Prevention of Malaria in Long-term Travelers

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Traveler arrivals worldwide exceeded 800 million in 2005.1 Today’s mobile populations and global economies lead to extended stays for many travelers. For long-term travelers visiting malaria-endemic countries, recommendations for prevention have been difficult to standardize due to the diversity of long-term travelers and their itineraries, the variation in quality of and access to medical care, the limited data on malaria incidence in travelers overseas, and the lack of controlled studies on long-term safety and efficacy of antimalarial agents. Further complicating the recommendations are the evolution in the intensity of transmission and resistance patterns of the malaria parasites, the seasonality of transmission, and the wide range of international guidelines and travelers’ beliefs and expectations.

Evidence Acquisition
We searched the literature using MEDLINE via both OVID and PubMed for relevant studies and articles with a cutoff date of July 2006, using the search terms long-term travel and malaria prevention, long-term malaria chemoprophylaxis, and insect repellent and malaria. Additional references were obtained from searching the bibliographies of the selected articles, from dissertations, and from the proceedings of relevant conferences on travel medicine. There were no language restrictions.

Evidence Synthesis
Long-term travelers have a higher risk of malaria than short-term travelers. Long-term travelers underuse personal protective measures and adhere poorly to continuous chemoprophylaxis regimens. A number of strategies are used during long-term stays: discontinuation of chemoprophylaxis after the initial period, sequential regimens with different medications for chemoprophylaxis, stand-by emergency self-treatment, and seasonal chemoprophylaxis targeting high-incidence periods or locations. All strategies have advantages and drawbacks. Counterfeit drugs sold in countries endemic for malaria pose serious concern for long-term travelers who purchase their medications overseas. Vivax malaria causes significant illness in travelers, but relapses of vivax malaria are not prevented with the current first-line chemoprophylaxis regimens. Consensus guidelines are needed for prevention of malaria in long-term travelers.

Conclusions
Prevention of malaria in long-term travelers is a complex issue and requires expert advice from travel medicine specialists. Recommendations for prevention of malaria in long-term travelers must be individualized.

Context
Long-term travelers, defined here as those traveling for periods of 6 months or longer, face particular challenges regarding malaria prevention. Current guidelines for malaria prevention primarily address prevention of Plasmodium falciparum infections in short-term travelers.

Objectives
To examine the risk of malaria in long-term travelers, recent developments in personal protective measures, and the safety and tolerability of malaria chemoprophylaxis during long-term use and to consider prevention strategies including continuous chemoprophylaxis, stand-by emergency self-treatment, seasonal prophylaxis, and strategies to prevent primary infection and relapses from P vivax malaria.

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east Asian Journal of Tropical Medicine and Public Health, Transactions of the Royal Society of Tropical Medicine, and Tropical Medicine and International Health. We placed emphasis on the more recent reports, especially systematic reviews, randomized controlled trials, and analyses of travelers’ databases. All 3 authors performed the searches and added supplemental references; there were no disagreements.

EVIDENCE SYNTHESIS

Who Are Long-term Travelers?

In the GeoSentinel database (http://ism.org/gesosentinel/main.html), 16% of patients with malaria had traveled for longer than 6 months.2 For the purpose of our discussion, we defined nonimmune travelers as persons who reside in areas without malaria and who therefore do not have immunity to malaria parasites (although even residence in an endemic area does not result in fully protective immunity) and defined long-term travelers as nonimmune travelers visiting endemic areas for longer than 6 months. This is consistent with UK guidelines on the prevention of malaria in long-term travelers.3 However, many travelers visiting a destination for periods of less than 6 months will confront similar issues. Examples of long-term travelers include diplomats, students, missionaries, Peace Corps Volunteers, military personnel, teachers, field researchers, corporate employees, backpackers, and travelers who have frequent transient stays in malaria-endemic countries, such as airline crews.

Risk of Malaria in Long-term Travelers

An estimated 30 000 cases of malaria, 10 000 of them reported, are imported annually to nonendemic industrialized countries.4,5 The risk of malaria varies widely by geographic region. Between 1985 and 1988, the incidence of malaria in European travelers using no chemoprophylaxis was 15.2/1000 travelers per month in East Africa, and 24.2/1000 travelers per month in West Africa.6 Investigators using Plasmodium falciparum circumsporozoite antibody titers as a measure of malaria exposure found large variation in the proportion of seropositive travelers depending on the area visited: West Africa (22.2%), East Africa (21.8%), and southern Africa (15.4%), in contrast to Central America (4.2%), Southeast Asia (3.4%), East Asia (3.3%), South America (2.4%), and the Indian subcontinent (2.2%).7 Recent analyses of traveler databases have found the highest risk of acquiring malaria in Africa and Oceania, an intermediate risk in South Asia, and a lower risk in Central America, Southeast Asia, and South America.8 Long-term travelers, particularly occupational travelers such as miners, are at an even higher risk. In Zambia, 82% of expatriates working for a multinational mining company allegedly had malaria.9

