Educating travelers about malaria: Dealing with resistance and patient noncompliance

**ABSTRACT**

Malaria is a risk to travelers in many parts of the world. Physicians need to tailor chemoprevention strategies to take into account resistance patterns. Patient education is important, especially for those travelers least likely to comply with prevention strategies. Most travelers who contract malaria do not become ill until they return home, so recognition and treatment are crucial.

**KEY POINTS**

- Health information should be targeted to travelers who are likely to use suboptimal chemoprophylaxis or may be non-compliant with prophylaxis—men and people traveling alone.
- Mosquito bed nets, insecticides, insect repellents, and preventive drugs effectively reduce the risk of malaria.
- Plasmodia have developed resistance to traditional preventive drugs, including chloroquine and sulfadoxine-pyrimethamine, in vast areas of the world.
- Mefloquine (taken weekly), doxycycline (taken daily), and atovaquone-proguanil (taken daily) are the preventive drugs of choice in most areas.
- Chloroquine is still effective in Haiti, the Dominican Republic, Central America west of the Panama Canal Zone, Egypt, and most countries in the Middle East; in other areas, plasmodia have gained resistance to it.

This paper was funded by an unrestricted grant provided by Hoffmann-La Roche Inc.

**FOR PHYSICIANS** counseling patients going to Africa, Asia, or other tropical areas, the problem of malaria prevention is growing more complex.

Chemoprevention must be tailored to a patient’s travel itinerary because of the growing problem of resistance. For instance, chloroquine, once the mainstay of chemoprevention, is no longer effective in Africa, but still is effective in Haiti.

Compliance with chemoprevention is a problem, especially with young travelers and those traveling for more than a month, and physicians need to focus their prevention message to them.

Finally, most travelers who contract malaria do not become ill until they return home, so physicians must know how to recognize and treat the disease.

**A WORLDWIDE PROBLEM**

Malaria affects approximately 300 million persons worldwide and kills about 1 million people each year. Almost 90% of these deaths occur in sub-Saharan Africa, which has the largest number of cases and where children are the most affected. Malaria is endemic in more than 100 countries and territories (FIGURE 1).

**TRAVELERS OFTEN EXPOSED**

The risk to a nonimmune traveler of acquiring malaria ranges from a relatively low 0.01% in Central America to 8% in the Solomon Islands.

Many more travelers are exposed to malar-
ia without developing symptoms. For example, Jelinek et al \(^3\) found that 48.8% of travelers returning from independent trips to sub-Saharan Africa tested positive for circumsporozoite (CS) antibodies, indicating they had been infected with falciparum malaria. Exposure was much lower in travelers on package tours to the same areas: only 5.6%.

**LIFE CYCLE OF MALARIA**

Humans acquire malaria from the bite of female Anopheles mosquitoes infected with plasmodia, a protozoan (FIGURE 2). Four species of plasmodia infect humans: *Plasmodium falciparum*, *P vivax*, *P ovale*, and *P malariae*.

Plasmodia have a complex life cycle. They are injected into the blood stream as sporozoites—their infective, motile stage—which travel rapidly from the mosquito saliva to the human liver cells. In the hepatocytes, sporozoites mature to a multinucleated stage capable of asexual reproduction, called tissue schizonts. These contain large numbers of infectious daughters, or merozoites.

Merozoites rupture from the liver cell and pour into the blood stream to invade erythrocytes. Once inside the red blood cells, the parasite matures through a series of asexual erythrocytic stages: ring, trophozoite, and schizont. After 48 to 72 hours, the schizont lysesthe host erythrocyte, freeing up to 332 merozoites, which then invade other erythrocytes, thus repeating the cycle. Toxins are released into the blood, making the patient feel sick.

