CLINICAL PRACTICE

Malaria Prevention in Short-Term Travelers

David O. Freedman, M.D.

This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.*

A family of three persons is planning a safari to southern Africa. The itinerary includes 3 days in Cape Town, South Africa, 3 days in Kruger National Park, South Africa, and 3 days in Victoria Falls, Zambia. The 31-year-old husband takes no medications currently, but he recently discontinued fluoxetine, which he had taken for depression. His 29-year-old wife, who won the trip in a corporate sales competition, is healthy and 15 weeks pregnant. Their 7-year-old child is in good health. How should the risk and prevention of malaria be managed in this family?

THE CLINICAL PROBLEM

From the William C. Gorgas Center for Geographic Medicine, Division of Infectious Diseases, University of Alabama at Birmingham, Birmingham.

N Engl J Med 2008;359:603-12.

Malaria is caused by a protozoan parasite within erythrocytes and is transmitted in nature from person to person by the bite of an anopheles mosquito vector that bites only between dusk and dawn. Four principal plasmodium species cause human malaria: *Plasmodium falciparum* (which is potentially fatal in nonimmune travelers), *P. vivax*, *P. ovale*, and *P. malariae*. Of the approximately 1500 imported cases of malaria reported annually in the United States, almost two thirds are due to *P. falciparum* and almost one third are due to *P. vivax*; cases caused by *P. ovale* and *P. malariae* are uncommon.[1] In 2006, six deaths from malaria were reported in the United States. Imported *P. falciparum* malaria occurs almost exclusively in persons receiving no chemoprophylaxis or inadequate chemoprophylaxis. Most imported cases of malaria are not in tourists but in immigrants and their children who have returned to the country of their family's origin to visit friends and relatives (so-called VFR travelers) and have forgone chemoprophylaxis; this often occurs either for economic reasons or because of the mistaken belief that lifelong immunity to malaria is retained after immigration.[1-4]

Ongoing transmission of malaria occurs in part or all of more than 100 countries[5] (Fig. 1), including tropical countries with year-round transmission as well as some temperate countries where transmission occurs only during warmer months. The extent of transmission varies widely and may be focal even within the countries and areas of countries indicated by shading in Figure 1. Authoritative maps often show levels of transmission that are epidemiologically insignificant for travelers, reflecting an effort to be both comprehensive and cautious, particularly in the absence of recent country-specific data.

Malaria in travelers is usually characterized by fever and influenza-like symptoms, including headache and back pain.[7] Vomiting, diarrhea, abdominal cramping, and cough may occur and may be confused with symptoms associated with common infections. Textbooks often describe the fever as occurring in discrete episodes lasting a few hours every 2 to 3 days; however, in travelers the fever usually has an irregular pattern throughout the day. Disease caused by *P. falciparum* in travelers most often occurs 9 to 14 days after an infectious bite, but it may occur

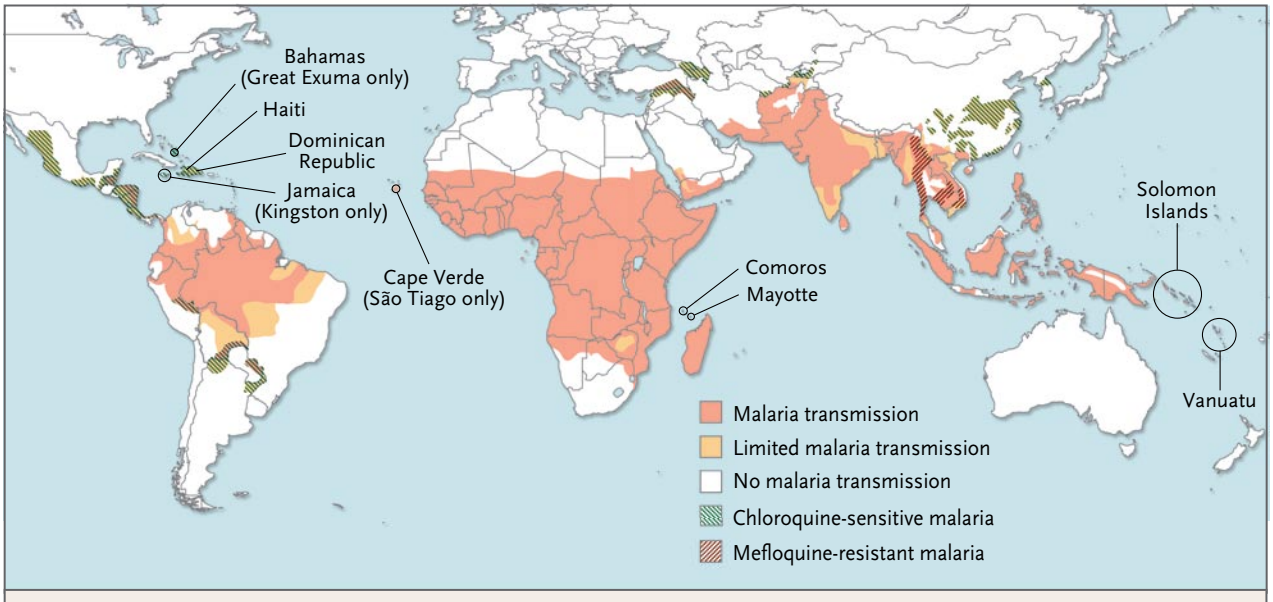

Figure 1. Areas Where Malaria Is Endemic.
Data are from the World Health Organization and from the Centers for Disease Control and Prevention.[5,6]

up to months later, especially in patients who have received suboptimal prophylaxis. Approximately 95% of cases of malaria occur within 30 days after a return from travel. Without prompt diagnosis and treatment, red cells containing parasites can sequester in end-organ capillaries, leading to cerebral or severe malaria and death. Symptoms caused by the other three species of malaria may appear from 12 days to many months after infection, but these infections are rarely fatal.

