Malaria Chemoprophylaxis in the Age of Drug Resistance. I. Currently Recommended Drug Regimens

Kevin C. Kain, G. Dennis Shanks, and Jay S. Keystone

As international travel becomes increasingly common and resistance to antimalarial drugs escalates, a growing number of travelers are at risk for contracting malaria. Parasite resistance to chloroquine and proguanil and real or perceived intolerance among patients to standard prophylactic agents such as mefloquine have highlighted the need for new antimalarial drugs. Promising new regimens include atovaquone and proguanil, in combination; primaquine; and a related 8-aminoquinoline, tafenoquine. These agents are active against the liver stage of the malaria parasite and therefore can be discontinued shortly after the traveler leaves an area where malaria is endemic, which encourages adherence to the treatment regimen. Part 1 of this series reviews currently recommended chemoprophylactic drug regimens, and part 2 will focus on 8-aminoquinoline drugs.

Malaria is the most important parasitic disease in the world. Malaria incidence has increased during the last 2 decades, and it is now estimated that ~270 million people are infected annually, resulting in 1.5–2.7 million deaths [1]. This increase can be attributed, in large part, to the appearance and spread of *Plasmodium falciparum* that is resistant to antimalarial drugs [2]. Superimposed on this global resurgence in cases has been a major increase in travel to and emigration from countries where malaria is endemic. It was estimated that >650 million people crossed international boundaries in 1999; judging by current growth rates, this number will rise to 1 billion annually before 2010 [3]. Travel to areas where risk for malaria is high, such as sub-Saharan Africa, has increased >20-fold since the 1960s. As a result of the combination of increased travel to areas where malaria is endemic and escalating drug resistance, a growing number of travelers are at risk for contracting malaria. It is now estimated that as many as 30,000 travelers from industrialized countries contract malaria each year, with record numbers of cases being documented in North America and Europe [4–9]. However, the incidence likely is underestimated as a result of failure to take into account individuals who receive diagnosis and treatment abroad and because of the prevalence of underreporting.

The overall case-fatality rate associated with imported *P. falciparum* malaria varies from 0.6% to 3.8%. The fatality rate may be ≥20% among elderly patients or patients who have severe malaria, even when treatment is administered in modern intensive care units [4–9]. Yet malaria-associated deaths are largely preventable. Almost all fatal cases of imported malaria occur because the traveler did not use or did not comply with appropriate chemoprophylactic regimens, because of misdiagnosis by physicians or laboratories, or because the chosen prophylactic regimen was inappropriate. Recent reports of fatal cases of malaria in North America and Europe highlight these problems [5–8]. The majority of patients with fatal malaria either were not using chemoprophylaxis or used an inappropriate regimen, had a delay in the diagnosis of malaria, or received incorrect initial chemotherapy. A number of prophylaxis failures and several deaths resulting from malaria have been reported in travelers to Africa who were taking chloroquine or a combination of chloroquine and proguanil (CP), which highlights the need for more efficacious and acceptable drug regimens.
CHEMOPROPHYLAXIS AGAINST MALARIA

All travelers to areas where malaria is endemic need to be aware of the risk of contracting malaria, to understand that it is a serious infection, to know how to help prevent infection by using insect-protection measures and chemoprophylaxis (where appropriate), and to realize that medical attention should be sought immediately if they develop a fever during or after travel. Here, we only review currently recommended chemoprophylactic drugs [10–12]. We refer readers to part 2 of this series on malaria chemoprophylaxis [13] and elsewhere [10–12] for other important methods of malaria prevention, such as the use of insect repellents and insecticide-treated bed nets.