**Differences among plasmodia**

*P falciparum* can result in higher levels of parasitemia than the other species of *Plasmodia* because it can invade erythrocytes of all ages. In contrast, *P vivax* and *P ovale* invade only young cells.\(^4\)

On the other hand, *P vivax* and *P ovale* have persistent liver stages, called hypnozoites, that can remain dormant in the liver for 11 months or more. When the hypnozoites finally mature to tissue schizonts and release merozoites, they can cause either a relapse or a delayed primary attack. (A delayed primary attack occurs if the patient was taking chemoprophylactic drugs and did not develop symptomatic parasitemia within 4 weeks after the initial infection.)

**No protective immunity**

It is important to note that there is no protective immunity to malaria—one can become infected multiple times with the same or other species. However, multiple infection does confer a state of “partial immunity” that attenuates the severity of the infection. In other words, if you are lucky enough to survive your first few infections then you may acquire subsequent infections with minimal symptoms, eg, a slight fever for a few days, but not cerebral malaria.

**PREVENTION STRATEGIES**

All persons who intend to visit malarious areas should be aware of the risk, know how to help prevent the disease, and understand the importance of obtaining medical attention immediately in the event of fever during or after travel (see Protecting yourself against malaria, page 480).

**AVOIDING MOSQUITO BITE**

The best way to prevent malaria is to avoid exposure to the Anopheles mosquito. This is
**Life cycle of *Plasmodium***

1. Female *Anopheles* mosquito bites human, injecting plasmodial sporozoites.

2. Sporozoites infect hepatocytes and reproduce asexually, producing daughter cells called merozoites.

3. Merozoites enter red blood cells and reproduce asexually; some merozoites form gametocytes, the parasite’s sexual stage.

4. Gametocytes are ingested by another mosquito, fuse, and produce a new generation of sporozoites.

_Some merozoites can remain dormant in the liver for long periods._

_Photo courtesy of Dr. Dickson Despommier._
sometimes difficult because many accommodations in tropical and subtropical countries lack window screens.

**Mosquito bed nets** can be useful, particularly if the net is treated every 6 months with permethrin (300–500 mg/m²) or deltamethrin.⁵

**Insect repellents.** Use of insect repellents on exposed skin should be encouraged. Those containing N,N-diethyl-3-methylbenzamide (DEET) are the most effective. High concentrations of DEET are not necessary for effective protection. Hour Guard, a 35% DEET polymer formulation (3M Corporation, St. Paul, MN) provides up to 12 hours of protection, depending on the species of mosquito and environmental conditions.⁶ DEET-based repellents used in combination with permethrin-treated clothing can provide nearly complete protection against mosquito bites.⁶

Concerns about the neurotoxicity of DEET in children are generally misplaced. Fourteen cases of encephalopathy have been reported, but these cases were not due to DEET exposure. The possibility of neurotoxicity should be considered in patients receiving DEET in high concentrations, but it is not a major concern in the general population.⁷

