An update on malaria prevention, diagnosis and treatment for the returning traveller

Effrossyni Gkrania-Klotsas a,*, Andrew M.L. Lever b,1

a Department of Infectious Diseases, Box 25, Addenbrooke’s Hospital, Hills Road, Cambridge, CB2 2QQ, UK
b Department of Medicine, University of Cambridge, Level 5, Addenbrooke’s Hospital, Cambridge CB2 2QQ, UK

Summary The diagnosis of malaria needs to be considered for every returning traveller with a fever. Compliance with prevention, both pharmaceutical and non-pharmaceutical, is essential for every traveller. New tests for diagnosis are now available. Treatment options have recently expanded to include the artemisinin derivatives that used to be unavailable in the western countries.

INTRODUCTION / BURDEN OF DISEASE WORLDWIDE

Malaria is a protozoan disease transmitted by the bite of the blood-feeding female anopheline mosquito. Four species of the genus Plasmodium, P. falciparum, P. vivax, P. malariae and P. ovale, are responsible for the vast majority of human infections. Plasmodium falciparum causes the most severe disease and is responsible for most malaria related deaths. From its influence on human genetic variation, and the toll it exacts in morbidity and mortality, malaria is considered to be the most important parasitic disease of man. Genetic mutations in haemoglobin genes are the commonest single gene disorders in man and their geographic coincidence with the malaria prone areas of the world illustrates their survival benefit for this disease. Although it has been eradicated from Europe, North America and Russia, malaria is still found in the Middle East, China and the Indian Subcontinent and, particularly, the tropics where the emergence of resistance to antimalarial drugs has partly contributed to a recent resurgence of the disease.

The exact incidence and prevalence are difficult to estimate but approximately 270 million people suffer from malaria and at least 1 million people die from malaria every year.1 Although human interventions during the 20th century have markedly reduced its distribution, they have failed to eradicate the disease. It is currently estimated that a malaria risk exists in 88 countries and territories with populations of more than 100 000, and that...
this risk extends over 27% of the Earth’s land surface.²

Burden of disease in travellers

Although drugs for the prevention of acquisition of malaria are widely available, travellers from developed countries continue to suffer morbidity and mortality from the disease. According to a recent systematic review,³ nearly 1500 malaria cases occur each year in the United States; approximately 60% of those are among travellers. Between 1963 and 2001, 185 fatal cases of malaria were reported to the National Malaria Surveillance System. 123 (66.5%) among U.S. travellers and of these 114 (92.7%) were attributed to Plasmodium falciparum. According to the authors, 85.4% of these deaths were considered preventable. Potentially contributing factors included failure to seek pre-travel advice but also failures of prescribing, obtaining and adhering to chemoprophylaxis and delays in diagnosis and initiating treatment. In the year 2000, 27.7 million U.S. travellers visited countries affected by malaria.³ In recent years, cases among U.S. civilians have increased and cases among foreign-born civilians in the U.S. have decreased.⁴ These trends are probably a result of both increased travel among U.S. citizens and decreased immigration since 2001. Most cases of imported civilian malaria in the USA in the years 1999–2002 were in people who had visited their families (36–45%).³–⁸ European short-term travellers were found to contract malaria at an incidence rate of 12 per 1000 travellers per month to East Africa and 24 per 1000 travellers per month to West Africa or 0.4 to 0.8 per thousand persons per night in high transmission areas.⁹

Deaths secondary to travel-associated malaria have also been recently reported from Canada, associated with inappropriate chemoprophylaxis.¹⁰ A study analyzing travel-associated imported infections in England and Wales during the years 1998 and 1999 estimated that the total annual cost of Infectious Diseases Unit treatment for imported infections in England and Wales is in excess of £800,000. 29% of the imported infectious diseases cases in that study were cases of malaria.¹¹

The risk of acquiring travel-associated malaria also appears to be increasing as increasing numbers of people engage in international travel and the fact that malaria control in Sub-Saharan Africa has deteriorated the last decade. Reasons for the latter are felt to be climate instability, global warming, changing travel patterns, civil disturbances, HIV infection, and drug and insecticide resistance.¹²

All of these factors mean that it is important for Western doctors to be able to advise patients on prevention of acquisition of malaria when travelling to endemic areas, to diagnose malaria accurately and swiftly, and to be able to prescribe an appropriate and effective therapeutic regimen when malaria is suspected or diagnosed.

Malaria prevention for travellers

Each year more than 7 million Americans travel to areas where malaria is common.¹³ Many of the travellers present themselves to travel clinics but also to their family doctors who need to be able to provide up-to-date information. Four steps remain essential to prevent damage to health due to malaria:¹⁴

1. Awareness: Many online sources are available to the clinician and the general public that provide up-to-date information on malaria risk, but also information about current research.¹⁵ Comprehensive internet sites include the ones listed in Table 1.