This review focuses on the management of the risk of malaria during short-term travel. "Short-term" is variably defined but generally is considered to be 3 weeks or less. Long-term travel presents unique issues that are discussed elsewhere.[8]

STRATEGIES AND EVIDENCE

The risk assessment should be individualized on the basis of a complete travel itinerary that is brought to the pretravel consultation, which ideally should occur 1 month before the person's departure. Brief country-specific statements regarding malaria transmission and interactive resources that are regularly updated are available from the Centers for Disease Control and Prevention (CDC) (wwwn.cdc.gov/travel/yellowBookCh5-MalariaYellowFeverTable.aspx) and the World Health Organization (WHO) (www.who.int/ith/countries/en/index.html) to guide risk assessment.[5,6,9] Clinicians who are unfamiliar with locations within individual countries can consult detailed maps of individual countries that show the incidence of malaria; these maps are available from several reliable sources.[9-11] However, even with the use of these resources, reliable and timely quantitative data on area-specific risks within countries are incomplete.

Although consideration of the reported rates of the incidence of malaria among local populations is integral to the assessment of risk, the behaviors and living conditions of travelers may result in lower risks than those among native populations. An exception is sub-Saharan Africa, where most of the malaria in the world occurs; the risk is very high no matter what the individual behaviors are. Elsewhere, transmission, and particularly high-intensity transmission, is more focal even within the areas indicated with shading in Figure 1. As compared with the rates of malaria in local populations, the rates among travelers that are reported for given countries or regions largely reflect usual travel patterns in those areas. For example, GeoSentinel conducted surveillance of travelers at 32 worldwide sites. Among these ill travelers who had just returned

home, there was a minimal relative risk among travelers to South America[12] (Table 1); this is explained by the disproportionate number of travelers visiting coastal and urban areas where malaria is not endemic, as compared with the number of travelers visiting the rural interior, where malaria is highly endemic (Fig. 1). Studies of European travelers to India indicate a low overall incidence of disease, probably because of the high volume of low-risk urban business and tourist travel to that country.[13,14] Risks in certain rural regions and among travelers who have gone to visit friends and relatives in the country of their family's origin are higher than among other travelers to India. In 2006, India ranked second (with 121 cases) among all countries in the acquisition of imported malaria recorded by the CDC.[1]

In addition to the precise itinerary, the risk of malaria may be influenced by the length of the trip, the season, whether the traveler adheres to precautions concerning mosquitoes, and whether the traveler will spend the evening and nighttime hours in locations where considerable exposure to the vector may occur. In particular, the restriction of a person's nighttime hours to air-conditioned hotels or other environments where there are few mosquitoes reduces the risk.

Table 1. Relative Risk of Malaria among Travelers, 2000 through 2002.*

Region Visited	Relative Risk (95% CI)
Very-low-risk area†	1.0
Caribbean	3.8 (1.9–7.5)
North Africa	6.9 (3.6–13.3)
South America	8.3 (4.9–13.9)
Southeast Asia	11.5 (8.3–15.9)
Central America	37.8 (24.0–59.6)
South Asia	53.8 (37.4–77.4)
Oceania	76.7 (50.8–115.9)
Sub-Saharan Africa	207.6 (164.7–261.8)

* Approximate relative risks were based on 1140 cases of malaria among travelers in the GeoSentinel database, with areas visited as numerators and tourist arrivals in that region (according to World Tourism Organization data) as estimates for denominators. Adapted from Leder et al.[12]

† Very-low-risk areas were Europe, Northeast Asia, Australia, New Zealand, North America, and the Middle East.

With the exception of sub-Saharan Africa and certain cities in India, travel restricted to capital cities and other urban areas (as is typical of business travel) is associated with no risk or an insignificant risk of malaria, despite the risk in areas nearby. The lifetime range of flight of an anopheles mosquito is 1 km. Daytime side trips to areas where malaria is endemic present no risk. Conversely, exposure to infective mosquitoes for even a few hours in a single evening in an area where the risk of transmission is high may result in infection. The decision regarding whether to prescribe chemoprophylaxis should also take into account the possibility of deviation from the preset itinerary brought to the pretravel consultation, as well as the traveler's personal tolerance of what may be an epidemiologically insignificant level of risk for the specific trip.

MANAGEMENT

BEHAVIORAL AND NONDRUG INTERVENTIONS

All travelers to regions where malaria is endemic should be thoroughly educated regarding personal and environmental measures to provide protection against mosquito bites. These measures include a repellent containing *N,N*-diethyl-3-methylbenzamide (DEET), the use of long sleeves and pants and footwear that provides full coverage, and properly screened or air-conditioned sleeping areas (Table 2). Although only one limited study has directly shown the efficacy of these measures in reducing the incidence of malaria among travelers,[16] their effectiveness in reducing the incidence of arthropod bites is indisputable.[16-18]

CHEMOPROPHYLAXIS

Current first-line strategies for chemoprophylaxis were designed to prevent death due to severe falciparum malaria. These drugs also have the benefit of largely preventing primary attacks due to non-falciparum species, although not the later relapses that can occur with *P. vivax* and *P. ovale* (see below).