---

**TABLE 1**

**Drugs used in malaria prophylaxis* **

<table>
<thead>
<tr>
<th>Drug</th>
<th>Use</th>
<th>Adult dose:</th>
<th>Pediatric dose:</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Chloroquine (Aralen)</em></td>
<td>Use: In areas with chloroquine-sensitive <em>P falciparum</em></td>
<td>300 mg base (500 mg salt) orally, once weekly</td>
<td>5 mg/kg; (salt: 8.3 mg/kg), orally once weekly, up to the maximum adult dose of 300 mg base</td>
</tr>
<tr>
<td><strong>Pediatric dose:</strong></td>
<td></td>
<td></td>
<td>300 mg base</td>
</tr>
<tr>
<td><strong>Adverse reactions:</strong></td>
<td></td>
<td></td>
<td>Mild nausea, blurred vision, headache, psoriasis flare-ups; itching in dark-skinned persons; very rare agranulocytosis, photosensitivity, neuropsychiatric effects</td>
</tr>
<tr>
<td><strong>Contraindications:</strong></td>
<td></td>
<td></td>
<td>Hypersensitivity to 4-aminoquinolone derivatives; retinal or field changes attributable to drug therapy; psoriasis; use with caution in patients with liver disease or alcoholism</td>
</tr>
<tr>
<td><em>Mefloquine (Lariam)</em></td>
<td>Use: In areas with chloroquine-resistant <em>P falciparum</em></td>
<td>228 mg base (250 mg salt) orally, once weekly</td>
<td>&lt; 15 kg: 4.6 mg/kg base (salt: 5 mg/kg) orally once weekly</td>
</tr>
<tr>
<td><strong>Pediatric dose:</strong></td>
<td></td>
<td></td>
<td>15–30 kg: 1/3 tab/week</td>
</tr>
<tr>
<td><strong>Adverse reactions:</strong></td>
<td></td>
<td></td>
<td>Nausea and vomiting (3%); other adverse reactions (≤ 1%) include abdominal pain, anorexia, arthralgia or myalgia, chills, diarrhea, dizziness, ECG changes, extrasystoles, fatigue, fever, first-degree AV block, headache, skin rash, syncope, or tinnitus</td>
</tr>
<tr>
<td><strong>Contraindications:</strong></td>
<td></td>
<td></td>
<td>Hypersensitivity to related compounds such as quinine; active depression or a history of seizures or severe psychiatric disorders; use with caution in patients with cardiac conduction abnormalities</td>
</tr>
<tr>
<td><em>Doxycycline (Vibramycin)</em></td>
<td>Use: Alternative to mefloquine</td>
<td>100 mg orally, once daily</td>
<td>&gt; 8 years of age: 2 mg/kg orally per day</td>
</tr>
<tr>
<td><strong>Pediatric dose:</strong></td>
<td></td>
<td></td>
<td>up to adult dose of 100 mg</td>
</tr>
<tr>
<td><strong>Adverse reactions:</strong></td>
<td></td>
<td></td>
<td>Photosensitivity reactions to doxycycline after sunlight (UV) exposure can occur; discontinue at the first sign of erythema; skin reactions can increase when used with sulfonamide, sulfonylureas, or thiazide diuretics</td>
</tr>
<tr>
<td><strong>Contraindications:</strong></td>
<td></td>
<td></td>
<td>Hypersensitivity to any of the tetracyclines; some commercially available preparations contain sulfites that can result in increased asthmatic attacks in such persons, as well as anaphylaxis</td>
</tr>
<tr>
<td><em>Hydroxychloroquine (Plaquenil)</em></td>
<td>Use: Alternative to chloroquine</td>
<td>310 mg base (400 mg salt) orally, once weekly</td>
<td>5 mg/kg; (salt: 6.5 mg/kg), orally, once weekly up to maximum adult dose of 310 mg base</td>
</tr>
<tr>
<td><strong>Adverse reactions:</strong></td>
<td></td>
<td></td>
<td>Same as for chloroquine</td>
</tr>
<tr>
<td><strong>Contraindications:</strong></td>
<td></td>
<td></td>
<td>Same as for chloroquine</td>
</tr>
<tr>
<td><em>Atovaquone + proguanil (Malarone)</em></td>
<td>Use: In areas with chloroquine-resistant <em>P falciparum</em></td>
<td>Each tablet contains atovaquone 250 mg/ proguanil 100 mg; adults, adolescents, and children ≥ 3 years of age weighing &gt; 40 kg: 1 tablet orally once daily</td>
<td>≥ 3 yrs old and 31–40 kg: 3 oral tablets once daily</td>
</tr>
<tr>
<td><strong>Pediatric dose:</strong></td>
<td></td>
<td></td>
<td>≥ 3 yrs old and 21–30 kg: 2 oral tablets once daily</td>
</tr>
<tr>
<td><strong>Adverse reactions:</strong></td>
<td></td>
<td></td>
<td>Nausea, vomiting, headache, diarrhea, asthenia, anorexia, dizziness, pruritus</td>
</tr>
<tr>
<td><strong>Contraindications:</strong></td>
<td></td>
<td></td>
<td>Any known hypersensitivity to proguanil or atovaquone</td>
</tr>
</tbody>
</table>

*Refer to the manufacturer’s complete product information for additional descriptions of these agents.
reported, 13 in children younger than 8 years; all but three of the children recovered without sequelae. Most had used DEET long-term, in excessive amounts, or otherwise inappropriately.6

As with any product, the labeling and instructions should be read and understood before use.