Table 1 summarizes studies that assessed malaria risk in long-term travelers.9-16 Most were observational studies or surveys and may include overdiagnosis of malaria, which occurs commonly in malaria-endemic regions (often resource-poor settings).17-19 Febrile illnesses may be presumed to be malaria and treated without confirmatory blood smears; blood smears, if performed, may be incorrectly read as positive for plasmodial parasites. In addition, blood smears in residents of endemic areas may be positive for malaria parasites even when malaria is not causing the illness. Nonetheless, these studies document that malaria is a serious problem and illustrate an increasing trend in malaria according to the duration of stay. Additionally, medical treatment or materials (eg, reused needles, syringes, blood transfusions) pose a risk of transmitting human immunodeficiency virus, hepatitis B virus, and other blood-borne infections, including malaria.20

What options are available to reduce the risk of morbidity and mortality from malaria? Although no intervention is 100% effective, several approaches are available and can be used in combination. The following sections will review ways to minimize risk of infection and poor outcome if infection occurs. Any preparation should begin with education about basic elements of malaria transmission that will be tailored to the region where the person will be living and working. Key messages include seriousness of the in-
fection, protein manifestations of malaria, potential for rapid progression, need for rapid assessment, and possible onset many months after exposure, especially with vivax malaria.

**Personal Protective Measures**

The importance and effectiveness of personal protective measures should be emphasized with long-term travelers, including behaviors to minimize exposure to mosquitoes (eg, stay indoors from dusk to dawn, choose screened accommodations), barrier clothing, insecticide-impregnated bed nets, spraying of residence with insecticide, and application of effective insect repellent. Long-term travelers need concise instructions on clothing and bedding impregnation. Insecticides (eg, deltamethrin and permethrin) are designed to kill mosquitoes and can be used effectively as knockdown sprays or in the impregnation of clothes and bed nets. Colombian soldiers who used permethrin-impregnated clothing had a reduced incidence of malaria (3%) compared with controls (14%). Insecticide-treated bed nets are also highly effective in malaria prevention.

Repellents are substances applied to the skin to reduce the attractiveness of humans to mosquitoes and other arthropods. The US Environmental Protection Agency has registered a number of active ingredients as insect repellents: DEET (N,N-diethyl-m-toluamide [or N,N-diethyl-3-methylbenzamide]), picaridin (1-methyl-propyl 2-[2-hydroxyethyl]-1-piperidinecarboxylate [also known as KBR 3023 or Bayrepel]), PMD (p-menthane 3,8-diol [or oil of lemon eucalyptus]), MGK-326 (dipropyl isocinchomerone), MGK-264 (N-octyl bicycloheptane dicarboximide), IR3535 (ethyl butylacetylaminopropionate), and oil of citronella. DEET has the best evidence and longest history of use, and is considered the most reli-

### Table 2. Main Results of Recent Comparative Studies on Insect Repellents

<table>
<thead>
<tr>
<th>Source</th>
<th>Repellents Compared</th>
<th>Type of Study</th>
<th>Location</th>
<th>Anopheles Species Tested</th>
<th>Efficacy and Duration of Protection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fradin and Day, 2002</td>
<td>DEET (23.8%) vs other repellents</td>
<td>Arm-in-cage study</td>
<td>Indoors</td>
<td>None (study tested against Aedes aegypti)</td>
<td>DEET protected for 5 h; efficacy was best of those tested</td>
</tr>
<tr>
<td>Frances et al, 2002</td>
<td>Picaridin (0.3%)† and 19.2% vs DEET (20%, 33%, and 35%)</td>
<td>Field trial</td>
<td>Northern Queensland, Australia</td>
<td><em>A. farauti ss Laveran</em></td>
<td>Picaridin (19.2%) is comparable to DEET (35%); nighttime use provided 95% protection for &gt;7-9 h; picaridin (0.3%)† provided &gt;95% protection for only 2 h</td>
</tr>
<tr>
<td>Badolo et al, 2004</td>
<td>Picaridin (diluted in ethanol) vs DEET</td>
<td>Arm-in-cage study</td>
<td>Laboratory in Burkina Faso</td>
<td><em>A. gambiae s.l.</em></td>
<td>Picaridin similar to DEET for <em>A. gambiae</em> complex</td>
</tr>
<tr>
<td>Frances et al, 2004</td>
<td>Picaridin (19.2%) vs DEET (20% and 35%)</td>
<td>Field trial</td>
<td>Northern Territory, Australia</td>
<td><em>A. meruakensis</em> Vanhuis, <em>A. bancrofti</em> Giles</td>
<td>Picaridin provided &gt;95% protection against <em>Anopheles</em> mosquitoes for only 1 h, similar to DEET (35%); DEET (20% in ethanol) protected poorly against <em>Anopheles</em> mosquitoes</td>
</tr>
<tr>
<td>Costantini et al, 2004</td>
<td>Picaridin vs IR3535 and DEET</td>
<td>Field trial</td>
<td>Burkina Faso</td>
<td><em>A. gambiae s.l.</em></td>
<td>Picaridin provided best protection for <em>A. gambiae</em> complex after exposure of 10 h; picaridin lasted longer, has longer half life after application on skin than other 2 agents</td>
</tr>
<tr>
<td>Trigg, 1996</td>
<td>PMD vs DEET</td>
<td>Human-landing catches</td>
<td>Tanzania</td>
<td><em>A. gambiae</em> and <em>A. funestus</em></td>
<td>PMD and DEET protected for 6-7.75 h</td>
</tr>
<tr>
<td>Govere et al, 2000</td>
<td>PMD (0.574 g) vs DEET (15%) vs Bio-Skincare (BSC)†</td>
<td>Arm-in-cage study</td>
<td>Indoors</td>
<td><em>A. arabiansis</em> Patton</td>
<td>PMD and DEET provided 90%-100% protection for up to 5-6 h; BSC protected for up to 3-4 h</td>
</tr>
<tr>
<td>Moore et al, 2002</td>
<td>PMD (30%) vs DEET (15%)</td>
<td>Human-landing catches</td>
<td>Bolivia</td>
<td><em>A. darlingi</em></td>
<td>PMD provided 97% protection for 4 h; DEET provided 85% protection</td>
</tr>
<tr>
<td>Trongtokit et al, 2005</td>
<td>PMD (10% and 20%), citronella (40%), DEET (50%)</td>
<td>Arm-in-cage or mosquito-proof room study</td>
<td>Indoors</td>
<td><em>A. stephensi</em></td>
<td>PMD (20%) provided complete repellency for 7-8 h but PMD (10%) for only 30 min; citronella (40%) provided for 7 h; DEET (50%) protected for 30 h</td>
</tr>
</tbody>
</table>