The resistance of *P. falciparum* to chloroquine is nearly universal; chloroquine remains effective only in Mexico, areas of Central America that are west of the Panama Canal, the Caribbean, East Asia, and a few Middle Eastern countries. In all other areas where malaria is endemic, atovaquone–proguanil,[19-22] mefloquine,[23,24] or doxycy-

Table 2. Instructions for Travelers during the Pretravel Consultation.*

Use effective personal protection against mosquitoes.

Anopheles mosquitoes bite between dusk and dawn.

Wear long sleeves, long pants, and fully closed shoes with socks after dark.

Use permethrin-treated mosquito nets if accommodations are neither well screened nor air-conditioned.

Repellent containing 30%–50% DEET obtained from an outdoors store or travel-supply vendor should be applied to exposed areas of skin every 4 to 6 hours. More frequent application is required for agents containing lower concentrations of DEET. Agents containing 20% or higher concentrations of picaridin (KBR 3023) are similar to those containing DEET at the same concentration with regard to activity against anopheles mosquitoes.†

Adhere to an antimalarial regimen.

Take weekly medications on the same day each week. (Sunday may be easiest to remember.)

Take daily medications with the same meal each day.

Continue medications after the trip for the recommended duration.

If intolerable side effects occur, make every effort to contact the health care provider who prescribed the medications or the covering physician by telephone (or by e-mail if offered by the practice) for advice. Physicians at the destination may have poor knowledge of drugs and regimens used by travelers. (The severity of side effects must be weighed against the risk of a potentially fatal infection with *Plasmodium falciparum*.)

Remember that no chemoprophylactic regimen against malaria is 100% effective.

Symptoms of malaria may be mild and may mimic influenza, gastroenteritis, or other common infections; any fever that develops during or after travel to an area where there is a risk of malaria infection should raise the suspicion of malaria.

Early treatment is usually effective, whereas delay of appropriate therapy can have serious or even fatal consequences; therefore, if symptoms of malaria occur, seek prompt medical attention.

If fever develops within 3 mo after return from travel, a physician should be informed of the recent travel, and blood films or a rapid card test for malaria with immediate reporting should be requested; waiting for next-day results may increase the risk of death. If the blood film or card test is negative, two additional tests (including at least one blood film) should be performed 12–24 hr apart for confirmation, and other diagnoses should be considered at the same time.

Ask health care providers who need assistance with diagnosis or management of suspected cases of malaria to call the CDC Malaria Hotline: 770-488-7788.

* CDC denotes Centers for Disease Control and Prevention, and DEET *N,N*-diethyl-3-methylbenzamide.

† Effective concentrations are available worldwide, but concentrations currently available in the United States (≤15%) are suboptimal for protection against malaria. Data are from Constantini et al.[15]

cline[25] is recommended by the CDC and WHO. All these agents have been shown to have more than 95% efficacy in preventing malaria due to *P. falciparum*. Randomized trials have compared both atovaquone–proguanil and doxycycline with other agents in travelers or other nonimmune persons in areas where malaria is endemic; placebo-controlled, randomized trials of mefloquine have been conducted in semi-immune native populations, and retrospective surveillance studies have compared the efficacy of mefloquine with that of other agents in travelers.

Mefloquine resistance occurs in limited rural areas of Southeast Asia (Fig. 1); short-term travel to these areas is infrequent. The choice of a drug for a person traveling to areas where there is chloroquine-resistant malaria depends on traveler-related factors,[26] including the duration of the trip, the person's age and medical history, whether the person is pregnant, and whether there has been previous drug intolerance, as well as economic considerations. Information relevant to the choice of agent, including contraindications and side effects, is summarized in Table 3. Atovaquone–proguanil is the best-tolerated drug overall, but cost considerations significantly increase with the length of the trip. Clear instructions on adherence to prescribed drugs should be given (Table 2).

Contrary to a common perception, antimalarial agents such as chloroquine, mefloquine, and doxycycline do not prevent initial malaria infection in humans; rather, they act later on parasites that infect erythrocytes once they have been released from the initial maturation phase in the liver (Fig. 2). Therefore, these drugs must be continued for 4 weeks after the last exposure to infective mosquitoes in order to eradicate any parasites that may still be released from the liver in the next month. However, atovaquone–proguanil not only acts on these blood-stage parasites but also interferes with the development of actively replicating parasites in the liver (Fig. 2); therefore, it can be discontinued 1 week after exposure ends.

Antimalarial chemoprophylaxis with atovaquone–proguanil and doxycycline should begin 1 to 2 days before travel to areas where malaria is endemic, and chemoprophylaxis with chloroquine should begin 1 week before travel. Treatment with mefloquine should begin at least 2 weeks — and preferably 3 weeks — before travel, mostly to allow for the assessment of possible adverse effects that might warrant discontinuation and prescription of an alternative drug. Unexplained acute anxiety, depression, restlessness, and confusion are indications for discontinuation and a switch to an alternative agent. The first

day in an area where malaria is endemic may not correspond to the arrival date in the country where there is a risk of malaria.