Staying inside at night. The Anopheles mosquito feeds from dusk to dawn. The risk of malaria is reduced by limiting evening exposure to mosquitoes, or, if traveling from a malaria-free urban area to the malarious countryside on day trips, returning to the city before dusk.7

### CHEMOPROPHYLAXIS

Most travelers to high-risk, malaria-endemic areas should also take a preventive drug (TABLE 1).8,9 The decision to give a chemoprophylactic drug (and which one to give) depends on:
- Expected exposure to malaria
- Expected exposure to drug-resistant P falciparum
- The availability of prompt medical care should malaria occur
- Any contraindications to a chemoprophylactic agent.

The most commonly prescribed drugs in the United States for preventing malaria are chloroquine (Aralen), mefloquine (Lariam) doxycycline (Vibramycin), and the combination drug atovaquone and proguanil (Malarone). The combination of sulfadoxine and pyrimethamine is no longer used for chemoprophylaxis and is reserved for presumptive therapy in the event of febrile illness. Since November 2000, the Centers for Disease Control and Prevention (CDC) has recommended mefloquine, atovaquone-proguanil, or doxycycline for malaria chemoprophylaxis in areas with chloroquine-resistant malaria. Chloroquine combined with proguanil is no longer recommended.10

Recently updated maps identifying risk areas are available from many sources on the Internet:
- The CDC at www.cdc.gov
- The World Health Organization (WHO) at www.who.int

Since November 2000, the Centers for Disease Control and Prevention (CDC) has recommended mefloquine, atovaquone-proguanil, or doxycycline for malaria chemoprophylaxis in areas with chloroquine-resistant malaria. Chloroquine combined with proguanil is no longer recommended.10

Recently updated maps identifying risk areas are available from many sources on the Internet:
- The CDC at www.cdc.gov
- The World Health Organization (WHO) at www.who.int

#### TABLE 2

<table>
<thead>
<tr>
<th>DESTINATION</th>
<th>MEDICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>Mefloquine or atovaquone-proguanil</td>
</tr>
<tr>
<td>Asia</td>
<td>Mefloquine (except Thailand, Myanmar, Cambodia) or atovaquone-proguanil</td>
</tr>
<tr>
<td>Cambodia</td>
<td>Doxycycline or atovaquone-proguanil</td>
</tr>
<tr>
<td>Caribbean</td>
<td>Chloroquine</td>
</tr>
<tr>
<td>Central America (west of the Panama Canal)</td>
<td>Chloroquine</td>
</tr>
<tr>
<td>Dominican Republic</td>
<td>Chloroquine</td>
</tr>
<tr>
<td>Egypt</td>
<td>Chloroquine</td>
</tr>
<tr>
<td>Haiti</td>
<td>Chloroquine</td>
</tr>
<tr>
<td>India</td>
<td>Mefloquine or atovaquone-proguanil</td>
</tr>
<tr>
<td>Middle East</td>
<td>Chloroquine</td>
</tr>
<tr>
<td>Myanmar</td>
<td>Doxycycline or atovaquone-proguanil</td>
</tr>
<tr>
<td>South America</td>
<td>Mefloquine or atovaquone-proguanil</td>
</tr>
<tr>
<td>Thailand</td>
<td>Doxycycline or atovaquone-proguanil</td>
</tr>
</tbody>
</table>

P falciparum has become resistant to chloroquine in many countries.

Chloroquine

Chloroquine inhibits the parasite’s production of heme, a toxic byproduct of hemoglobin digestion.11 It has been the principal antimalarial drug in use worldwide for almost 50 years.