The potential adverse effects associated with the use of antimalarial drugs must be weighed against the risk of acquiring malaria. A traveler’s risk is estimated based on a detailed travel itinerary and specific risk behaviors of the traveler. The risk of acquiring malaria varies according to the geographic area visited (e.g., Africa vs. Southeast Asia), travel destination within different geographic areas (e.g., urban vs. rural), type of accommodation (camping vs. well-screened or air-conditioned sites), duration of stay (1-week business travel vs. 3-month overland trek), time of travel (high- or low-transmission season), elevation of destination (transmission is rare above 2000 m), and efficacy of and compliance with preventive measures (e.g., treated bed nets and chemoprophylactic drugs). Detailed sources for researching country-specific malaria risks are available online (listed in table 1) [10–12].

The following questions should be considered before antimalarial therapies are prescribed: Will the traveler be exposed to malaria in a region where the causative parasites are resistant to antimalarial drugs? Will the traveler have prompt access to medical care (including properly analyzed blood smears that were prepared with sterile equipment) if malaria symptoms occur? Are there any contraindications to the use of a particular drug?

An overview of antimalarial drug regimens based on drug-resistance zones is provided in figures 1 and 2 and in table 2. It is important to note that most travelers to low-risk areas such as urban areas and tourist resorts of Southeast Asia do not require antimalarial drugs, because the risk of infection is minimal. Travelers should be informed that personal protection measures and antimalarial drugs will markedly decrease the risk of contracting malaria, but that these interventions do not guarantee complete protection. The most important factors that determine the outcome of malaria are early diagnosis and appropriate therapy. Travelers and health care providers alike must consider and immediately rule out malaria when any febrile illness occurs during or after travel to an area where malaria is endemic.

CURRENT CHEMOPROPHYLACTIC DRUG REGIMENS

Antimalarial drugs are selected on the basis of individual risk assessment (as discussed earlier) and drug-resistance patterns (figures 1 and 2, tables 1 and 2) [10–12]. Chloroquine-resistant \textit{P. falciparum} \textit{(CRPF)} is now widespread in all areas of the world where malaria is endemic, except for Mexico, the Caribbean, Central America, Argentina, and parts of the Middle East and China. \textit{P. falciparum} that is resistant to chloroquine and mefloquine (MFQ) is still rare, except on Thailand’s borders with Cambodia and Myanmar (Burma). Resistance to sulfadoxine-pyrimethamine is now common in the Amazon Basin and Southeast Asia and is emerging in various regions of Africa. Chloroquine-resistant \textit{Plasmodium vivax} is also becoming an important problem, particularly in Papua New Guinea, West Papua (Irian Jaya), Vanuatu, Myanmar, and Guyana.

Areas with Chloroquine-Sensitive \textit{P. falciparum}

Chloroquine is the drug of choice for people who travel to areas where chloroquine resistance has not been reported. It is suitable for all ages and may be used during pregnancy. Except for its bitter taste, chloroquine is usually well tolerated. Dark-skinned people may experience generalized pruritus, which is not indicative of drug allergy. Retinal toxicity, which may occur with the long-term administration of high doses of chloroquine used for the treatment of other diseases, is extremely unlikely when chloroquine is given weekly for chemosuppression. Concurrent use of chloroquine interferes with antibody response to intradermal human diploid rabies vaccine [10–12].

Table 1. Selected Web site recommendations for information about country-specific malaria risk.

<table>
<thead>
<tr>
<th>Site sponsor (URL)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>US Centers for Disease Control and Prevention (<a href="http://www.cdc.gov">http://www.cdc.gov</a>)</td>
<td>See Travelers’ Health section. Online references include full-text Health Information for International Travel, 2001–2002, with full adult and pediatric recommendations, including malaria risks and recommendations. Information is also available via telephone (877-FYI-TRIP) or fax (888-232-3299).</td>
</tr>
<tr>
<td>World Health Organization (<a href="http://www.who.int/ith/">http://www.who.int/ith/</a>)</td>
<td>See International Travel and Health information resource page for travelers. Includes updates on country-specific malaria risk.</td>
</tr>
<tr>
<td>Health Canada (<a href="http://www.hc-sc.gc.ca/hpb/cdcdoshs/htm_e.html">http://www.hc-sc.gc.ca/hpb/cdcdoshs/htm_e.html</a>)</td>
<td>See recommendations and updates for preventing and treating malaria in travelers.</td>
</tr>
</tbody>
</table>
Figure 1. Map of areas in which malaria is endemic and of zones of drug resistance [11]. This map is meant only as a visual aid. Additional important details about malaria drugs and country-specific malaria risk are available online (see table 1). The presence of chloroquine-resistant organisms that cause malaria in the western provinces of Saudi Arabia has been confirmed.