PREGNANT WOMEN

Malaria infection is more severe in pregnancy, and the risks of adverse outcomes (for both the mother and the fetus) are increased. No chemoprophylactic agent is 100% effective. The WHO and the CDC both recommend that pregnant women not travel to areas where malaria is endemic.[5,6] Most women refrain from traveling to these areas during pregnancy, but for pregnant women who decide to travel or must travel, mefloquine is the drug of choice for chloroquine-resistant malaria (Table 3). Because data are limited on the use of this drug during the first trimester of pregnancy, a delay of the trip to later in pregnancy is recommended if feasible.[27,28] The use of agents containing 20% DEET has been shown to be safe in pregnancy,[29] although agents containing this concentration should be applied frequently because they have a shorter duration of effect than agents with a concentration of 30% or more.

CHILDREN

The choice of drug in children is similar to that in adults, except that it is recommended that doxycycline not be used in children who are younger than 8 years of age. Weight-based recommendations for doses of antimalarial agents in children have been published. Tablets containing pediatric doses of atovaquone–proguanil are available (each tablet contains one quarter of the adult dose). However, pediatric mefloquine tablets are not available, so tablets containing adult doses must be divided into quarters. For children at the lowest weights, the bitter-tasting tablets must be crushed and weighed by a pharmacist and then dissolved in a syrup containing sugar or chocolate. Weekly dosing makes mefloquine administration convenient in young children. Formulations of 30% DEET or less are considered to be safe in children,[30] whereas higher concentrations have not been tested.

LATE RELAPSES

Chloroquine, mefloquine, doxycycline, and atovaquone–proguanil, when used as described above, prevent primary clinical attacks of all four species of pathogens that cause malaria, as long as these medications are continued and adequate blood levels are maintained.[31] For example, atovaquone–proguanil is 84 to 100% effective in preventing primary *P. vivax* disease.[21,32] However, these drugs do not act within the liver on specialized dormant forms of the parasite (hypnozoites), which exist only in *P. vivax* and *P. ovale* (Fig. 2).[33,34] Hypnozoites spontaneously reactivate weeks or many months after the initial exposure to infective mosquitoes; their release into the bloodstream results in late-onset or relapsing clinical disease. (Only blood-stage, not liver-stage, plasmodia organisms cause fever and clinical malaria.) Each year, several hundred cases of late-onset *P. vivax* or *P. ovale* relapses occur in the United States in returned travelers who adhered to their prescribed regimen of chloroquine, mefloquine, doxycycline, or atovaquone–proguanil.[1,35,36] Such late relapses do not occur in *P. falciparum* and *P. malariae* infections, which have no hypnozoite stage.

Primaquine is the only available drug that acts on the hypnozoites of *P. vivax* and *P. ovale* in the liver.[37] It generally is indicated for persons who have had either prolonged or intense short exposure to infective mosquitoes in areas where there is a substantial risk of *P. vivax* or *P. ovale* transmission, even if *P. falciparum* is the predominant local pathogen. The daily use of primaquine for 14 days after the trip is referred to as presumptive antirelapse therapy.[38] Because the risk of relapsing malaria is extremely difficult to quantify for a given location, and because the use of a second, nonconcurrent drug makes prophylaxis more complicated, presumptive antirelapse therapy is used infrequently in practice and only in patients with the most obvious and prolonged exposure to infective mosquitoes.

PRIMAQUINE FOR PRIMARY PROPHYLAXIS

Primaquine has a unique dual action in the liver (Fig. 2) and thus is recommended by some authorities as a second-line agent to prevent primary attacks of all four species of malaria during the actual period of exposure to infective mosquitoes.[36,38,39] The use of primaquine for primary prophylaxis has the advantage of obviating the need for its subsequent use as presumptive antirelapse therapy. However, wide use of primaquine for primary chemoprophylaxis is limited by its ability to cause hemolysis in persons with glucose-6-phosphate dehydrogenase (G6PD) deficiency,

Table 3. Drug Regimens for Prophylaxis against Malaria.*

Drug	Tablet Size	Adult Dose	Use in Children†	Use in Pregnancy
Areas with chloroquine-resistant *Plasmodium falciparum*				
Atovaquone–proguanil (Malarone)	Adult: 250 mg of atovaquone and 100 mg of proguanil once daily; pediatric: 62.5 mg of atovaquone and 25.0 mg of proguanil	250 mg and 100 mg once daily	Yes; FDA-approved for children ≥11 kg (in children 5 to <11 kg, recommended off-label use by CDC)	No; insufficient data on use in pregnancy, not recommended by CDC
Mefloquine hydrochloride (Lariam and generic agents)	250 mg (228-mg mefloquine base)‡	250 mg once weekly	Yes; approved for children ≥5 kg (in children <5 kg, recommended off-label use by CDC)	Yes; limited data available on first-trimester use
Doxycycline hyclate (Vibramycin, Vibra-Tabs, other brands, and generic agents); doxycycline monohydrate (Monodox, Adoxa, and generic agents)	Doxycycline hyclate: 20 mg, 50 mg, or 100 mg; doxycycline monohydrate: 100 mg	100 mg once daily	Contraindicated for children <8 yr old because of staining of dental enamel	No; teratogenic
Areas with chloroquine-sensitive *P. falciparum*				
Chloroquine phosphate (Aralen and generic agents)	500 mg (300-mg chloroquine base); some generic agents available in 250-mg (150-mg base) tablet	500 mg once weekly	Yes; approved for all ages	Yes
Areas with *P. vivax* and *P. ovale*, with or without *P. falciparum*				
Primaquine phosphate for primary prophylaxis (off-label use; second-line agent for this purpose)	26.3 mg (15-mg primaquine base)	30-mg base once daily	Yes; approved for all ages	No; contraindicated because of potential toxic effects on fetal erythrocytes
Primaquine phosphate for relapse prevention (presumptive antirelapse therapy)	26.3 mg (15-mg primaquine base)	30-mg base once daily	Yes; approved for all ages	No