However, P falciparum has become resistant to chloroquine in many areas of the world (FIGURE 1). Resistance to chloroquine (and to sulfadoxine-pyrimethamine) is widespread in sub-Saharan Africa, Thailand, Myanmar, Cambodia, and the Amazon basin area of South America. Other chemoprophylactic agents should be considered for travelers to these countries. The drug is still effective in Haiti, the Dominican Republic, Central America west of the Panama Canal Zone, Egypt, and most countries in the Middle East.9
Hydroxychloroquine
Hydroxychloroquine is used less often than chloroquine and carries the same potentially severe adverse reactions. It is not effective against chloroquine-resistant Plasmodia. Both hydroxychloroquine and chloroquine are contraindicated in patients with any ocular disease, especially retinal diseases such as macular degeneration. Retinopathy has been reported with long-term use of these drugs. They should be used cautiously in patients with hepatic disease or alcoholism.

Mefloquine
Mefloquine kills schizonts in the blood, but its exact mechanism of action is not known. It has superseded chloroquine as the standard antimalarial chemoprophylactic agent, and the CDC recommends it for travelers to most regions where Plasmodia is resistant to chloroquine. However, resistance to mefloquine has been confirmed in limited areas of Thailand and the western provinces of Cambodia, with possible mefloquine-resistant strains in the Amazon Basin.

Mefloquine has a half-life of about 3 weeks and is highly effective in preventing malaria caused by P. falciparum and P. vivax. Taking a 250-mg mefloquine tablet once weekly has resulted in a 91% prophylactic effectiveness in East Africa, 99.8% in sub-Saharan Africa, and 100% in the Indonesian province of Irian Jaya. Italian soldiers deployed to Mozambique who received a combination of chloroquine and proguanil experienced 17 cases of malaria per 1,000 soldiers per month. When the combination was replaced by mefloquine, the rate dropped to 1.8.

Neuropsychiatric adverse reactions associated with mefloquine include psychosis, confusion, depression, and hallucinations, as highlighted in case reports. Weinke et al. calculated the incidence of mefloquine-related neuropsychiatric side effects as 1 in 8,000 among patients who took the drug as therapy for malaria, and 1 in 13,000 among those using it for chemoprophylaxis. In multiple clinical trials, rates of serious neuropsychiatric reactions were not significantly greater with prophylactic dosages of mefloquine than with alternative agents.

Milder neuropsychiatric effects such as vivid dreams, insomnia, and vertigo are seen more commonly with mefloquine than with the combination atovaquone and proguanil.

Nonetheless, patients with active neuropsychiatric conditions need to be monitored when using mefloquine for long periods, and they should not take mefloquine to prevent malaria if they have active depression, a history of seizures, or severe psychiatric disorders. Since 70% of such problems occur within the first three doses, travelers should start taking mefloquine before they depart, making them less likely to stop taking the drug on their own because of side effects and go without any chemoprevention whatsoever.

Patients should take mefloquine with food, as food increases its bioavailability without affecting its elimination half-life. Concurrent use of mefloquine and chloroquine, quinine, or quinidine may result in an increased risk of seizures and electrocardiographic abnormalities.

Doxycycline
Doxycycline attacks the parasite both in the liver and in the red blood cells by preventing its ribosomes from producing proteins. It is effective against multidrug-resistant P. falciparum and is the most effective prophylactic drug for travelers to malaria-endemic areas of Thailand bordering Myanmar and Cambodia. However, in a study in American troops in Somalia, the attack rate of falciparum malaria was five times higher among users of doxycycline than among users of mefloquine.

Doxycycline can cause photosensitivity; therefore, sunscreens and protective clothing are needed during the daylight hours. Daily dosing is necessary because of its relatively short half-life of 16 hours.

Proguanil
Proguanil inhibits dihydrofolate reductase, disrupting the ability of the parasite to synthesize nucleic acids in its pre-erythrocytic phase. Proguanil has been used since the mid-1940s, but when used alone has an effectiveness of only slightly more than 50%. A regimen of proguanil once a day plus chloroquine once a week is more effective, but still...
much less effective than other alternatives. This drug is not available in the United States.

