-malaria neurological syndrome. *Lancet* 1996;348(9032):917–21.
44. Kain KC, Harrington MA, Tennyson S, Keystone JS. Imported malaria: prospective analysis of problems in diagnosis and management. *Clin Infect Dis* 1998;27(1):142–9.
45. Isaacson M. Airport malaria: a review. *Bull World Health Organ* 1989;67(6):737–43.
46. Evans RJ. Nosocomial malaria. *Lancet* 1997;349(9051):574.
47. Moro ML, Romi R, Severini C, Casadio GP, Sarta G, Tampieri G, et al. Patient-to-patient transmission of nosocomial malaria in Italy. *Infect Control Hosp Epidemiol* 2002;23(6):338–41.
48. Luxemburger C, Nosten F, Kyle DE, Kiricharoen L, Chongsuphajaisiddhi T, White NJ. Clinical features cannot predict a diagnosis of malaria or differentiate the infecting species in children living in an area of low transmission. *Trans R Soc Trop Med Hyg* 1998;92(1):45–9.
49. Chandramohan D, Carneiro I, Kavishwar A, Brugha R, Desai V, Greenwood B. A clinical algorithm for the diagnosis of malaria: results of an evaluation in an area of low endemicity. *Trop Med Int Health* 2001;6(7):505–10.
50. Moody A. Rapid diagnostic tests for malaria parasites. *Clin Microbiol Rev* 2002;15(1):66–78.
51. Pattanasin S, Proux S, Chompasuk D, Kuwiradaj K, Jacquier P, Looareesuwan S, et al. Evaluation of a new pLDH assay (Optimal-IT) for detection of malaria. *Trans R Soc Trop Med Hyg* 2004.
52. Arya SC. Limitations of rapid tests for malaria diagnosis by travelers. *J Travel Med* 2000;7(6):340.
53. Risch L, Bader M, Huber AR. Self-use of rapid tests for malaria diagnosis. *Lancet* 2000;355(9199):237.
54. Bell D. Malaria rapid diagnostic tests: one size may not fit all. *Clin Microbiol Rev* 2002;15(4):771 (discussion 771–2).
55. Behrens RH, Whitty CJ. Self-use of rapid tests for malaria diagnosis. *Lancet* 2000;355(9199):237.
56. Whitty CJM, Armstrong M, Behrens RH. Self-testing for falciparum malaria with antigen-capture cards by travelers with symptoms of malaria. *Am J Trop Med Hyg* 2000;63(5–6):295–7.
57. Luxemburger C, Nosten F, Raimond SD, Chongsuphajaisiddhi T, White NJ. Oral artesunate in the treatment of uncomplicated hyperparasitemic falciparum malaria. *Am J Trop Med Hyg* 1995;53(5):522–5.
58. McIntosh HM, Olliaro P. Artemisinin derivatives for treating severe malaria. *Cochrane Database Syst Rev* 2000;2.
59. White NJ, Looareesuwan S, Warrell DA, Warrell MJ, Chanthavanich P, Bunnag D, Harinasuta T. Quinine loading dose in cerebral malaria. *Am J Trop Med Hyg* 1983;32:1–5.
60. Crawley J, Waruiru C, Mithwani S, Mwangi I, Watkins W, Ouma D, et al. Effect of phenobarbital on seizure frequency and mortality in childhood cerebral malaria: a randomised, controlled intervention study. *Lancet* 2000;355(9205):701–6.
61. Macallan DC, Pocock M, Bishop E, Bevan DH, Parker-Williams J, Harrison T, et al. Automated erythrocytapheresis in the treatment of severe falciparum malaria. *J Infect* 1999;39(3):233–6.
62. Whitby M. Drug resistant *Plasmodium vivax* malaria. *J Antimicrob Chemother* 1997;40(6):749–52.
63. Maguire J, Sumawinata IW, Masbar S, Laksana B, Prodjodipuro P, Susanti I, et al. Chloroquine-resistant *Plasmodium malariae* in south Sumatra, Indonesia. *Lancet* 2002;360(9326):58–60.
64. McGready R, Cho T, Samuel, Villegas L, Brockman A, van Vugt M, et al. Randomized comparison of quinine-clindamycin versus artesunate in the treatment of falciparum malaria in pregnancy. *Trans R Soc Trop Med Hyg* 2001;95(6):651–6.

65. McGready R, Keo NK, Villegas L, White NJ, Looareesuwan S, Nosten F. Artesunate-atovaquone-proguanil rescue treatment of multidrug-resistant *Plasmodium falciparum* malaria in pregnancy: a preliminary report. *Trans R Soc Trop Med Hyg* 2003;**97**(5):592-4.
66. Assessment of the safety of artemisinin compounds in pregnancy: World Health Organization; 2003. Report No.: WHO/CDS/MAL/2003.1094.
67. McGready R, Stepniewska K, Edstein MD, Cho T, Gilveray G, Looareesuwan S, et al. The pharmacokinetics of atovaquone and proguanil in pregnant women with acute falciparum malaria. *Eur J Clin Pharmacol* 2003;**59**(7):545-52.
68. McGready R, Stepniewska K, Ward SA, Cho T, Gilvary G, S L, et al. Pharmacokinetics of dihydroartemisinin following oral artesunate treatment of pregnant women with acute uncomplicated falciparum malaria. *Eur J Clin Pharmacol* 2005, in press.
69. Falade C, Makanga M, Premji Z, Ortmann CE, Stockmeyer M, de Palacios PI. Efficacy and safety of artemether-lumefantrine (Coartem) tablets (six-dose regimen) in African infants and children with acute, uncomplicated falciparum malaria. *Trans R Soc Trop Med Hyg* 2005;**99**(6):459-67.
70. Luxemburger C, Price RN, Nosten F, Ter Kuile F, Chongsu-phajaisiddhi T, White NJ. Mefloquine in infants and young children. *Ann Trop Paediatr* 1996;**16**(4):281-6.
71. World Health Organisation. *Stand-by emergency treatment*. 2004.
72. Newton P, Proux S, Green M, Smithuis F, Rozendaal J, Looareesuwan S, et al. Fake artesunate in Southeast Asia. *Lancet* 2001;**357**:1948-50.
73. Kassianos G. Standby emergency treatment, the 'third option': malaria advice for travellers. *Int J Clin Pract* 2001;**55**(9):580-1.
74. Barrett PJ, Emmins PD, Clarke PD, Bradley DJ. Comparison of adverse events associated with use of mefloquine and combination of chloroquine and proguanil as antimalarial prophylaxis: postal and telephone survey of travellers [see comments]. *BMJ* 1996;**313**(7056):525-8.
75. Leder K, Black J, O'Brien D, Greenwood Z, Kain KC, Schwartz E, et al. Malaria in travelers: a review of the GeoSentinel surveillance network. *Clin Infect Dis* 2004;**39**(8):1104-12.
76. Luzzi G, Peto TEA. Adverse effects of antimalarials. An update. *Drug Saf* 1993;**8**:295-311.
77. Schlagenhauf P. Mefloquine for malaria chemoprophylaxis 1992-1998: a review. *J Travel Med* 1999;**6**(2):122-33.
78. SouthEast Asian Quinine Artesunate Malaria Trial Group. Artesunate versus quinine for treatment of severe falciparum malaria; a randomised trial. *The Lancet* 2005;**366**: 717-25.

Available online at [www.sciencedirect.com](http://www.sciencedirect.com)