* AV denotes atrioventricular, CDC Centers for Disease Control and Prevention, FDA Food and Drug Administration, and G6PD glucose-6-phosphate dehydrogenase.
† See Wilder-Smith[5] and Arguin et al.[6] for doses.
‡ In some countries, 250-mg tablets of Lariam contain 250 mg of mefloquine base, equivalent to 274 mg of mefloquine hydrochloride.

which is prevalent among blacks, persons of Mediterranean descent, and Asians.[40] G6PD testing is required before the use of primaquine either for primary prophylaxis or for prevention of late relapse.

AREAS OF UNCERTAINTY

SAFETY OF MEFLOQUINE

Neuropsychiatric and other adverse events due to mefloquine (Table 3) have received widespread media attention. Mefloquine has been used by more than 30 million persons since 1989, and a large published database exists.[24,41-45] In doses used for chemoprophylaxis, severe side effects such as seizures and psychosis occur rarely (in approximately 1 of 6500 to 1 of 10,600 persons using the drug).[46,47] The rates of less serious but potentially disruptive neuropsychological problems (e.g., insomnia, nightmares, irritability, and depression) appear to be in the range of 1 per 200 to 1 per 500 users[26,45]; however, data on rates of

Initiation (Time before First Exposure to Malaria)	Discontinuation (Time after Last Exposure)	Advantages	Disadvantages
1–2 days	7 days	Short courses for brief trips; best-tolerated antimalarial agent; discontinuation rates of 0–1.2% in randomized clinical trials	Expensive; cost may be prohibitive for long trips; contraindicated if creatinine clearance <30 ml/min; must be taken with food
3 wk preferable; 1–2 wk acceptable	4 wk	Most convenient antimalarial agent for long trips; long experience with prolonged use	Mefloquine resistance in remote areas of Southeast Asia; contraindicated in persons with active or recent depression, history of psychosis, seizure disorder, AV-node conduction abnormalities; adverse events include vivid dreams or nightmares, insomnia, mood alteration, first-degree AV block, prolonged QT interval, and seizures (rare); approximately 5% rate of premature discontinuation; well tolerated by most travelers; extra counseling required because of adverse publicity
1–2 days	4 wk	Inexpensive; widely available worldwide	Photosensitivity (particular concern in tropical sun); gastritis and esophagitis; must be taken on full stomach with glass of liquid, and traveler must remain in upright position for 30 min; candidal infections, including vaginitis in humid tropical climates; risk of vaginal yeast infection (women travelers should take along medication for self-administered treatment); approximately 5% rate of premature discontinuation
1 wk	4 wk	60-yr record of safety	Useful in very limited geographic areas; pruritus in dark-skinned persons; rare blood dyscrasias; cannot use if traveler has psoriasis, history of psychosis, or prolonged QT interval; rare retinopathy (with >100-g total dose)
1 day	7 days	Short courses for brief trips; protection against primary clinical episode as well as late relapses due to *P. vivax* or *P. ovale*	G6PD testing required before first dose; contraindicated in travelers with G6PD deficiency due to hemolysis; must be taken with a meal to prevent gastric irritation; methemoglobinemia
As soon as possible after exposure for which another prophylactic drug taken	Total of 14 days	Protection against late relapses when another agent taken for primary prophylaxis	G6PD testing required before first dose; contraindicated in travelers with G6PD deficiency; must be taken with a meal; use of second drug after the trip, with different regimen and different adverse-effect profile, can be complex; incomplete global data on risk of *P. vivax* and *P. ovale*; methemoglobinemia

these symptoms among travelers who are not receiving mefloquine remain inadequate.[45] Vivid dreams occur in 15 to 25% of users, but they are generally tolerable. Overall, approximately 95% of mefloquine users are able to complete the prescribed course of treatment.

STANDBY EMERGENCY THERAPY

In some countries, especially in Europe,[48] health care providers do not routinely recommend continuous chemoprophylaxis in persons planning short-term travel to areas with a low-to-moderate risk of malaria.[13,14,48,49] Travelers to these areas are advised to bring with them a course of antimalarial treatment for self-administration in case a febrile illness occurs and medical care is not available within 24 hours. Since many travelers self-administer medication even when competent medical care is nearby and they may not use correct doses, especially when ill,[45] this approach has not been adopted in most other areas of the world.

GUIDELINES FROM PROFESSIONAL SOCIETIES

The Infectious Diseases Society of America has developed guidelines for travel medicine that ad-