**Atovaquone-proguanil**

Atovaquone prevents parasite replication by selectively inhibiting mitochondrial electron transport. A new combination of atovaquone and proguanil (Malarone) is reported to act synergistically against blood parasites, although the exact mechanism of this synergy is unknown.

The atovaquone-proguanil combination is effective against early liver stages of malaria and is therefore an effective prophylactic. However, it is not effective in killing the hypnozoite stage of *P. vivax* or *P. ovale*. Therefore, travelers still need to take primaquine as “terminal prevention” after returning home if they have had extensive exposure to these strains of malaria.

In studies of atovaquone-proguanil as chemoprophylaxis against *P. falciparum*, the effectiveness rates ranged from 95% to 100% in semi-immune subjects.

A study in nonimmune travelers compared atovaquone-proguanil with chloroquine-proguanil. Most people experienced at least one adverse reaction with either combination, although those taking atovaquone-proguanil had significantly fewer gastrointestinal problems. Both combinations were almost 100% effective.

Another study in nonimmune travelers compared atovaquone-proguanil (taken once daily) with mefloquine (taken once a week). The drugs were equally effective, but side effects were fewer and less severe with atovaquone-proguanil.

Atovaquone should be taken with meals. If the patient has difficulty with this, consider alternate treatment. Patients with certain types of gastrointestinal disease may have decreased atovaquone absorption.

**Primaquine as terminal prevention**

Certain *Plasmodium* species (*P. vivax* and *P. ovale*) are known to produce relapsing malaria infections years after a person has left a malarious country or has stopped taking preventive malaria medication. For this reason, the CDC advises that travelers who have had prolonged exposure to malaria (for example, Peace Corps workers or missionaries) should consider using primaquine to kill the dormant liver stage (hypnozoite) of the malaria parasite.

Primaquine must not be used in those deficient in G6PD enzyme, owing to the risk of hemolytic anemia. A test for G6PD is mandatory before taking primaquine.

The standard adult dose of primaquine is 15 mg base (26.3 mg salt) once daily for 14 days after leaving the malarious area.

**When to start, when to stop**

Each antimalarial drug is taken on a specific schedule based on its pharmacokinetic and antiplasmodial properties.

- **Chloroquine** should be started 2 weeks before departure and continued for 4 weeks after return.
- **Mefloquine** should be started 1 week before departure and continued for 4 weeks after return.
- **Doxycycline** should be started 1 to 2 days before departure and continued for 4 weeks after return.
- **Atovaquone-proguanil** should be started 1 to 2 days before departure and continued for 1 week after return.

**SPECIAL POPULATIONS**

**Nursing infants**

Minute amounts of antimalarial drugs are secreted in breast milk. This is not believed to be toxic to the nursing infant. However, if this is a concern, a decision should be made to discontinue either the drug or the breast-feeding. The importance of the drug to the mother must be considered.

The amount of antimalarial drug secreted in breast milk is not enough to prevent malaria in the infant; therefore, infants who require protection against malaria need to receive antimalarial drugs in recommended doses (Table 1).

**Infants and children**

Severe malaria is common among infants and children in areas where transmission is intense, so chemoprophylaxis is essential for children of all ages.

According to the CDC, mefloquine is
well tolerated by infants weighing less than 15 kg (6.8 lb) and can be used in children who are traveling to regions with chloroquine-resistant P falciparum. Experience is limited in infants younger than 3 months and weighing less than 5 kg, and the safety of mefloquine has not been established in those younger than 6 months.

Atovaquone-proguanil is available in a pediatric tablet for children weighing 11 kg or more. Doxycycline is contraindicated in children younger than 8 years. Chloroquine remains the agent of choice in areas with chloroquine-sensitive malaria.