Areas with CRPF
The most common options for chemoprophylaxis for travelers to areas with CRPF are MFQ, atovaquone-proguanil (AP; Malarone), and doxycycline. Less commonly, primaquine or CP may be used. Deciding which agent is best requires an individual assessment of risk of malaria and the specific advantages and disadvantages of each regimen (tables 2–4). For drugs such as MFQ, doxycycline, and CP to be optimally effective, they need to be taken for 4 weeks after the traveler leaves an area where malaria is endemic, although adherence to this component has traditionally been poor. Agents such as AP and primaquine are causal prophylactics that kill malaria parasites at the liver stage, and therefore they may be discontinued 1 week after the traveler leaves an endemic area. This advantage makes these agents attractive for high-risk but short-duration or repeated travel. It is important to note that none of these agents is ideal, and all carry a risk of adverse events that are distressing enough to travelers that ∼1%–7% will discontinue the prescribed drug regimen.

MFQ. MFQ is efficacious (protective efficacy, >90%) as a chemoprophylactic agent against drug-resistant P. falciparum and P. vivax [reviewed in 14–17]. It is currently listed as a drug of choice by the US Centers for Disease Control and Prevention and the World Health Organization for use as prophylaxis in most individuals who are traveling to high-risk regions where chloroquine-resistant parasites are known to exist [10, 12]. Although there is general agreement regarding MFQ’s efficacy, observational studies and anecdotal reports of excess neuropsychological adverse effects have raised concerns about the tolerability of this drug. Data from well-designed (prospective, randomized) trials do not appear to support this concern and indicate that, overall, MFQ is relatively well tolerated [reviewed in 14–17]. A systematic review of MFQ prophylaxis trials available in the Cochrane library yielded 5 randomized, comparative studies that failed to demonstrate significant differences between the overall adverse events or discontinuation rates associated with MFQ and those associated with other chemoprophylactic drug regimens [16, 17]. In randomized, placebo-controlled trials, sig-
significantly more participants discontinued use of MFQ (3.3% overall; 95% CI, 0.6%–6%; discontinuation was most commonly the result of gastrointestinal upset and dizziness) than use of placebo. In a recent randomized trial comparing MFQ with AP in >1000 nonimmune travelers, both agents were effective and well tolerated, but AP was better tolerated. The overall discontinuation rate for MFQ was 5%, and 3.9% of MFQ users discontinued the drug because of prophylaxis-associated neuropsychological events [18].

Approximately 25%–50% of MFQ users report side effects, the majority of which are mild and self-limited [14–17]. The most frequent adverse events reported by MFQ users are nausea, strange dreams, dizziness, mood changes, insomnia, headache, and diarrhea. Severe neuropsychiatric reactions (psychosis or convulsions) are infrequently reported with prophylactic doses (~1 per 10,000 users) [reviewed in 14]. Less severe but nonetheless troublesome neuropsychological adverse events (anxiety, depression, nightmares, etc.) that are disabling enough to result in drug discontinuation are reported in 0.2%–3.9% of users [14–18]. There is no evidence that the long-term use of MFQ (>1 year) is associated with additional adverse effects, and side effects may decrease with long-term use [10, 14].