   The CDC website presents a vast amount of information, divided into sections for either the general public or the health professional. It is user-friendly and frequently updated. It includes details on malaria risk in specific countries / regions and links to the Yellow Book (Health Information for International Travel, 2005–2006, http://www.cdc.gov/travel/yb/). The Yellow Book is published every two years by CDC as a reference primarily for health care providers

Table 1 Useful websites on malaria.

<table>
<thead>
<tr>
<th>Web site name</th>
<th>Address</th>
</tr>
</thead>
<tbody>
<tr>
<td>Centers for Disease Control and Prevention</td>
<td><a href="http://www.cdc.gov/malaria/">http://www.cdc.gov/malaria/</a></td>
</tr>
<tr>
<td>World Health Organization</td>
<td><a href="http://www.who.int/topics/malaria/en/">http://www.who.int/topics/malaria/en/</a></td>
</tr>
<tr>
<td>The Malaria Foundation</td>
<td><a href="http://www.malaria.org">http://www.malaria.org</a></td>
</tr>
</tbody>
</table>
who advise international travellers of health risks.16 The website also gives the user the option to build a custom report tailored to his/her needs.

The WHO website is, in general, less user-friendly compared to the CDC website. It provides a link to the WHO Roll Back Malaria Department and a link to the International Travel and Health publication, edition of 2005, but the bibliography at the end of the malaria chapter is dated from the year 2000.

The Malaria Foundation provides a website with multiple links rather than offering original content. Some of the links are out of date; however the site can serve as a portal to the CDC and WHO sites mentioned above as well.

2. Avoidance of mosquito bites: Malaria transmission to man depends on a number of interrelated factors.17 The optimum conditions for transmission are high humidity and an ambient temperature between 20° and 30 °C. The Anopheles mosquito feeds from dusk to dawn. From the Donald formula18 it becomes obvious that reducing the number of blood meals on man per day affects malaria transmission substantially. Travellers should be advised to wear long-sleeved clothing, long trousers and socks after sunset, all preferably of a lighter color. Travellers should be advised to sleep in screened rooms, with close fitting gauze over doors and windows and no unscreened potential mosquito entry points. Alternatively, the evidence suggests that impregnated bed nets are independently effective in preventing malaria and permit reduced DDT spraying of rooms.19 Examples of appropriate bed nets include nylon nets impregnated with permethrin (or another pyrethroid) 0.2 g/m² of material every six months.20 Development of resistance or tolerance of different mosquito strains to pyrethroids is expected to affect future recommendations.21 Synthetic pyrethroids can be vaporized or mosquito coils can be burnt. Using an insect repellent that contains more than 30% N, N-diethyl-meta-toluamide (DEET) is also effective and clothing can be treated with DEET as well. Insect repellents with higher than 50% percent DEET carry a possible risk of neurotoxicity22 when used repeatedly for small children and are best avoided.23 DEET should be applied as sparingly as needed and washed off from skin with soap and water when indoors.

An alternative to DEET, with similar efficacy, is picaridin,24 an insect repellent used for many years in Europe and Australia. Picaridin is marketed as a 7% formulation in the United States, however the efficacy of such a concentration is yet unknown. Picaridin is odorless, does not feel sticky when applied, and does not damage clothing.25

Chemoprophylaxis

General principles

None of the present prophylactic regimens provides 100 percent protection against malaria,26 and research efforts to develop more effective antimalarial agents lag behind work in many other fields.27 A clinician discussing malaria prevention should weigh the risk of malaria with the risk of adverse reactions to antimalarials. The risk depends on host factors, the place that will be visited, the duration of the visit, the degree of exposure and the level and type of drug resistance. The risk of acquiring malaria if prophylaxis is not used, extrapolated from morbidity data, after one month of travel in West Africa is estimated to be 1:40 and in East Africa is estimated to be 1:70 (1:17 in Solomon Islands and Papua New Guinea).28 Business travellers may have a higher risk for malaria because of decreased compliance, despite being well informed about the malaria risk.29

Antimalarial drugs should be purchased before travel; drugs purchased overseas may not be manufactured according to developed countries standards and may not be effective.30 They may also be dangerous, contain the wrong drug or an incorrect amount of active drug, be contaminated or simply be fake.

Medication should be started before going abroad (1–2 days for atovaquone/proguanil31 one week for chloroquine/proguanil). When mefloquine is used, it should be started two and a half weeks before travelling32 so that if adverse effects occur there will be time to switch to another medication.14 Medications should be continued throughout the stay in the malarious area and be discontinued four weeks after leaving it (atovaquone/proguanil should be continued for a week after leaving).31

The need for compliance with the regimen should be emphasized. Although lack of compliance appears to be only partly responsible for acquisition of malaria, it is more frequently noted in patients who acquired malaria compared to controls.33 Formal controlled studies on the subject have not been performed. A study from Austria34 revealed that only 60% of patients completed the full course of prophylaxis.