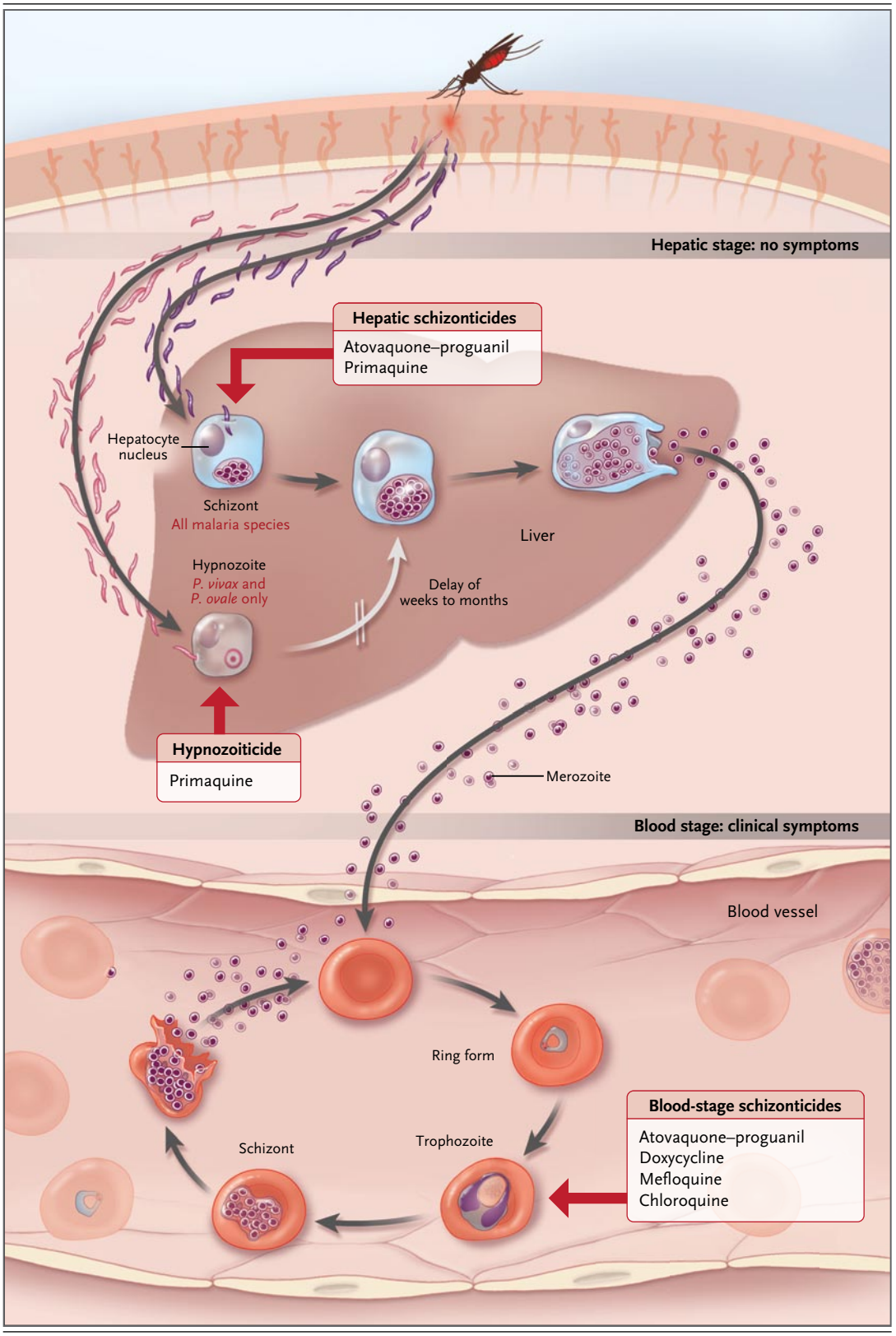

Figure 2 (facing page). Three Different Sites of Action of Antimalarial Drugs.

Schizonts are multinucleated stages of parasites that undergo mitotic division within host cells. Hepatic-stage schizonticides such as atovaquone–proguanil and primaquine kill malaria parasites during the brief period of initial active development within hepatocytes in the liver, and they act on the liver schizonts of all four species of organisms that cause human malaria. Only primaquine is able to kill quiescent hypnozoites (*Plasmodium vivax* and *P. ovale* only), thus preventing secondary attacks (relapses) of clinical malaria. As compared with other drugs, atovaquone–proguanil and primaquine each act at two separate points in the life cycle. Atovaquone–proguanil acts on hepatic schizonts during initial infection but does not act on hypnozoites, so it does not prevent late-onset relapses of *P. vivax* and *P. ovale*. Blood-stage schizonticides such as atovaquone–proguanil, doxycycline, mefloquine, and chloroquine interrupt schizogony within red cells, preventing clinical manifestations of malaria infection. Not all parasite life-cycle stages are shown in this figure.

dress the use of chemoprophylaxis against malaria.[50] Primary prophylaxis with chloroquine when appropriate and a choice of atovaquone–proguanil, mefloquine, or doxycycline for other areas according to traveler circumstances is recommended. The use of primaquine as an alternative for primary prophylaxis is discussed, with no specific recommendation for when to use it; presumptive antirelapse therapy is not discussed.

CONCLUSIONS AND RECOMMENDATIONS

Resources that are readily accessible to nonspecialist clinicians[5,6] indicate that the family members in the vignette face a risk of chloroquine-resistant malaria during the portion of their visit in Kruger National Park and Victoria Falls. For the husband, I would recommend daily atovaquone–proguanil. (Mefloquine is contraindicated because of his history of depression. The side effects of doxycycline, including photosensitivity and vaginal yeast infections in women, are drawbacks for its use in travelers in the tropics, although its lower cost may balance this risk for some travelers.) Atovaquone–proguanil should be started on the second day in Cape Town, 2 days before the first possible exposure to malaria, and continued for 7 days after his departure from the areas where malaria is endemic. The 7-year-old child should also receive atovaquone–proguanil on the same schedule, but tablets containing pediatric doses should be used. The pregnant wife should be advised not to travel, but if she insists (as is common once someone has planned a trip and come for pretravel counseling), I would prescribe mefloquine according to the usual regimen and advise diligent precautions against mosquitoes including repellents containing 20% DEET, protective clothing, and air-conditioned or well-screened sleeping quarters. Since no chemoprophylactic regimen is 100% effective, this family should receive clear instructions about what to do if fever develops on their return home (see Table 2).