*See “Personal Protective Measures” section for chemical and alternate names of repellents.
†The only product available in the United States contains low effective concentration.
‡A product containing oils of coconut, jojoba, rapeseed, and vitamin E.
able. Most repellents are water soluble and need to be reapplied frequently when profuse sweating occurs.

No systematic analyses address the safety of long-term use of repellents, though no reports of problems with long-term use have been published. DEET-containing repellents have been widely used since the 1950s, and toxicity is extremely rare and associated with inappropriate rather than prolonged duration of use.28 Moreover, experience with the use of 20% DEET during the second and third trimesters of pregnancy in women on the Thai-Myanmar border with follow-up of infants through 1 year of age demonstrated no increase in adverse neurologic, gastrointestinal tract, or dermatologic effects.27 More recently, DEET-containing products have been sanctioned for use in infants younger than 2 months.25,28

The activity of a repellent may not be the same against all species of mosquitoes or other arthropods, such as ticks. Anopheline, Aedes, and Culex mosquitoes are important vectors of human pathogens, but only anopheline mosquitoes transmit malaria. One comparison showed that DEET-based products provided the longest protection against Aedes mosquito bites; higher concentrations lasted longer, and 23.8% DEET protected a mean of 5 hours.29 Some recent studies have found picaridin, DEET, and PMD effective against Anopheles mosquitoes.30-37 (TABLE 2).

Because picaridin has a longer half-life after application on skin, it may be particularly useful in areas with high vector densities.33 However, the available products in the United States do not contain the optimal effective concentration and are not currently recommended for prevention of malaria. Long-term travelers also need to be aware of the biting habits of the local Anopheles populations, although this information is not readily available before travel. Anopheles gambiae bites mainly late at night, emphasizing the importance of impregnated bed nets in Africa, whereas A. darlingi (an important vector in the Amazon basin) bites earlier in the evening, suggesting that repellents would be pivotal in this area.36,38-40

### Table 3. Evidence Regarding Efficacy of Personal Protective Measures

<table>
<thead>
<tr>
<th>Source</th>
<th>Type of Report</th>
<th>Method</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keiser et al.,22 2005</td>
<td>Systematic literature review</td>
<td>Environmental management</td>
<td>Environmental modification (to reduce vector habitats) and modification of human habitation reduced the risk ratio of malaria by 80%-88%†</td>
</tr>
<tr>
<td>Lengeler,24 2004</td>
<td>Systematic review of randomized controlled trials</td>
<td>Insecticide-treated bed nets</td>
<td>Areas with stable malaria: treated bed nets reduced uncomplicated malaria incidence by 50% vs no nets and 39% vs untreated nets Areas with unstable malaria: treated nets reduced Plasmodium falciparum by 62% vs no nets and 43% vs untreated nets Protective efficacy of 45% for severe malaria, 15% for parasite prevalence, 29% for high parasitemia, 30% for splenomegaly</td>
</tr>
<tr>
<td>Soto et al,23 1995</td>
<td>Double-blind, randomized study</td>
<td>Permethrin-impregnated clothing</td>
<td>Method reduced malaria incidence to 3% in Colombian soldiers vs 14% in controls</td>
</tr>
<tr>
<td>Durheim and Govere,40 2002</td>
<td>Observational study in endemic area</td>
<td>DEET</td>
<td>Application of 15% DEET to ankles and feet of villagers in Kruger National Park, South Africa, reduced bites from Anopholes arabiensis and restored malaria incidence to pre-epidemic levels</td>
</tr>
<tr>
<td>Govere et al,40 2001</td>
<td>Human-bait study in open air</td>
<td>DEET</td>
<td>Application of 15% DEET to human ankles and feet reduced bites by A. arabiensis patent by 69%</td>
</tr>
</tbody>
</table>

*See “Personal Protective Measures” section for chemical names of DEET.
†These measures included installing drains and underground pipes; filling swamps, pits, pools, and ponds; modifying river boundaries to improve flow; clearing of undergrowth and mangroves; changing irrigation to intermittent systems; screening houses; closing eaves and ceilings.