Medications should be taken after meals, with water. Doxycycline should not be taken lying down. Oral typhoid and oral cholera vaccines and intradermal rabies vaccination are recommended to be
given before starting antimalarial prophylaxis, although the subject warrants further research. The usual regimens for chemoprophylaxis for adults and children, as there are currently recommended are presented in Tables 2 and 3.

Notes on the prevention regimens

- Primaquine should only be used after consultation with experts and in travellers with no G6PD deficiency (glucose-6-phosphate-dehydrogenase). Primaquine primary prophylaxis should begin 1–2 days before travel to the malaria-risk area. It should be continued once a day, at the same time each day, while in the malaria-risk area, and daily for 7 days after leaving the malaria-risk area.
- Chloroquine plus Proguanil for areas with little Chloroquine resistance: the regimen is recommended by the Health Protection Agency Advisory Committee on Malaria Prevention for UK Travellers. It is not recommended by the Centers of Disease Control because of concerns regarding reduced efficacy.
- There is less evidence for the effectiveness of hydroxychloroquine sulfate as an antimalarial drug. It can not be used in areas where chloroquine resistance has been reported.

Table 2 Malaria chemoprophylaxis for adults.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usage</th>
<th>Adult dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atovaquone/proguanil</td>
<td>Areas with chloroquine-resistant or mefloquine-resistant <em>Plasmodium falciparum</em></td>
<td>250 mg atovaquone and 100 mg proguanil hydrochloride. 1 tablet orally, daily</td>
</tr>
<tr>
<td>Chloroquine phosphate</td>
<td>Areas with chloroquine-sensitive <em>P. falciparum</em></td>
<td>300 mg base (500 mg salt) orally, once/week</td>
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<tr>
<td></td>
<td></td>
<td>This is the equivalent of two tablets orally weekly (one tablet has 150 mg of base)</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>Areas with chloroquine-resistant or mefloquine-resistant <em>P. falciparum</em></td>
<td>100 mg orally, daily (tablet or capsule)</td>
</tr>
<tr>
<td>Chloroquine PLUS proguanil</td>
<td>Areas with little chloroquine resistance.</td>
<td>2 tablets weekly (150 mg base/tablet) PLUS 2 tablets daily (100 mg/tablet)</td>
</tr>
<tr>
<td>Hydroxychloroquine sulfate</td>
<td>An alternative to chloroquine for primary prophylaxis only in areas with chloroquine-sensitive <em>P. falciparum</em></td>
<td>310 mg base (400 mg salt) orally, once/week</td>
</tr>
<tr>
<td>Mefloquine</td>
<td>Areas with chloroquine-resistant <em>P. falciparum</em></td>
<td>228 mg base (250 mg salt) orally, once/week</td>
</tr>
<tr>
<td>Primaquine</td>
<td>An option for primary prophylaxis in special circumstances.</td>
<td>30 mg base (52.6 mg salt) orally, daily</td>
</tr>
<tr>
<td>Primaquine</td>
<td>Used to decrease risk of relapses of <em>P. vivax</em> and <em>P. ovale</em></td>
<td>30 mg base (52.6 mg salt) orally, once/day for 14 days after departure from the malarious area.</td>
</tr>
</tbody>
</table>
Fansidar (500 mg of long-acting sulfadoxine and 25 mg of pyrimethamine in a single tablet once a week) has caused severe mucocutaneous reactions even after a few doses and is no longer recommended.

Precautions / adverse reactions of antimalarial prophylaxis

1. Atovaquone/proguanil: Atovaquone/proguanil should not be used in infants <11 kg, pregnant women, women breast-feeding infants <11 kg, or patients with severe renal impairment (creatinine clearance <30 mL/min). Common side-effects include abdominal pain, nausea, vomiting, and headache.

2. Chloroquine phosphate and Hydroxychloroquine sulfate: either of them may exacerbate psoriasis. Neurological side-effects include headache, blurry vision and insomnia. Gastrointestinal problems can also complicate treatment. Retinopathy is very unusual in small doses.

3. Doxycycline: can cause photosensitivity and esophagitis. It should not be taken by children or pregnant women. Travellers who start doxycycline but must switch to atovaquone/proguanil during or after travel must continue their atovaquone/proguanil for 4 weeks after switching or 1 week after returning, whichever is longer.

4. Mefloquine: the drug has been linked with a higher risk of insomnia, fatigue, depression and anger compared to other antimalarials and is,
therefore, contraindicated in persons with history of seizures or psychiatric disorders. It is also not recommended for persons with cardiac conduction abnormalities. The risk of side-effects appears to be higher for first time users, women and leaner persons. Travellers who start mefloquine but must switch to atovaquone/proguanil during or after travel must continue their atovaquone/proguanil for 4 weeks after switching or 1 week after returning, whichever is longer. Mefloquine resistance areas have been reported (Amazon basin, Thailand-Myanmar and Thailand-Cambodia borders).