Dr. Freedman reports receiving consulting and lecture fees from Novartis and consulting fees from Shoreland. No other potential conflict of interest relevant to this article was reported.

I thank Dr. Paul Arguin, Centers for Disease Control and Prevention, Atlanta, Dr. Eli Schwartz, Sheba Medical Center, Tel Hashomer, Israel, and Dr. Alan J. Magill, Walter Reed Army Institute of Research, Washington, DC, for thoughtful discussion and detailed comments on an earlier version of the manuscript; and D. Adam Plier for research assistance.

An audio version of this article is available at www.nejm.org.

REFERENCES

1. Mali S, Steele S, Slutsker L, Arguin PM. Malaria surveillance — United States, 2006. MMWR Surveill Summ 2008;57 (SS-5):24-39.
2. Bacaner N, Stauffer B, Boulware DR, Walker PF, Keystone JS. Travel medicine considerations for North American immigrants visiting friends and relatives. JAMA 2004;291:2856-64.
3. Leder K, Tong S, Weld L, et al. Illness in travelers visiting friends and relatives: a review of the GeoSentinel Surveillance Network. Clin Infect Dis 2006;43:1185-93.
4. Behrens RH, Barnett ED. Visiting friends and relatives. In: Keystone JS, Kozarsky PE, Freedman DO, Nothdurft HD, Connor BA, ed. Travel medicine. 2nd ed. Expert consult. St. Louis: Mosby Elsevier, 2008:291-8.
5. Wilder-Smith A, ed. International travel and health 2008. Geneva: World Health Organization, 2008. (Accessed July 14, 2008, at http://www.who.int/ith.)
6. Arguin PM, Kozarsky PE, Reed C, eds. Health information for international travel 2008. Atlanta: Centers for Disease Control and Prevention, 2007. (Accessed July 14, 2008, at http://www.cdc.gov/travel.)
7. Genton B, D'Acremont V. Clinical features of malaria in travelers and migrants. In: Schlagenhauf-Lawlor P, ed. Travelers' malaria. 2nd ed. Hamilton, ON, Canada: BC Decker, 2008:269-83.
8. Chen LH, Wilson ME, Schlagenhauf P. Prevention of malaria in long-term travelers. JAMA 2006;296:2234-44.
9. Malaria risk map application. Atlanta: Centers for Disease Control and Prevention, 2008. (Accessed July 14, 2008, at http://www.cdc.gov/malaria/risk_map/.)
10. Keystone JS, Kozarsky PE, Freedman DO. Internet and computer-based resources for travel medicine practitioners. Clin Infect Dis 2001;32:757-65.
11. Mimouni D, Gdalevich M. Review of: *Travax*. N Engl J Med 1998;338:927-8.
12. Leder K, Black J, O'Brien D, et al. Ma-