### Table 4. Evidence of Chemoprophylaxis

<table>
<thead>
<tr>
<th>Source</th>
<th>Type of Report</th>
<th>Method</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>World Health Organization</td>
<td>Literature review</td>
<td>Insecticide-treated bed nets</td>
<td>Areas with stable malaria: treated bed nets reduced uncomplicated malaria incidence by 50% vs no nets and 39% vs untreated nets Areas with unstable malaria: treated nets reduced Plasmodium falciparum by 62% vs no nets and 43% vs untreated nets Protective efficacy of 45% for severe malaria, 15% for parasite prevalence, 29% for high parasitemia, 30% for splenomegaly</td>
</tr>
</tbody>
</table>

### Malaria Chemoprophylaxis

Although personal protective measures and environmental and behavioral modifications can reduce the risk of exposure to infective mosquitoes, these interventions cannot eliminate risk of infection. In combination with these measures, chemoprophylaxis can further reduce the risk of poor outcome if a person is bitten by infective mosquitoes.46 Most chemoprophylactic regimens provide about 75% to 95% protection, even if taken correctly, and no chemoprophylactic regimen is 100% effective. Long-term travelers may plan pregnancy while in malarious areas, but malaria during pregnancy is associated with severe consequences to both mother and fetus, and special considerations are needed because some chemoprophylactic drugs are contraindicated during pregnancy (TABLE 4).

### Restrictions on the Duration of Use of Chemoprophylaxis

In general, the drugs used for chemoprophylaxis have been used widely for many years, though primarily in short-term travelers, and their adverse effects are well known. Concerns arise when these drugs are considered for...
prolonged use. The licensing restrictions probably contributed to concerns about long-term use of some chemoprophylactic medications. Table 4 summarizes these restrictions, the clinical data on long-term use, and the duration of use approved by the UK Advisory Committee on Malaria Prevention.34,48-51

**Safety of Malaria Chemoprophylaxis for Long-term Travel**

Chloroquine has been used in a continuous manner for years by travelers as well as patients with rheumatologic disorders. Retinal toxicity is of concern when a 100-g cumulative dose of chloroquine base is reached, usually after 5 to 6 years of weekly dosing. The UK Advisory Committee on Malaria Prevention recommends ophthalmologic examination every 6 to 12 months after 5 to 6 years of use.3 Similar caution and screening are recommended for hydroxychloroquine.

For areas with chloroquine-resistant malaria, mefloquine is considered a convenient option for long-term chemoprophylaxis due to its simple dosage schedule (once weekly), wide experience (especially from Peace Corps studies in Africa), pharmacokinetic data indicating that drug accumulation does not occur after long-term intake, and good tolerability during prolonged use.48,52,53

Adverse effects of mefloquine have caused concern. The incidence of serious adverse effects associated with mefloquine was previously estimated to be 1 in 6000 to 1 in 10 600.54,55 A double-blind, placebo-controlled study of airline pilots using a flight simulator found that mefloquine was associated with nonserious sleep-related adverse effects but no significant adverse influence on performance.56 Another double-blind study comparing the tolerability of mefloquine, chloroquine-proguanil, doxycycline, and atovaquone-proguanil as chemoprophylactic regimens showed relatively poor tolerability for all regimens, with more than 80% of participants reporting at least 1 adverse event; severe adverse events (ie, those requiring medical attention) were reported in 12% of mefloquine users, compared with 11% with chloroquine-proguanil, 6% with doxycycline, and 7% with atovaquone-proguanil.57 In contrast, mefloquine use among US service members from 2002-2004 was not associated with severe health effects.58 Mefloquine was well tolerated when used for more than 3 months in Italian soldiers in Somalia and Mozambique59 as well as in Peace Corps Volunteers, where it was used for up to 2.5 years.48 Only 0.3% of Dutch marines who used mefloquine for 6 months reported adverse effects requiring medical attention.60 Mefloquine adverse events tend to occur early in prophylaxis; if users initially tolerate mefloquine, they are unlikely to have late-onset adverse events.48

Postmarketing surveillance of the use of atovaquone-proguanil for up to 34 weeks has found some association with gastrointestinal tract adverse events (diarrhea, abdominal pain, mouth ulcers, nausea, vomiting) and neuropsychiatric adverse events (dizziness, insomnia, vivid dreams) in 10% and 8.5% of users, respectively, but only 1% discontinuation (due to diarrhea).49 Australian soldiers deployed to Somalia for 4 months and to Cambodia for 12 months used doxycycline; adverse events led to a medication change in