Chemoprophylaxis during pregnancy and lactation

Malaria can cause stillbirth and it poses a great risk on the maternal health as well because of the severity of the disease during pregnancy. Pregnant women preferably should avoid traveling to malarious areas. If traveling is unavoidable, hydroxychloroquine or chloroquine can be used for areas with chloroquine-sensitive *P. falciparum*. For areas with chloroquine resistant *P. falciparum*, mefloquine is recommended since limited data suggest safety although it was previously associated with spontaneous abortions. Atovaquone/proguanil is not recommended during pregnancy due to a lack of sufficient safety data although preliminary data are encouraging. Doxycycline is contraindicated during pregnancy because of the known risks of tetracycline on the fetus. Primaquine should not be used during pregnancy because the drug may pass to a G6PD-deficient fetus.

Very small amounts of chloroquine and mefloquine are excreted in breast milk and, according to the Centers for Disease Control, the amount of drug is not sufficient to harm the infant nor is the quantity sufficient to protect the child from malaria. Breastfeeding infants should receive weight appropriate prophylaxis.

Very limited data are available on the use of doxycycline in lactating women. It is generally thought to be safe. Primaquine should only be given to lactating women if both the woman and her infant have been tested for G6PD deficiency and have normal G6PD levels documented.

Because safety data is not yet available, atovaquone/proguanil is not currently recommended for women breastfeeding infants <11 kg.

Tafenoquine

Tafenoquine is an investigational long-acting primaquine analog with proven efficacy against malaria. The efficacy of the drug was illustrated in a randomized controlled trial of Thai soldiers. Further study is required before the drug is used.

Diagnose malaria swiftly and present to medical attention

Travellers who will remain in a malarious area for more than one week and will be unable to obtain medical advice within 24 hours of becoming ill, may be provided with an emergency regimen to self-medicate in the event of them documenting a temperature of 38 °C or more or an influenza-like illness. It is important that the breakthrough regimen is different from the medication taken for prophylaxis purposes. Medical advice should be sought as soon as possible thereafter.

A proposed self treatment regimen, as recommended by CDC, is included in Table 4. This regimen is contraindicated in persons with severe renal impairment. Persons who were already taking atovaquone/proguanil as prophylaxis or pregnant women or children weighing less than 11 kg cannot use this regimen.

Alternative regimens recommended by the Health Protection Agency Advisory Committee on Malaria Prevention for UK Travellers include:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adult dose</th>
<th>Pediatric dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atovaquone/proguanil</td>
<td>4 tablets (each dose contains 1,000 mg atovaquone and 400 mg proguanil) orally as a single daily dose for 3 consecutive days.</td>
<td>Daily dose to be taken for 3 consecutive days using adult strength tablets: 11–20 kg: 1 tablet 21–30 kg: 2 tablets 31–40 kg: 3 tablets ≥41 kg: 4 tablets</td>
</tr>
</tbody>
</table>

Table 4 Self treatment regimen for malaria.
• Co-artemether (20 mg artemether plus 120 mg lumefantrine per tablet): 6 doses of 4 tablets over a period of 60 hours for areas with multidrug resistant *P. falciparum*.
• Quinine plus doxycycline (200 mg quinine, 100 mg doxycycline): quinine 2 tablets 3 times a day for 3 days accompanied by 1 tablet of doxycycline twice daily for 7 days for areas with multidrug resistant *P. falciparum*.
• Chloroquine (150 mg chloroquine base- Nivaquine or 155 mg chloroquine base Avloclor): 4 tablets on days 1 and 2, 2 tablets on day 3 for areas with no chloroquine resistance and patients who were not receiving chloroquine prophylaxis. If already taking chloroquine, atovaquone-proguanil should be used instead.
• Quinine (300 mg tablet) 2 tablets 3 times a day for 5–7 days is recommended for pregnant women.
• Halofantrine is no longer recommended because of QT interval prolongation.54

**The long term traveller**

Data from the United Kingdom IPS (International Passenger Survey) indicate that the majority of travellers to malarious regions are those on short-term visits of less than one month.55 A considerable number of travellers, though, will remain in areas of malaria risk for long periods. These travellers should be advised keeping in mind that while the risk of drug side effects falls over time, the risk of contracting malaria continues to increase roughly linearly as exposure to the vector continues.56 At the same time, most antimalarials are not licensed for extended use because of lack of clinical experience. Individualized counselling is appropriate for these travellers, in order to discuss the most appropriate practical prophylactic regimen and the importance of other prevention measures. Guidelines on malaria prophylaxis in the case of the long-term traveller are provided by the Health Protection Agency Advisory Committee on Malaria Prevention for UK Travellers.56

**Malaria vaccines**

Research aimed at development of a malaria vaccine is currently ongoing. Substantial progress has been made during the past few years and one candidate vaccine, RTS,S/AS02, shows promise.57 The vaccine is aimed at inducing immunity to a malaria antigen expressed in the liver stage of the life cycle and to induce sterilizing immunity to sporozoites before they are transformed to merozoites. Unfortunately, complete protection is not achieved58 and studies are expected to evaluate its efficacy in preventing severe forms of malaria. No vaccine for primary or secondary prophylaxis of travellers is available at this time.