laria in travelers: a review of the GeoSentinel surveillance network. Clin Infect Dis 2004;39:1104-12.
13. Nothdurft HD, Bialek R, Burchard GD, et al. Consensus recommendations for malaria prophylaxis. Dtsch Med Wochenschr 2005;130:1392-6. (In German.)
14. Behrens RH, Bisoffi Z, Björkman A, et al. Malaria prophylaxis policy for travellers from Europe to the Indian Subcontinent. Malar J 2006;5:7.
15. Costantini C, Badolo A, Ilboudo-Sanogo E. Field evaluation of the efficacy and persistence of insect repellents DEET, IR3535, and KBR 3023 against *Anopheles gambiae* complex and other Afrotropical vector mosquitoes. Trans R Soc Trop Med Hyg 2004;98:644-52.
16. Soto J, Medina F, Dember N, Berman J. Efficacy of permethrin-impregnated uniforms in the prevention of malaria and leishmaniasis in Colombian soldiers. Clin Infect Dis 1995;21:599-602.
17. Fradin MS. Mosquitoes and mosquito repellents: a clinician's guide. Ann Intern Med 1998;128:931-40.
18. Fradin MS, Day JF. Comparative efficacy of insect repellents against mosquito bites. N Engl J Med 2002;347:13-8.
19. Boggild AK, Parise ME, Lewis LS, Kain KC. Atovaquone-proguanil: report from the CDC expert meeting on malaria chemoprophylaxis (II). Am J Trop Med Hyg 2007;76:208-23.
20. Hogh B, Clarke PD, Camus D, et al. Atovaquone-proguanil versus chloroquine-proguanil for malaria prophylaxis in non-immune travellers: a randomised, double-blind study. Lancet 2000;356:1888-94.
21. Ling J, Baird JK, Fryauff DJ, et al. Randomized, placebo-controlled trial of atovaquone/proguanil for the prevention of *Plasmodium falciparum* or *Plasmodium vivax* malaria among migrants to Papua, Indonesia. Clin Infect Dis 2002;35:825-33.
22. Overbosch D, Schilthuis H, Bienzle U, et al. Atovaquone-proguanil versus mefloquine for malaria prophylaxis in nonimmune travelers: results from a randomized, double-blind study. Clin Infect Dis 2001;33:1015-21.
23. Schlagenhauf-Lawlor P. Mefloquine. In: Schlagenhauf-Lawlor P, ed. Travelers' malaria. 2nd ed. Hamilton, ON, Canada: BC Decker, 2008:134-47.
24. Lobel HO, Kozarsky PE. Update on prevention of malaria for travelers. JAMA 1997;278:1767-71.
25. Ohrt C, Richie TL, Widjaja H, et al. Mefloquine compared with doxycycline for the prophylaxis of malaria in Indonesian soldiers: a randomized, double-blind, placebo-controlled trial. Ann Intern Med 1997;126:963-72.
26. Chen LH, Keystone JS. New strategies for the prevention of malaria in travelers. Infect Dis Clin North Am 2005;19:185-210.
27. Vanhauwere B, Maradit H, Kerr L. Post-marketing surveillance of prophylactic mefloquine (Lariam) use in pregnancy. Am J Trop Med Hyg 1998;58:17-21.
28. Phillips-Howard PA, Steffen R, Kerr L, et al. Safety of mefloquine and other antimalarial agents in the first trimester of pregnancy. J Travel Med 1998;5:121-6.
29. McGready R, Hamilton KA, Simpson JA, et al. Safety of the insect repellent N,N-diethyl-M-toluamide (DEET) in pregnancy. Am J Trop Med Hyg 2001;65:285-9.
30. Prevention of mosquitoborne infections. In: Pickering LK, Baker, CJ, Long SS, McMillan JA, ed. 2006 Red book: report of the Committee on Infectious Diseases. 27th ed. Elk Grove Village, IL: American Academy of Pediatrics, 2006:197-9.
31. Baird JK. Effectiveness of antimalarial drugs. N Engl J Med 2005;352:1565-77.
32. Soto J, Toledo J, Luzz M, Gutierrez P, Berman J, Duparc S. Randomized, double-blind, placebo-controlled study of Malarone for malaria prophylaxis in non-immune Colombian soldiers. Am J Trop Med Hyg 2006;75:430-3.
33. Chen N, Auliff A, Rieckmann K, Gatton M, Cheng Q. Relapses of *Plasmodium vivax* infection result from clonal hypnozoites activated at predetermined intervals. J Infect Dis 2007;195:934-41.
34. Collins WE. Further understanding the nature of relapse of Plasmodium vivax infection. J Infect Dis 2007;195:919-20.
35. Schwartz E, Parise M, Kozarsky P, Cetron M. Delayed onset of malaria — implications for chemoprophylaxis in travelers. N Engl J Med 2003;349:1510-6.
36. Baird JK, Schwartz E, Hoffman SL. Prevention and treatment of vivax malaria. Curr Infect Dis Rep 2007;9:39-46.
37. Baird JK. Primaquine as anti-relapse therapy for *Plasmodium vivax.* Trans R Soc Trop Med Hyg 1998;92:687.
38. Hill DR, Baird JK, Parise ME, Lewis LS, Ryan ET, Magill AJ. Primaquine: report from CDC expert meeting on malaria chemoprophylaxis I. Am J Trop Med Hyg 2006;75:402-15.
39. Baird JK, Fryauff DJ, Hoffman SL. Primaquine for prevention of malaria in travelers. Clin Infect Dis 2003;37:1659-67.
40. Chinevere TD, Murray CK, Grant E Jr, Johnson GA, Duelm F, Hospenthal DR. Prevalence of glucose-6-phosphate dehydrogenase deficiency in U.S. Army personnel. Mil Med 2006;171:905-7.
41. Lobel HO, Miani M, Eng T, Bernard KW, Hightower AW, Campbell CC. Long-term malaria prophylaxis with weekly mefloquine. Lancet 1993;341:848-51.
42. Schlagenhauf P, Steffen R, Lobel H, et al. Mefloquine tolerability during chemoprophylaxis: focus on adverse event assessments, stereochemistry and compliance. Trop Med Int Health 1996;1:485-94.
43. Schlagenhauf P, Steffen R. Neuropsychiatric events and travel: do antimalarials play a role? J Travel Med 2000;7:225-6.
44. Schlagenhauf P, Tschopp A, Johnson R, et al. Tolerability of malaria chemoprophylaxis in non-immune travellers to sub-Saharan Africa: multicentre, randomised, double blind, four arm study. BMJ 2003;327:1078.
45. Chen LH, Wilson ME, Schlagenhauf P. Controversies and misconceptions in malaria chemoprophylaxis for travelers. JAMA 2007;297:2251-63.
46. Meier CR, Wilcock K, Jick SS. The risk of severe depression, psychosis or panic attacks with prophylactic antimalarials. Drug Saf 2004;27:203-13.
47. Steffen R, Fuchs E, Schildknecht J, et al. Mefloquine compared with other malaria chemoprophylactic regimens in tourists visiting east Africa. Lancet 1993;341:1299-303.
48. Schlagenhauf P, Steffen R. Stand-by treatment of malaria in travellers: a review. J Trop Med Hyg 1994;97:151-60.
49. Behrens RH, Carroll B, Beran J, et al. The low and declining risk of malaria in travellers to Latin America: is there still an indication for chemoprophylaxis? Malar J 2007;6:114.
50. Hill DR, Ericsson CD, Pearson RD, et al. The practice of travel medicine: guidelines by the Infectious Diseases Society of America. Clin Infect Dis 2006;43:1499-539.