Contraindications to the use of MFQ include a history of psychiatric illness, seizure disorder, or past severe reaction to MFQ [10–12]. MFQ should be prescribed with caution for pregnant women, especially during the first trimester, and for children who weigh <5 kg; MFQ is not recommended for travelers who have cardiac conduction disturbances or arrhythmia or for travelers who will be using quinine-like drugs concurrently (halofantrine and MFQ should not be used together) [10–12]. The manufacturer of MFQ also recommends that the drug be used with caution by drivers, pilots, and machine operators, because of concerns that it may affect spatial orientation and fine motor coordination.

For travelers in whom drug tolerance may be a concern, the use of a loading dose of MFQ should be considered. Data from several trials indicate that administration of MFQ once daily for 3 days before travel and then in standard weekly doses is an effective method of rapidly achieving therapeutic blood levels (in 4 days, compared with 7–9 weeks with standard weekly dosing of MFQ) [11, 15, 19]. Approximately 2%–3% of loading-dose recipients discontinued use of MFQ (most commonly because of gastrointestinal upset and dizziness), and most of these did so during the first week. Alternatively, use of MFQ can be initiated 2–3 weeks before travel [12]. Either strategy permits an assessment of tolerance before travel and allows a change to a suitable alternative if required.

**AP.** AP is a fixed-dose combination of atovaquone and proguanil hydrochloride. Atovaquone acts by inhibition of parasite mitochondrial electron transport at the level of the cytochrome b/c1 complex and collapses mitochondrial membrane potential [20]. Proguanil is metabolized to cycloguanil, which impedes the synthesis of folate cofactors required for parasite DNA synthesis. However, it appears that the mechanism of synergy of proguanil with atovaquone is not mediated through its cycloguanil metabolite. Rather, proguanil acts directly to enhance the ability of atovaquone to collapse mitochondrial membrane potential [20]. Resistance to atovaquone is associated with mutations in the cytochrome b gene [21, 22].

Volunteer challenge studies have established that atovaquone and proguanil have causal prophylactic activity (i.e., activity against the liver-stage parasite) [23]. For this combination to be effective for causal chemoprophylaxis, travelers need to take AP daily during periods of exposure and for only 1 week after departure from areas where malaria is endemic. The need for the traveler to complete 4 weeks of prophylaxis after exposure (a common reason for nonadherence) is thus avoided, and this regimen may be particularly useful for travelers who undergo short or repeated exposures in high-risk areas.

Three double-blind, randomized, placebo-controlled chemoprophylaxis trials have been conducted in semi-immune residents in Kenya, Zambia, and Gabon [24–26]. The overall efficacy of AP in preventing malaria in these trials was 98% (95%
CI, 91.9%–99.9%). The most commonly reported adverse events attributed to use of the study drug were headache, abdominal pain, dyspepsia, and diarrhea. However, it is of note that all adverse events occurred with similar frequency among individuals treated with placebo and those treated with AP, and there were no serious adverse events.

Studies among nonimmune travelers have recently been completed. In randomized, double-blind studies, ~2000 nonimmune subjects traveling to an area where malaria is endemic received AP daily, from 1–2 days before travel until 7 days after travel, or MFQ or CP, from 1–3 weeks before travel until 4 weeks after travel. Doxycycline and proguanil are taken daily, starting 1 day before the traveler enters malarial areas, during the stay, and for 4 weeks after departure. Atovaquone-proguanil and primaquine are taken once daily, starting 1 day before the traveler enters the endemic area, during the stay, and for 7 days after departure from the endemic area.

Contraindicated in glucose-6-phosphate dehydrogenase (G6PD) deficiency and during pregnancy. This drug is not presently licensed for use in preventing malaria. Doctors must assess the traveler’s G6PD level before prescribing this drug.