**Diagnosis of malaria in the returning traveller**

A recent study59 examined the epidemiology of imported malaria in Canadian children using cases diagnosed at British Columbia’s Children’s Hospital (BCCH) between 1984 and 2001. Malaria was diagnosed 42 times in 40 children. Twenty-four of 36 cases (66.7%) had seen from 2 up to more than 4 doctors before the diagnosis of malaria was made. This study underlines the difficulty of making a swift diagnosis of malaria in a clinical setting where the disease is otherwise unusual.

The diagnosis of malaria should be considered in any febrile individual who has traveled to or resided in a malarious region, even if only in transit (Fig. 1). The diagnosis should also be considered in cases of pyrexia of unknown origin, even if there is no known exposure since there have been cases of transmission in the USA where no clear link has been identified and nosocomial transmission in the UK through reuse of a heparin saline flush in consecutive patients.60 Malaria has also been transmitted by the use of a glucometer so a risk for nosocomial transmission exists if the diagnosis is not made promptly.61

Specific diagnostic methods include:

1. The gold standard for malaria diagnosis has been the combination of thick and thin smears examination by light microscopy,62 although deficiencies in its accuracy have been demonstrated in different settings.63,64 MMWR describes the appropriate technique for creation of the smears.62 Because the parasitemia is cyclical, smears should be taken every 6 to 12 hours for two or three consecutive days before the diagnosis is excluded. The first smear is positive in 95% of cases57 so if repeated smears are negative the diagnosis of malaria becomes progressively more remote. The thin smear is used for species diagnosis, based on morphological characteristics.

The thin smear also allows quantification of percentage of parasitized red cells, which is correlated with the severity of the clinical disease. The presence of hemoglobin, the malaria pigment in neutrophils, and of the more mature form of
the parasite should be evaluated because both of these factors are associated with a worse outcome.

The light microscopy characteristics of Plasmodium species are presented in Table 5.\textsuperscript{65}

Parasite densities are based on counting the asexual parasites seen relative to a given number of white blood cells. The ratio is then multiplied by the assumed number of white blood cells per microliter of blood. For example, if there are 30 parasites per 200 white blood cells on a thick smear and the patient has 8000 white blood cells/μL, 30 is multiplied by 40 (=8000/200) and the patient has approximately 1200 parasites per μL.

2. Fluorescent microscopy: The quantitative buffy coat technique (QBC), which utilizes acridine orange to stain the nucleic acid of the parasite is the best known. Compared to conventional microscopy this technique is 88 to 98% sensitive and 58 to 90% specific\textsuperscript{66} but the sensitivity drops dramatically with parasite counts <100 parasites/μL. The technique requires special training.

3. PCR based techniques: a number of PCR based techniques have recently been developed including some real-time PCRs.\textsuperscript{67,69,68} The techniques detect DNA, mRNA or small subunit rRNA specific to the Plasmodium and can be used for follow-up of treatment or for diagnostic purposes. PCR based techniques are extremely sensitive (in a specific study the sensitivity of the thick blood film was 72.3% compared to PCR\textsuperscript{69}), especially for low-grade parasitemias, and can also detect mixed infections.\textsuperscript{67} PCR based methods are labor intensive, expensive,
require expertise for interpretation and specialized equipment. The real-time PCR can be performed in one hour.

4. Antigen Detection Methods: These are methods developed primarily for use in the field. A small blood sample from a finger prick is used for rapid detection of a parasite antigen, either the histidine rich protein-2 (HRP-2), present only in \textit{P. falciparum}, or the parasite lactate-dehydrogenase (pLDH) antigen, produced by all four \textit{Plasmodium} species. Other antigens that have been evaluated include the \textit{Plasmodium} aldolase, an enzyme of the glycolytic pathway produced by all four species\textsuperscript{70} and an antigen specific to \textit{P. vivax}\textsuperscript{71} These rapid diagnostic tests have low sensitivities under 100 parasites/\mu l and they tend to be relatively expensive. Their use is also hampered by study design limitations, production and post-manufacture quality assurance but they are straightforward to interpret after appropriate training.\textsuperscript{72}

Performance characteristics of rapid diagnostic tests have been previously reviewed.\textsuperscript{73–75,72}

In general, rapid diagnostic tests do not differentiate non \textit{P. falciparum} species from one another and are, at best, only semiquantitative.\textsuperscript{72} Cross reactivity with rheumatoid factor appears to be a problem. HRP-2 persists in the blood after acute infection; thus, the tests remain positive even after therapy.