Giving proper doses of antimalarial medication to children can be difficult. No liquid preparations of commonly used antimalarial medications are available in the United States. Chloroquine and mefloquine are bitter. If the tablets are crushed, the bitter taste must be masked by mixing the powder with sweet syrup or by placing it in food or a capsule. These extemporaneous dosing forms are not approved by the US Food and Drug Administration but are widely used; to ensure accurate dosing, a pharmacist should prepare them.

HIV-infected patients
Many HIV-infected persons travel from temperate zones to tropical and subtropical destinations. While concern about opportunistic infections in HIV-positive persons is justified, research does not indicate a biological link between malaria and HIV infection. Malaria is not an opportunistic infection, is not exacerbated by HIV (as are toxoplasmosis and cryptosporidiosis), and does not hasten the clinical progression of HIV infection.

Generally, most HIV-infected travelers have a low risk of severe health problems if they adhere to the same sound medical advice given to HIV-negative travelers. However, one needs to anticipate HIV-specific immigration issues, the medical resources available abroad, and problems regarding travel with multiple medications.

In addition, when prescribing specific chemoprophylactic agents, you need to consider the stage of immunodeficiency and drug interactions with antiretroviral drugs. For example:

- Didanosine may decrease the bioavailability of doxycycline, owing to the buffering agents used in didanosine tablets or powder. Delayed-release didanosine capsules do not contain a buffering agent and would not be expected to interact with tetracycline antibiotics.
- The combination of lopinavir and ritonavir decreases the plasma levels of atovaquone. The clinical significance is unknown, but an increase in atovaquone dosage may be required.
- Rifampin (used to treat tuberculosis, an opportunistic infection in HIV-infected patients) is a potent inducer of the cytochrome P450 hepatic enzyme system and can reduce the plasma concentrations and possibly the efficacy of atovaquone.
- Sulfadoxine and pyrimethamine should not be used concurrently with sulfamethoxazole-trimethoprim (used in Pneumocystis carinii prophylaxis) or other sulfonamides, because the adverse effects of the drugs may be additive.
- In vitro data involving mefloquine indicate that the formation of its metabolite may be inhibited by drugs metabolized by the cytochrome P450 3A4 isoenzyme, such as the protease inhibitors indinavir and nelfinavir. However, pharmacokinetic profiles of HIV-infected patients who took mefloquine for malaria chemoprophylaxis show that the metabolism of mefloquine was not inhibited by the protease inhibitors.

COMMON ERRORS

Studies of Western travelers who contracted malaria reveal several common errors: they didn’t take precautions to avoid mosquito bites, they didn’t take a preventive drug, or they received an ineffective drug (eg, chloroquine in an area of chloroquine resistance).

Muehberger et al studied 51 German travelers who contracted malaria in Kenya and found that ineffective chemoprophylaxis and lack of prophylaxis were the principal reasons. Ineffective chemoprophylaxis was primarily the result of inappropriate medical advice (88%). Most patients (58%) who did not comply with medical advice did so because of carelessness or concern about side effects. Malaria Dardick
effects. Diagnosis and medical care were unnecessarily delayed in 28% of cases; this was primarily due to failure to examine blood smears in a timely manner. The researchers concluded that 94.5% of cases associated with inappropriate medical advice could have been prevented by giving an effective prophylactic medication.

The CDC\(^2\) has reported 4,685 cases of imported malaria in American travelers between 1992 and 2001 (not counting military personnel and non-US citizens). Of these patients, 19% had received an inappropriate chemoprophylactic regimen and 56% took no chemoprophylactic medication. The most common inappropriate chemoprophylaxis was chloroquine in areas with known chloroquine resistance. During January through March 2001, two American citizens died of malaria after taking chloroquine alone or chloroquine plus proguanil in countries with chloroquine-resistant malaria.

Who is least compliant?
Lobel et al\(^4\) recently surveyed travelers returning to North America and Europe from Africa and found that 97% were aware of the risk of malaria and more than 90% received medical advice before going. More than 95% used chemoprophylaxis, but only 62% used both regular chemoprophylaxis and two or more antimosquito measures. Adherence to drug therapy was lowest for travelers:
- Who took a daily medication rather than a weekly one
- Who believed they had an adverse event related to the drug
- Younger than 40 years
- Traveling for more than 1 month.