The combination of chloroquine and proguanil is less efficacious than mefloquine, doxycycline, or atovaquone-proguanil in these areas.

doxycycline has been shown to have efficacy equivalent to that of MFQ, with a reported protective efficacy of >90% [19, 30, 31]. Doxycycline is also efficacious as a prophylactic agent against malaria caused by MFQ-resistant P. falciparum, but it must be taken every day during travel. Noncompliance with this daily regimen is the major reason for failure of doxycycline to prevent malaria. Doxycycline is contraindicated during pregnancy, in women who are breast-feeding, and in children aged <8 years. The safety of long-term use (>3 months) of doxycycline has not been established. Doxycycline may cause gastrointestinal upset and, rarely, esophageal ulceration, which are less likely to occur if the drug is taken with food and copious amounts of fluid. It should not be taken simultaneously with Pepto-Bismol or antacids. Doxycycline may be photosensitizing in some people; use of a sunscreen (one that blocks ultraviolet A and B light) may reduce this problem. Doxycycline may also increase the risk of vaginal candidiasis; therefore, women at risk for yeast vaginitis should carry antifungal vaginal suppositories or cream or a treatment course of fluconazole.

**Primaquine.** Primaquine is an 8-aminoquinoline that has activity against both blood and tissue (liver) stages of malaria parasites and therefore can eliminate infections that are developing in the liver (causal prophylaxis). Randomized, controlled trials of the use of primaquine as a prophylactic agent (for children, 0.5 mg/kg base per day; for adults, 30 mg base per day) have demonstrated a protective efficacy of 85%–95% against both P. falciparum and P. vivax infections, but the agent is not currently licensed for this indication [reviewed in 13]. Use of primaquine is contraindicated in patients who have glucose-6-phosphate dehydrogenase deficiency or who are pregnant. If the risk of P. vivax infection is thought to be particularly high (e.g., among long-term expatriates and soldiers), consideration may be given to the use of primaquine to eliminate latent hepatic parasites (“terminal” prophylaxis); this is given at the conclusion of the standard posttravel chemoprophylactic agent against P. falciparum. The most commonly common adverse effects are gastrointestinal, and travelers can reduce these by taking AP with food. Additional data are required to establish the efficacy against non–P. falciparum malaria, and such trials are under way. Preliminary data from a randomized, controlled trial in nonimmune transmigrants in Papua indicate a protective efficacy of 84% (95% CI, 45%–95%) against P. vivax and 96% (95% CI, 71%–99%) against P. falciparum [29].

**Doxycycline.** Another alternative for people who are unable to take MFQ or AP is doxycycline. In comparative trials, doxycycline and proguanil were 0.2% versus 2% (P < .015) [18, 27]. In a comparative trial of AP versus doxycycline in 175 Australian military participants, AP was significantly better tolerated; use of this agent was associated with a lower rate of gastrointestinal adverse events (29% vs. 53%) [28].

These studies indicate that AP is a well tolerated and efficacious chemoprophylactic agent against P. falciparum. The most common adverse effects are gastrointestinal, and travelers can reduce these by taking AP with food. Additional data are required to establish the efficacy against non–P. falciparum malaria, and such trials are under way. Preliminary data from a randomized, controlled trial in nonimmune transmigrants in Papua indicate a protective efficacy of 84% (95% CI, 45%–95%) against P. vivax and 96% (95% CI, 71%–99%) against P. falciparum [29].

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**Table 2. Agents recommended for chemoprophylaxis against malaria for individuals traveling to areas in which malaria is endemic, according to zones of drug resistance.**

<table>
<thead>
<tr>
<th>Zone</th>
<th>Drug of choicea</th>
<th>Alternatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>No chloroquine resistance</td>
<td>Chloroquine</td>
<td>Mefloquine, doxycycline, or atovaquone-proguanil</td>
</tr>
<tr>
<td>Chloroquine resistance</td>
<td>Mefloquine, atovaquone-proguanil, or doxycycline</td>
<td>First choice, primaquinеб; second choice, combination of chloroquine and proguanilc</td>
</tr>
<tr>
<td>Chloroquine and mefloquine resistance</td>
<td>Doxycycline</td>
<td>—</td>
</tr>
</tbody>
</table>