**Table 4. Data on Duration of Use of Malaria Chemoprophylactic Drugs**

<table>
<thead>
<tr>
<th>Source</th>
<th>Drug (Proprietary Name)</th>
<th>Licensed Duration in United States</th>
<th>Restrictions on Duration of Use Elsewhere</th>
<th>Longest Published Clinical Use</th>
<th>Safety in Pregnancy</th>
<th>UK ACMP Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lobel et al,48 1993</td>
<td>Chloroquine phosphate (Aralen) or hydroxychloroquine sulfate (Plaquenil)</td>
<td>No limit</td>
<td>No limit, but caution in use &gt;5 y</td>
<td>2-2.5 y in Peace Corps Volunteers</td>
<td>Yes</td>
<td>No limit, but retinal toxicity a possible concern when cumulative dose exceeds 100 g; ophthalmologic examination every 6-12 mo after taking chloroquine for &gt;5-6 y</td>
</tr>
<tr>
<td>Lobel et al,48 1993</td>
<td>Mefloquine (Lariam)</td>
<td>No limit</td>
<td>No limit</td>
<td>2-2.5 y in Peace Corps Volunteers</td>
<td>Yes</td>
<td>Up to 3 y</td>
</tr>
<tr>
<td>Overbosch,49 2003</td>
<td>Atovaquone-proguanil (Malarone)</td>
<td>No limit</td>
<td>Maximum of 28 d-3 mo (most European countries)</td>
<td>34 wk postmarketing surveillance</td>
<td>Unknown, avoid</td>
<td>At least up to 3 mo, possibly up to ≥6 mo</td>
</tr>
<tr>
<td>Shanks et al,50 1995</td>
<td>Doxycycline (Vibramycin, Doxy, and others)</td>
<td>4 mo</td>
<td>2 y for acne treatment (United Kingdom)</td>
<td>12 mo in Australian Defense Force to Cambodia</td>
<td>Contraindicated</td>
<td>At least up to 2 y</td>
</tr>
<tr>
<td>Fryauff et al,51 1995</td>
<td>(Primaquine)*</td>
<td>No limit</td>
<td>No limit</td>
<td>52 wk in nonimmune Javanese transmigrants to Papua New Guinea</td>
<td>Contraindicated</td>
<td>No specific recommendation on duration</td>
</tr>
</tbody>
</table>

*Must screen for G6PD deficiency first.

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1.7% (Somalia) and 0.6% (Cambodia). A series of 35 patients with Q-fever endocarditis treated with doxycycline, 100 mg twice daily, for up to several years reported photosensitivity in all patients but irreversible skin pigmentation in only 1.61.

Primaquine (which can be used only in persons who do not have glucose-6-phosphate dehydrogenase [G6PD] deficiency), 30 mg daily, was well tolerated for up to 52 weeks as primary prophylaxis for *P falciparum* and *P vivax* in clinical trials in Javanese transmigrants.51,62

### Adherence With Chemoprophylaxis During Long-term Intake

Adherence to chemoprophylaxis in long-term travelers has been poor.16,43,48,63-67 The use of malaria prophylaxis in missionaries was dismal, ranging from 19% to 62%, even counting persons who missed doses.43,65 Only 38% of expatriate mine workers in Zambia used any chemoprophylaxis; of these, only half took the medication year around.66 Among expatriate workers at a construction site in Ghana, only 11% continued to take malaria prophylaxis for more than 7 months; half stopped their antimalarial agent or changed to a new agent based on medical advice, adverse effects, a perceived low risk of malaria, or advice of local colleagues.67 Commonly cited reasons for poor adherence include fear of long-term adverse effects, adverse events from medication, conflicting advice, and complicated regimens or daily medications. Developing malaria while taking chemoprophylactic drugs (ie, “breakthrough” malaria) or having febrile illnesses misdiagnosed as malaria also reduce confidence in chemoprophylaxis.3

Different approaches have evolved (Table 5). These include continuing the medication beyond licensed durations, using different chemoprophylactic regimens sequentially, using a regimen such as chloroquine-proguanil that has no time limit but has suboptimal efficacy, and discontinuing chemoprophylaxis in favor of establishing local medical care and stand-by treatment. “Mixing and matching” of antimalarial agents can lead to gaps in protection. This can occur when an individual shifts from one antimalarial agent to a different one because of drug unavailability or adverse reactions or because of travel to regions where parasites have different resistance patterns.