Well-designed studies of new generation rapid tests are needed before their use becomes widespread. Rapid malaria tests may be a useful diagnostic adjunct to microscopy in centers without major expertise in tropical medicine but expert microscopy is still required for species identification and confirmation.\textsuperscript{76}

5. Automated Systems: Automated systems, originally developed for different purposes, have also been proposed for malaria diagnosis. An example is the use of the Cell-Dyn 4000 analyzer (96% specificity and 62% sensitivity for malaria in general — 96% sensitivity for \textit{P. falciparum} malaria in patients with parasitemia levels of \(\geq 0.5\%\)).\textsuperscript{77} An advantage of this approach is that several laboratories already have the systems in place and no extra equipment needs to be purchased.

Treatment of malaria in the returning traveller

Rapid initiation of treatment for malaria after the diagnosis is established is necessary to avoid morbidity and mortality.\textsuperscript{78} Most symptomatic malaria infections are uncomplicated and the mortality is approximately 0.1% in the majority of cases of \textit{P. falciparum} malaria, if effective treatment is initiated. In the minority of patients with severe malaria, the mortality can be 15–20% despite treatment.\textsuperscript{79} The patient should be admitted to an appropriate hospital setting, depending on the severity of presentation.\textsuperscript{80} Treatment should not be initiated before the diagnosis is established because a fever in a returning traveler from the tropics will be malaria in less than 50% of cases.\textsuperscript{81} Thick and thin blood smears should be examined at least every 12 hours to monitor the efficacy of therapy until the parasitemia is below 1%. Smears should also be obtained at 3 days, one week and four weeks to exclude recurrence.

Recommended treatment for malaria, adapted from the Medical Letter,\textsuperscript{82} is included in the Table 6.

No medication kills all stages of the malaria parasite. The available drugs include

- Quinoline derivatives that include primaquine, that kills both intrahepatic forms and gametocytes, and the group of chloroquine, quinine, quinidine, amodiaquine, mefloquine, halofantrine that kill parasites in the intra-erythrocytic phase.
- Artemisinin derivatives that include artemisin, dihydroartemisin, artemether, artesunic acid or artesunate and artemelate.\textsuperscript{83} These drugs are active against all intraerythrocytic forms of the parasite and decrease parasite carriage as well.
- Antifolates, such as pyrimethamine, sulfonamides, dapsone and proguanil. These drugs kill intrahepatic forms of the parasite, but not hypnozoites. Pyrimethamine also kills gametocytes.
- Other medications including clindamycin, atovaquone, macrolides, pyronaridine, malarial protease inhibitors etc.

1. Chloroquine resistant \textit{P. falciparum}: Options for treatment include atovaquone-proguanil, mefloquine, an artemisinin derivative combination or a quinine based regimen.

a. Quinine based regimen: Commonly recommended is quinine sulfate 10 mg of salt/kg up to a maximum of 650 mg for three to seven days. The longer duration of treatment is recommended for infections originating from areas of relative quinine resistance\textsuperscript{84} or non-immune persons (a category which would include most returning travellers). Quinine should be combined with tetracycline/doxycycline or clindamycin (particularly for pregnant women or young children). Pyrimethamine/sulfadoxine can be used as the second drug when the
Table 6  Recommended treatment for malaria.