**NOTE.** Protection from mosquito bites (insecticide-treated bed nets, DEET-based insect repellents, etc.) is the first line of defense against malaria for all travelers. In the Americas and Southeast Asia, chemoprophylaxis is recommended only for travelers who will be exposed outdoors during evening or nighttime in rural areas.

a Chloroquine and mefloquine are to be taken once weekly, beginning 1 week before the traveler enters the malarial area, during the stay, and for 4 weeks after departure. Doxycycline and proguanil are taken daily, starting 1 day before the traveler enters malarial areas, during the stay, and for 4 weeks after departure. Atovaquone-proguanil and primaquine are taken once daily, starting 1 day before the traveler enters the endemic area, during the stay, and for 7 days after departure from the endemic area.

b Contraindicated in glucose-6-phosphate dehydrogenase (G6PD) deficiency and during pregnancy. This drug is not presently licensed for use in preventing malaria. Doctors must assess the traveler’s G6PD level before prescribing this drug.

c The combination of chloroquine and proguanil is less efficacious than mefloquine, doxycycline, or atovaquone-proguanil in these areas.
### Table 3. Antimalarial drugs, doses for chemoprophylaxis, and adverse effects.

<table>
<thead>
<tr>
<th>Generic name (trade name)</th>
<th>Packaging</th>
<th>Adult dose</th>
<th>Pediatric dose</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atovaquone-proguanil</td>
<td>250 mg of atovaquone and 100 mg of proguanil (adult tablet)</td>
<td>See text; 1 tablet/day</td>
<td>See text; 1 tablet/day</td>
<td>Nausea, vomiting, abdominal pain, diarrhea, increased transaminase levels, seizures, rash</td>
</tr>
<tr>
<td>Chloroquine phosphate</td>
<td>150 mg base</td>
<td>300 mg base once/week</td>
<td>5 mg base once weekly; 5–6 kg, 25 mg base; 7–10 kg, 50 mg base; 11–14 kg, 75 mg base; 15–18 kg, 100 mg base; 19–24 kg, 125 mg base; 25–35 kg, 200 mg base; 36–50 kg, 250 mg base; &gt;50 kg or aged ≥14 years, 300 mg base</td>
<td>Pruritus in black-skinned patients, nausea, headache, skin eruptions, reversible corneal opacity, nail and mucous membrane discoloration, nerve deafness, photophobia, myopathy, retinopathy (with daily use), blood dyscrasias, psychosis, seizures, alopecia</td>
</tr>
<tr>
<td>Doxycycline (Vibramycin, Vibra- Tabs, Doryx)</td>
<td>100 mg</td>
<td>100 mg once/day</td>
<td>1.5 mg/kg once daily (maximum, 100 mg daily); &lt;25 kg or aged &lt;8 years, contraindicated; 25–35 kg, 50 mg; 36–50 kg, 75 mg; &gt;50 kg or aged ≥14 years, 100 mg</td>
<td>Gastrointestinal upset, vaginal candidiasis, photosensitivity, allergic reactions, blood dyscrasias, azotemia in renal diseases, hepatitis</td>
</tr>
<tr>
<td>Mefloquine (Lariam, Mephaquin)</td>
<td>250 mg base (salt, in the United States)</td>
<td>250 mg base once/week (228 mg base once/week in the United States)</td>
<td>&lt;5 kg, no data; 5–15 kg, 5 mg/kg once weekly; 15–19 kg, one-quarter tablet; 20–30 kg, one-half tablet; 31–45 kg, three-quarters tablet; &gt;45 kg, 1 tablet once weekly</td>
<td>Dizziness, diarrhoea, nausea, vivid dreams, nightmares, irritability, mood alterations, headache, insomnia, anxiety, seizures, psychosis</td>
</tr>
<tr>
<td>Primaquine</td>
<td>15 mg base</td>
<td>Terminal prophylaxis or radical cure: 15 mg base per day for 14 days&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Terminal prophylaxis or radical cure, 0.3 mg base/kg/day for 14 days&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Gastrointestinal upset, hemolysis (in patients with glucose-6-phosphate dehydrogenase deficiency), methemoglobinemia</td>
</tr>
<tr>
<td>Proguanil (Paludrine)</td>
<td>100 mg</td>
<td>200 mg daily; not recommended as a single agent for prophylaxis</td>
<td>5–8 kg, 25 mg (one-quarter tablet); 9–16 kg, 50 mg (one-half tablet); 17–24 kg, 75 mg (three-quarters tablet); 25–35 kg, 100 mg (1 tablet); 36–50 kg, 150 mg (1 and one-half tablets); &gt;50 kg or aged ≥14 years, 200 mg (2 tablets)</td>
<td>Anorexia, nausea, mouth ulcers</td>
</tr>
</tbody>
</table>