### Stand-by Emergency Self-treatment

As defined by the World Health Organization, “stand-by emergency treatment (SBET) is the use of antimalarial drugs carried by the traveler for self-administration when malaria is suspected and prompt medical attention is unavailable within 24 hours of onset of symptoms.”4

The World Health Organization initially recommended SBET for short-stay travelers based on data that suggested that 22% of malaria infections had been treated abroad and at a time when chloroquine resistance emerged and mefloquine had not yet been approved by the US Food and Drug Administration.68 Stand-by treatment was recommended for travelers to areas with low malaria transmission but no reliable diagnostic and therapeutic facilities (parts of Southeast Asia) and areas at high risk for *P falciparum* where the prescribed chemoprophylactic drug, chloroquine, at that time was not considered to be highly effective (parts of East and Central Africa).68 A switch from continuous chemoprophylaxis to SBET in Swiss airline crews reduced by two thirds the number of malaria tablets used from 1984 to 1988, and there were no malaria fatalities.41 Since 1988, Swiss malaria guidelines for travelers have

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**Table 5. Advantages and Disadvantages of Malaria Prevention Approaches in Long-term Travelers**

<table>
<thead>
<tr>
<th>Approach</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personal protective measures</td>
<td>Effective with minimal toxicity</td>
<td>Cumbersome during a long trip or stay</td>
</tr>
<tr>
<td>Continuous chemoprophylaxis</td>
<td>Most reliable method for medication in high-risk regions</td>
<td>Adverse events from medication</td>
</tr>
<tr>
<td>Seasonal prophylaxis</td>
<td>Best for areas with clear seasons of transmission, knowledgeable and responsible travelers</td>
<td>Must have knowledge of local malaria epidemiology</td>
</tr>
<tr>
<td></td>
<td>Less medication</td>
<td>Weather pattern shifts can lead to variation in transmission of malaria</td>
</tr>
<tr>
<td>Initial prophylaxis followed by SBET</td>
<td>Best for knowledgeable and responsible travelers with long stays in 1 location</td>
<td>Traveler may not arrange medical care</td>
</tr>
<tr>
<td></td>
<td>traveler has control</td>
<td>Traveler may not seek medical care</td>
</tr>
<tr>
<td></td>
<td>Less medication</td>
<td>Traveler may not seek evaluation appropriately</td>
</tr>
<tr>
<td>SBET</td>
<td>Best for knowledgeable and responsible travelers with control</td>
<td>Misuse/overuse of medication</td>
</tr>
<tr>
<td></td>
<td>Less medication</td>
<td>Errors can occur regarding medication dose or schedule</td>
</tr>
<tr>
<td></td>
<td>Positive risk-benefit analysis for long-term travelers in low-risk areas</td>
<td>Traveler may not seek medical evaluation for febrile illness</td>
</tr>
<tr>
<td></td>
<td>May be life-saving in certain circumstances</td>
<td>Weather pattern shifts can lead to variation in transmission of malaria</td>
</tr>
<tr>
<td></td>
<td>Low cost</td>
<td>Requires detailed instructions</td>
</tr>
<tr>
<td>Combination of seasonal or initial prophylaxis with SBET</td>
<td>Best for knowledgeable and responsible travelers</td>
<td>Need detailed instructions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other problems as above</td>
</tr>
</tbody>
</table>

Abbreviation: SBET, stand-by emergency treatment.
recommended SBET for travelers to low-risk malaria areas.69

Much debate regarding SBET ensued. Assessment of Swiss and German travelers who used SBET found 4- to 10-fold overuse.70,71 The drugs can have adverse effects and can be inappropriately used for illnesses that require other treatment. Further study of Swiss travelers who were prescribed SBET found that one third of patients ill with malaria-like symptoms did not seek medical attention as advised.70 Adherence to SBET guidelines is a recognized problem with the SBET strategy, and travelers need concise oral and written instructions and personalized dosage schedules for family members.72 Errors associated with SBET use include changing chemoprophylaxis, ie, the tendency to replace chemoprophylaxis with SBET (11%); lack of confirmation of diagnosis after initiating SBET (25%); lack of medical evaluation (25%); and mistakes with medication (88%).71 Self-diagnosis of malaria is unlikely to be correct.70,71 Use of SBET can lead to delayed diagnosis of other serious conditions.72

Currently, SBET alone is recommended for Swiss and German travelers to low-risk areas of Asia and Central and South America, while chemoprophylaxis remains the best strategy for travelers going to areas with high \( P\) falciparum transmission, such as sub-Saharan Africa and Papua New Guinea.73 Recently some European experts have also adapted the SBET strategy for travelers to India, because new data on imported malaria from the Indian subcontinent showed a very low risk of infection74 and suggested that most imported infections are late-onset \( P\) vivax infections. In many European countries, atovaquone-proguanil or a fixed combination of artemether-lumefantrine (not available in the United States) are recommended as ideal SBET. Chloroquine can be recommended as SBET only in Central America due to widespread resistance elsewhere. Mefloquine can also be used as a reasonably priced SBET but has been associated with considerable adverse events at therapeutic doses.72 Quinine remains an option for pregnant women but has a complicated dosage schedule. Two older medications that were originally recommended for SBET are now contraindicated: sulfadoxine-pyrimethamine (due to fatal adverse events)76 and halofantrine (associated with sudden death in travelers due to fatal arrhythmias)77 (TABLE 6).

The US Centers for Disease Control and Prevention currently does not recommend SBET alone for travel to low-risk areas but does recommend atovaquone-proguanil for SBET, which applies to high-risk areas where SBET should be considered in addition to chemoprophylaxis in the event a traveler needs to self-treat.46 Because of the concern for resistance and additive toxicity, the medication used for SBET should differ from what the traveler uses for chemoprophylaxis.