<table>
<thead>
<tr>
<th>P. falciparum acquired in areas of chloroquine-resistance</th>
<th>Adult dose</th>
<th>Pediatric dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORAL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drugs of choice:</td>
<td>Atovaquone/ proguanil</td>
<td>2 adult tabs twice daily or 4 adult tabs once daily x 3d</td>
</tr>
<tr>
<td>OR Quinine sulfate plus doxycycline or plus tetracycline or plus clindamycin</td>
<td>Mefloquine</td>
<td>650 mg q8h x 3-7d</td>
</tr>
<tr>
<td>Alternatives:</td>
<td>Artesunate plus mefloquine</td>
<td>750 mg followed 12 hrs later by 500 mg</td>
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<table>
<thead>
<tr>
<th>P. vivax acquired in areas of chloroquine-resistance</th>
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<tbody>
<tr>
<td><strong>ORAL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug of choice:</td>
<td>Quinine sulfate plus doxycycline</td>
<td>650 mg q8h x 3-7d</td>
</tr>
<tr>
<td>OR Mefloquine</td>
<td>750 mg followed 12 hrs later by 500 mg</td>
<td>15 mg/kg followed 12 hrs later by 10 mg/kg</td>
</tr>
<tr>
<td>Alternatives:</td>
<td>Chloroquine plus primaquine</td>
<td>25 mg base/kg in 3 doses over 48 hrs</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>All Plasmodium except Chloroquine-resistant P. falciparum and Chloroquine-resistant P. vivax</th>
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<tbody>
<tr>
<td><strong>ORAL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug of choice:</td>
<td>Chloroquine phosphate</td>
<td>1 g (600 mg base), then 500 mg (300 mg base) 6 hrs later, then 500 mg (300 mg base) at 24 and 48 hrs</td>
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</tbody>
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<table>
<thead>
<tr>
<th>All Plasmodium</th>
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<th></th>
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<tbody>
<tr>
<td><strong>PARENTERAL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug of choice:</td>
<td>Quinidine gluconate</td>
<td>10 mg/kg loading dose (max. 600 mg) in normal saline over 1–2 hrs, followed by continuous infusion of 0.02 mg/kg/min until PO therapy can be started</td>
</tr>
<tr>
<td>OR Quinine dihydro-Chloride</td>
<td>20 mg/kg loading dose in 5% dextrose over 4 hrs, followed by 10 mg/kg over 2–4 hrs q8h (max. 1800 mg/d) until PO therapy can be started</td>
<td>20 mg/kg loading dose in 5% dextrose over 4 hrs, followed by 10 mg/kg over 2–4 hrs q8h (max. 1800 mg/d) until PO therapy can be started</td>
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| Alternative: | Artemether | 3.2 mg/kg IM, then 1.6 mg/kg daily x 5-7d | 3.2 mg/kg IM, then 1.6 mg/kg daily x 5-7d |

**Prevention of relapses: P. vivax and P. ovale only**

| Drug of choice: | Primaquine phosphate | 30 mg base/d x 14d | 0.6 mg base/kg/d x 14d |
An update on malaria prevention, diagnosis and treatment for the returning traveller

infection is acquired in an area without sulfonamide resistance. Unfortunately, pyrimethamine/sulfadoxine resistance is now widespread, with Southeast Asia and eastern Africa having high rates of parasitologic failure.26

b. Atovaquone-proguanil: the drug is available as a fixed combination (250 mg atovaquone plus 100 mg proguanil hydrochloride in adult strength and 62.5 mg atovaquone and 25 mg proguanil hydrochloride in pediatric strength).85 It is a generally well tolerated medication, superior to mefloquine, and it is associated with high cure rates.

c. Artemisinin derivatives: Artemisins are derived from a plant called sweet wormwood (Artemisia annua). Not yet licensed in the United States and in many developed countries available only on a named patient basis, the artemisinin derivatives have emerged as a very useful component of the antimalarial armamentarium. No resistance to artemisinin derivatives has yet been exhibited.29 The different artemisinin derivatives (dihydroartemisin, artemether and artesunate) result in more rapid parasite clearance in vitro because of activity against immature parasite forms and they are roughly equivalent. They can be given intravenously, intramuscularly, orally or rectally and they have very few side effects, including transient gastrointestinal disturbance and rare allergic reactions. Concerns about neurotoxicity based on animal studies have not been verified in humans, with the exception of ototoxicity and the discrepancy is attributed to the different dosing used. If given alone, artemisinin derivatives should be given for five to seven days. However since late recrudescence is common when given as a single agent (10–15%), an artemisinin derivative should preferably be combined with another agent. When used in combination with other drugs, the same total dose (10 to 12 mg/kg) is given over a shorter period (usually three to five days). The most widely used regimen is the combination of artesunate (4 mg/Kg per day for three days) with either mefloquine or doxycycline. Studies have shown that the combination of different derivatives with mefloquine is more than 90% effective.89,90 The combination of artemether (20 mg) and lumefantrine (120 mg) is not available in the United States but it is available in Europe. It is given as four tablets for six doses over three days. The combination was recently evaluated by a Cochrane Systematic Review in comparison to other regimens for uncomplicated malaria: Nine trials (4547 participants) tested the six-dose regimen. Total failure at day 28 for artemether-lumefantrine was lower when compared with amodiaquine, amodiaquine plus sulfadoxine-pyrimethamine, but not with chloroquine plus sulfadoxine-pyrimethamine. In comparisons with artemisinin derivative combinations, artemether-lumefantrine performed better than amodiaquine plus artesunate, worse than mefloquine plus artesunate, and no differently to dihydroartemisinin-naphthoquine-trimethoprim.91 Recently, intravenous artesunate has also been shown to significantly reduce mortality in adults by 35% in complicated and severe malaria when compared to intravenous quinine (15% as opposed to 22%) ($p = 0.0002$).

d. Mefloquine: dividing the mefloquine in two doses improves tolerance.82 Mefloquine treatment is complicated by emergence of resistance that has decreased the efficacy of the drug dramatically.26 Using 25 mg/kg improves the chance of remaining parasite free and is recommended for travellers returning from high resistance areas.82 Mefloquine can be combined with other medications, including artemisinin derivatives. The combination of mefloquine with 10 mg of artesunate decreased treatment failures compared to mefloquine alone, according to a recent Cochrane Systematic Review.93

2. Chloroquine sensitive P. falciparum: It is probably safer to consider P. falciparum to be chloroquine resistant, because chloroquine resistance occurs everywhere except in Central America (and Hispaniola) and in some regions of southwestern Asia.26 A chloroquine sensitive P. falciparum can be treated as Chloroquine sensitive P. ovale, P. vivax and P. malariae.