<sup>a</sup> In the United States, a pediatric formulation is available (one-quarter strength = 62.5 mg of atovaquone and 25 mg of proguanil).

<sup>b</sup> Chloroquine sulfate (Nivaquine) is not available in the United States and Canada, but it is available, in both tablet and syrup form, in most countries where malaria is endemic.

<sup>c</sup> Doses are increased to 30 mg base per day for primaquine-resistant or primaquine-tolerant *Plasmodium vivax*.

<sup>d</sup> Doses are increased to 0.5 mg base per kg of body weight per day for primaquine-resistant or primaquine-tolerant *P. vivax*. 
Table 4. Clinical utility scores for agents used for chemoprophylaxis against malaria.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Efficacy</th>
<th>Tolerance</th>
<th>Convenience</th>
<th>Causal</th>
<th>Cost</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mefloquine</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Chloroquine and proguanil</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Primaquine</td>
<td>2</td>
<td>2</td>
<td>1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Atovaquone-proguanil</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>11</td>
</tr>
</tbody>
</table>

**NOTE.** Efficacy: 1, <75%; 2, 75%–89%; 3, >90%. Tolerance: 1, occasional disabling side effects; 2, rare disabling side effects; 3, rare minor side effects. Convenience: 1, daily and weekly dosing required; 2, daily dosing required; 3, weekly dosing required. Causal: 0, no causal activity; 2, causal prophylactic (may be discontinued within a few days of leaving risk area). Cost: 1, >US$100 for 1 month of travel; 2, US$50–100; 3, <US$50. Scores and weighting are arbitrary and can be modified or individualized to specific travelers and itineraries.

<sup>a</sup> Requires a pretravel glucose-6-phosphate dehydrogenase level assessment, resulting in a lower convenience score.

prophylaxis regimen. More detailed information about primaquine is available in part 2 of this series [13].

**CP.** Another alternative for travelers who have contraindications against or intolerance to MFQ, AP, or doxycycline is the combination of weekly chloroquine and daily proguanil. This dosing schedule can be confusing to travelers, and to avoid potential toxicity (as might occur if chloroquine were taken daily), it needs to be carefully explained. Proguanil is not available in the United States but is available in Canada, Europe, and many endemic countries. Proguanil and chloroquine are considered to be safe to ingest during pregnancy [10–12]. Reported side effects associated with use of proguanil include gastrointestinal upset, mouth ulcerations, and hair loss. Travelers may lessen the gastrointestinal side effects by taking the drugs with meals. CP is more efficacious than chloroquine alone for travelers in sub-Saharan Africa, but it is less efficacious than doxycycline, MFQ, or AP. Studies performed from 1985 to 1991 involving short-term travelers in east Africa reported a protective efficacy of 72% (95% CI, 56%–82%) for CP versus 10%–42% for various doses of chloroquine [32]. In a more recent comparative trial in >1000 nonimmune travelers, minimum efficacy in the prevention of *P. falciparum* malaria was estimated to be 70% (95% CI, 35%–93%) for CP versus 100% (95% CI, 59%–100%) for AP [27]. In this trial, a significantly larger number of adverse events was reported among participants receiving CP (28%) than among those receiving AP (22%; *P* = .024), in particular, gastrointestinal events (20% vs. 12%; *P* = .001). Few recent data are available on the efficacy of CP outside of Africa (e.g., on the Indian subcontinent). A number of drug failures have been reported in travelers taking this combination, and users must be informed that they are taking a less efficacious regimen [6–8].