**Use of Rapid Diagnostic Tests**

A major drawback of SBET is the difficulty encountered by travelers in correctly diagnosing a malaria infection. In 1994 it was suggested that trained travelers could use rapid dipstick malaria tests,70 and thereafter self-testing has been evaluated in healthy and febrile travelers.78-80 Except for one study of UK travelers81 in which 91% of participants could successfully perform and interpret the test, the approach has been hampered by technical difficulties on the part of travelers and also by the issues of false-positive and false-negative results. Components of the rapid tests are likely to deteriorate during long-term storage in tropical climates.82 These tests currently are not

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**Table 6. Medications Recommended as Stand-by Emergency Self-treatment (SBET)**

<table>
<thead>
<tr>
<th>Medication (Proprietary Name)*</th>
<th>Adult Dosage</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Artemether-lumefantrine</strong> (20 mg/120 mg) (Riamet; Co-Artem)</td>
<td>80 mg/480 mg, then 80 mg/480 mg in 8 h, then 80 mg/480 mg every 12 h for 2 d (24 tablets over 3 d)</td>
<td>Effective against multiresistant ( P) falciparum, Rapid parasite and fever clearance, Good safety/tolerability profile for children &gt;10 kg</td>
<td>Not available in the United States, Short shelf life (&lt;2 y)</td>
</tr>
<tr>
<td><strong>Atovaquone-proguanil</strong> (250 mg/100 mg) (Malarone)</td>
<td>1000 mg/400 mg daily for 3 d (12 tablets over 3 d)</td>
<td>Effective against multiresistant ( P) falciparum</td>
<td>Potential for resistance development</td>
</tr>
<tr>
<td><strong>Mefloquine</strong> (Lariam, 250-mg base; Mephaquin, 250-mg base)</td>
<td>750-mg base, then 500 mg in 12 h (5 tablets in 1 d)</td>
<td>Inexpensive, Wide experience, Effective against all Plasmodial species, Can be used for children &gt;5 kg, Can be used in second and third trimesters of pregnancy</td>
<td>Increasing ( P) falciparum resistance, Neurotoxicity increases at treatment doses (1:216)71, Negative reports in media</td>
</tr>
<tr>
<td><strong>Chloroquine</strong> (Chlorochin, 150-mg base; Nivaquin, 100-mg base)</td>
<td>600-mg base, then 300 mg in 6 h, 300 mg daily for 2 d (10 tablets over 3 d)</td>
<td>Inexpensive, Can be used for children &gt;5 kg, Can be used in pregnancy</td>
<td>Widespread resistance, Can only be recommended for travelers to Central America and the Caribbean</td>
</tr>
</tbody>
</table>

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*Halofantrine (Halfan) and sulfadoxine-pyrimethamine (Fansidar) are no longer recommended as SBET.
available to travelers in the United States.

**Counterfeit Drugs**

Counterfeit drugs, including antimalarial drugs, are widely distributed, especially in Asia. Long-term travelers are likely to purchase their drugs in the country of temporary residence unless they return frequently to their home country or can arrange shipment or delivery of drugs. Problems with counterfeit drugs include incorrect amount of active ingredient, toxic or allergic additions to medication, and formulations that may have different pharmacokinetic properties. Long-term travelers must understand these issues and obtain safe, real, and effective medications. A recent report identified at least 12 different counterfeit artesunate products in circulation in Southeast Asia.

**Seasonal Prophylaxis**

No national or international guidelines recommend using chemoprophylaxis only periodically for long-term travel to areas of malaria risk. However, some long-term travelers prefer this approach over continuous chemoprophylaxis. However, if travelers take chemoprophylaxis only in seasons or locations with higher transmission seasons, they also need access to reliable medical care and SBET. Despite the lack of formal proposal or assessment of seasonal malaria prophylaxis in long-term travelers, the practice may be common among expatriates in some locations. Among the expatriate workers at a construction site in Ghana, 6.3% varied their use of antimalarial agents according to the time of the year.

Seasonal chemoprophylaxis for long-term travelers poses a number of problems. It requires knowledge of the local malaria epidemiology, but such data may be unavailable. Travelers using seasonal prophylaxis (eg, only during a high-transmission season, typically the rainy season) risk developing symptomatic malaria when they discontinue suppressive chemoprophylaxis. In contrast to residents in malaria-endemic areas who develop partial immunity over many years, long-term travelers are not immune and are at risk for severe and complicated malaria. Some countries, such as Botswana, Namibia, and South Africa have clearly defined high- vs low-transmission seasons, but unusual weather changes can alter the transmission pattern. Therefore, seasonal malaria prophylaxis should be considered an alternative strategy only for some long-term travelers who clearly understand these complex issues. All long-term travelers should identify medical facilities (and types of services offered) that are available to them locally and regionally.