About 95% of the Americans were taking an effective regimen, ie, mefloquine or doxycycline. Adverse events were judged to have a smaller impact on adherence than the dosing schedule. The authors concluded that health information should be targeted to travelers

### Table 3

**Malaria risk factors for nonimmune travelers**

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Most Risky</th>
<th>Less Risky</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Destination</strong></td>
<td>Africa</td>
<td>Central and South America</td>
</tr>
<tr>
<td><strong>Local traveling</strong></td>
<td>Rural areas</td>
<td>Urban areas</td>
</tr>
<tr>
<td><strong>Type of accommodations</strong></td>
<td>Camping</td>
<td>Well-screened or air-conditioned rooms</td>
</tr>
<tr>
<td><strong>Duration of stay</strong></td>
<td>&gt; 4 weeks</td>
<td>1–4 weeks</td>
</tr>
<tr>
<td><strong>Times of travel</strong></td>
<td>Local season of high malaria transmission (rainy season)</td>
<td>Local season of low malaria transmission (dry season)</td>
</tr>
<tr>
<td><strong>Destination elevation</strong></td>
<td>&lt; 2000 meters</td>
<td>&gt; 2000 meters</td>
</tr>
<tr>
<td><strong>Preventive measures</strong></td>
<td>No chemoprophylaxis</td>
<td>Use of preventive drugs and treated bed nets</td>
</tr>
<tr>
<td><strong>Travel companions</strong></td>
<td>None or nonfamily members*</td>
<td>Family members or partners</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td>Males†</td>
<td>Females</td>
</tr>
<tr>
<td><strong>Malaria knowledge</strong></td>
<td>Insufficient</td>
<td>Sufficient</td>
</tr>
</tbody>
</table>

*Those who travel alone or with friends have a 2.6-fold higher risk of infection than those traveling with family members or partners.
†Men have been reported to have twice the risk of women.

---

**Common errors:**
No precautions
No drug
Wrong drug

who are likely to use suboptimal chemoprophylaxis or may be noncompliant with prophylaxis (TABLE 3).

### MONITORING FOR DISEASE SYMPTOMS

No antimalarial prophylactic regimen guarantees complete protection. Because approximately 90% of travelers who contract malaria do not become ill until returning home, it is up to us—in an area where malaria is not common—to recognize malaria, make the laboratory diagnosis, and treat it.44,45

About 1,500 cases of malaria are diagnosed in the United States each year, 99.7% in travelers.10 Approximately 90% of travelers who contract malaria become ill after returning home.46 In addition, each year a few cases of malaria result from blood transfusions, from congenital infections, or from transmission by locally infected mosquitoes.16

When symptoms of malaria are recognized early, several effective treatments exist. When appropriate medical care is delayed, however, complications can ensue, such as renal failure, coma, and even death. The fatality rate of malaria in nonimmune travelers may be as high as 8.7%,47 although much lower rates are usually reported.44

Travellers should know that they can contract malaria both during the trip (as quickly as 6 days following initial exposure) or several months and even longer after they return home.8

Symptoms that could indicate malaria include:
- Myalgia
- Fever
- Headache
- Chills

Although a fever that develops during the first week of travel is rarely due to malaria, any elevated temperature should be treated as a medical emergency and the traveler should request a laboratory test for malaria. Blood smears should be repeated at least three times in 72 hours, as a single negative smear might fail to reveal the parasites that are released periodically.48

Parents should know that malaria can cause flulike symptoms in children up to a year after traveling in a malarious region.9 Such symptoms must be assessed by a health care professional at once.

### REFERENCES


ADDRESS: Kenneth Dardick, MD, Connecticut Travel Medicine, 34 Professional Park Road, Storrs, CT 06268; e-mail kdardick@dardick.com.

479