**Areas with Chloroquine- and MFQ-Resistant *P. falciparum***

In regions along the Thai-Myanmar and Thai-Cambodian border where parasites resistant to chloroquine and to MFQ are present, doxycycline is the chemosuppressive agent of choice. Limited data demonstrate that AP may also be effective in these areas.

**Azithromycin**

Azithromycin is an azalide antimicrobial agent that has been evaluated as a chemosuppressive agent in a number of studies. Although it is protective against *P. vivax* (>90%), its protective efficacy against *P. falciparum* (70%–83%) is generally considered to be too low for azithromycin to be relied on as a single agent to prevent *P. falciparum* malaria [30, 31].

**SPECIAL THERAPEUTIC CONSIDERATIONS**

**Pregnant and infant travelers.** Development of malaria during pregnancy is associated with significant maternal and perinatal morbidity and mortality. Use of the antimalarial regimens that are most effective against CRPF has not been adequately studied in pregnant women, especially during the first trimester. Travel by pregnant women or by women who might become pregnant to areas with high transmission rates of CRPF should be avoided or deferred if possible.

When an infant or a pregnant woman must travel to an area in which malaria caused by CRPF is endemic, the use of insect repellents and treated bed nets is strongly encouraged. When there is intense transmission of CRPF at the destination, the use of MFQ for chemoprophylaxis may be considered. Azithromycin, chloroquine, and proguanil, although safe to take during pregnancy, provide only partial protection in areas with CRPF.
There are insufficient data at present on the safety of taking AP during pregnancy. Most antimalarial drugs taken by breastfeeding mothers will be present in breast milk; however, drug concentrations in breast milk are not considered to be high enough to adequately protect the infant against malaria. For children who travel to chloroquine-sensitive areas, the chloroquine dose can be adjusted on the basis of weight (table 2). Chloroquine suspension is available in some destination countries but not in the United States or Canada. If the suspension is not available, chloroquine tablets can be ground by the pharmacist, and the weight-adjusted dose, combined with a filler, can be put into capsules. Once a week, the capsule can be opened and the chloroquine powder mixed into chocolate syrup, or something similar, to mask the bitter taste of the drug. The dose of MFQ can also be adjusted for children who weigh >5 kg. AP pediatric tablets (one-quarter strength) can be adjusted for children who weigh >15 kg. Use of doxycycline is contraindicated for pregnant women and for children aged <8 years.

HIV-infected travelers. P. falciparum malaria has been shown to increase HIV type 1 (HIV-1) replication and increase proviral loads and may cause faster progression of HIV-1 disease. HIV-1 infection also appears to make malaria worse and is associated with higher parasitemia infections and an increase in clinical malaria [33]. Therefore, insect-protection precautions and chemoprophylaxis appropriate to the itinerary are important for travelers infected with HIV.

In summary, the use of antimalarial drug regimens should be carefully directed at high-risk travelers where the benefit most clearly outweighs the risk of adverse events. None of the available regimens is ideal for all travelers, and the travel medicine practitioner should match the traveler’s risk of exposure to malaria to the appropriate regimen on the basis of drug efficacy, tolerance, safety, and cost. As a guide to facilitate decision-making, we have generated a clinical utility score in which different attributes of each drug regimen, such as efficacy, tolerance, convenience, and cost, are weighed on the basis of clinical trials and experience with these drugs (table 4). The scores assigned are arbitrary, and other groups and users may weigh each variable differently, depending on the specific needs of the patient and the risk of infection with drug-resistant organisms causing malaria. For example, a traveler to rural West Papua (Irian Jaya) may consider efficacy to be more important than cost or convenience.

References
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