3. Chloroquine sensitive P. ovale, P. vivax and P. malariae: Chloroquine resistant P. vivax isolates have been reported from India, South America, Southeast Asia and Africa but not all of them are equally clinically important.26 In Indonesian Papua resistance is almost uniform.94 Chloroquine resistant isolates can be treated with mefloquine or quinine sulfate plus doxycycline.95 Outside of these areas, chloroquine cure rates are excellent. The dose is 10 mg/kg of base followed by 5 mg/kg of base at 6, 24 and 48 hours (total of four doses). If oral treatment causes nausea, intravenous quinine (quinidine) can be used. The second arm of therapy is the prevention of relapse because chloroquine does not eliminate liver hypnozoites. Primaquine at 30 mg/kg for two weeks is recommended, after testing for G6PD deficiency. In patients with specific variants of deficiency, regardless of severity, 45 mg of base per week for eight weeks
can be given without significant hemolysis.\textsuperscript{96} If primaquine can not be given, oral chloroquine prophylaxis can be given instead for 12 months, but that will not prevent later relapses.

4. Treatment of malaria in pregnancy: the control of malaria infections is impaired in pregnancy.\textsuperscript{79} For \textit{P. falciparum} the adverse effects are greater in primigravidae and malaria also has detrimental effects on the fetus.\textsuperscript{97} There is insufficient research about treatment options in pregnancy\textsuperscript{98} but, from the available data, chloroquine, quinine and quinidine,\textsuperscript{44,99} clindamycin and progua-nil are safe, although folate supplementation is needed when proguanil is used. Data for artemisinin derivatives are still preliminary, but they appear to be safe. Mefloquine is associated with an increased risk of stillbirth (Odds ratio 4.72, CI 95% 1.7 to 12.7 compared to quinine\textsuperscript{100}). Tetracycline, doxycycline, primaquine and halofantrine are contraindicated in pregnancy. Primaquine and tetracyclines should also be avoided during breastfeeding.

5. Severe falciparum malaria: the criteria for "severe malaria" include severe anemia (Hematocrit less than 15\% in the presence of parasitemia of >10,000/\mu l), respiratory distress, cerebral malaria, renal failure, hypoglycemia, shock, coagulation failure, and for "complicated malaria" impaired consciousness of any degree plus prostration plus jaundice plus intractable vomiting plus parasitemia \(\geq 2\%\).\textsuperscript{101,102} These patients should be admitted to the Intensive Care Unit and receive close monitoring and support, including hemofiltration, mechanical ventilation and blood transfusions as necessary. Gram negative infections should always be excluded, since patients with \textit{P. falciparum} malaria are susceptible to other infections as well. Patients with severe malaria, as well as those unable to tolerate oral therapy, should be given parenteral, intravenous, therapy with quinine or an artemisin based regimen. Alternatives are IM artemether or artesunate, artemisin or artesunate suppository, or IM quinine in the thighs. When the patient improves, treatment can be changed to oral doxycycline or clindamycin.

Possible regimens include\textsuperscript{102–108}

- Quinine dihydrochloride 10 mg (salt) per kg by infusion over 4 hrs in 500 mls 5% dextrose, every 8 hours until parasites less than 1% and the patient can take by mouth, then quinine sulphate 600 mg three times a day orally until parasites have cleared, then doxycycline for seven days.
- Quinidine gluconate 10 mg/kg loading dose in normal saline (maximum 600 mg) over one to two hours, then continuous infusion of 0.02 mg/kg per minute until patient can swallow.
- Patients who have received other quinine derivatives or mefloquine within the last 12 hours should not receive a loading dose because of the risk of added toxicity. The dose of quinine or quinidine needs to be reduced by one-third to one-half after 48 hours. The patient should be attached to a cardiac monitor and the glucose level followed because of the associated hyperinsulinemia caused by the two drugs.
- Artesunate 2.4 mg/kg IV as a first dose followed by 1.2 mg/kg at 12 and 24 hours followed by 1.2 mg/kg once daily for six days, or Artemether 3.2 mg/kg IM followed by 1.6 mg/kg daily for six days or Artemisinin suppositories 40 mg/kg intrarectally followed by 20 mg/kg at 24, 48 and 72 hours followed by an oral drug.

Conflict of interest statement

All authors: no conflict of interest.

References