**Vivax Malaria in Long-term Travelers**

The primary goal of prophylaxis is prevention of severe morbidity and deaths from malaria. Most deaths are from falciparum malaria; vivax malaria, which can be severe, is rarely lethal. However, vivax malaria can have a long latency and present many months after a trip, at a time when the traveler may not recall the exposure. The malaria chemoprophylactic regimens commonly used (chloroquine, doxycycline, mefloquine, atovaquone-proquain) prevent the blood-stage infection but do not prevent relapses of vivax malaria because they do not eliminate the liver-stage parasites (hypnozoites). Falciparum and vivax are the dominant plasmodial parasites in all malarious areas, though the intensity of transmission and relative proportion contributed by each species varies by geographic area and may change over time. In most countries in sub-Saharan Africa, falciparum causes 85% or more of the malaria cases, yet absolute risk of vivax malaria may be higher than in countries in which vivax malaria accounts for all cases but the level of transmission is low. Approximately one third of vivax malaria cases imported to Europe from 1999 to 2003 and reported to TropNetEurop (http://www.tropnet.net) followed exposures in sub-Saharan Africa. Although severe complications were rare, 60% of the patients were hospitalized.

Vivax malaria accounts for one quarter to more than one half of malaria cases in travelers in some series and varies depending on the predominant destination. High attack rates of vivax malaria have been reported in short-term travelers after intense exposures, eg, a 50% infection rate was reported among Israeli travelers (taking mefloquine prophylaxis) to Ethiopia. Additionally, more than 60% to 80% of travelers with vivax malaria present at least 2 months after departure from the risk area (late onset), when clinical suspicion for malaria may be low.

In recent years, about one quarter of reported malaria cases in the United States (in US and foreign civilians and US military personnel) were due to P vivax (among cases where species was identified); an additional 2.6% to 3.6% were attributed to P ovale. Countries and regions contributing the largest numbers of vivax malaria cases were by order of contribution, starting with the region contributing the most cases: Asia (India and Pakistan mostly), Africa, Central America and the Caribbean, Mexico, Oceania (primarily Papua New Guinea), and South America. Among the cases of vivax malaria reported to the GeoSentinel database, exposures in Africa accounted for 29.5%; Asia, 27%; Oceania/the Pacific, 19.5%; and the Americas, 16.8%. More detailed global distribution of P vivax is described elsewhere.

Vivax and ovale are the 2 plasmodial species that have dormant forms, ie, hypnozoites, that remain in the liver and can later enter the bloodstream to cause clinical relapses. Korean War soldiers treated with chloroquine for vivax malaria experienced fewer relapses after the addition of primaquine, an 8-aminooquinoline; this was called radical cure. Use of drugs to eradicate incubating liver hypnozoites, also called presumptive antirelapse treatment or terminal prophylaxis, refers to the administration of primaquine to asymptomatic persons after their departure from an area where exposure to P vivax may have occurred and is usually administered during the last 2 weeks of malaria chemoprophylaxis.
The recommended primaquine dose for antirelapse treatment was recently increased from 15 mg to 30 mg daily for 14 days because of high failure rates with the lower dose. Relapses have been more common in travelers who have visited Papua New Guinea or eastern Indonesia, where the vivax strain (Chesson) appears to be more resistant to drugs. The timing and combination with other antimalarial agents appear to be important. A higher cure rate occurred in treating the Chesson strain of *P. vivax* with concurrent administration of primaquine with quinine or chloroquine rather than sequential administration of quinine followed by primaquine.

For travelers who may have had significant exposure to *P. vivax* (eg, long-term travelers to Papua New Guinea and other areas with substantial vivax transmission), primaquine, 30 mg daily, is currently recommended as antirelapse treatment to be given near the end of the course of chemoprophylaxis. Although data suggest that the combination of primaquine with chloroquine or quinine eradicates hypnozoites, so far there is no evidence that primaquine alone is effective in preventing relapse. Primaquine can generally be started after the traveler has returned home (and is still completing chemoprophylaxis), though travelers need to be advised before departure that they should schedule an appointment on return. Screening for G6PD deficiency is essential before administering primaquine. Some data suggest that a weekly dose of primaquine can be considered (for radical cure, not antirelapse treatment) in patients with mild G6PD (usually the A-variant) deficiency. Whether or not returned travelers receive antirelapse treatment, they should be informed of the potential for late relapse and the need to seek medical attention. They should inform their clinicians about their durations of exposures in malarious areas.

**CONCLUSIONS**

Long-term travelers to malaria-endemic areas face risk of death, morbidity, and reduced productivity because of malaria. General guidelines are desirable, but recommendations for malaria prevention in long-term travelers must be individualized and should be provided by travel medicine specialists (Table 5). Personal protective measures are paramount. Identification of reliable medical facilities at destinations is crucial for long-term travelers regardless of their malaria prevention strategies, and a number of resources are available to aid in this process (eg, the International Association of Medicine Web site [http://www.iamat.org] and the International Society of Medical Assistance to Travellers Web site [http://www.iamat.org]). Data on safety of chemoprophylaxis drugs show reasonable clinical support for long-term use, particularly for mefloquine. Many long-term travelers use a combination of strategies (Figure). Factors and decisions influencing the choice of ap-
PREVENTION OF MALARIA IN LONG-TERM TRAVELERS


25. Burdon J. Use of malarial prophylaxis amongst a

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population of expatriate church workers in North-