Long-term malaria prophylaxis is hampered by a lack of standardization and compliance. Advice should be individually optimized to achieve a high degree of protection and compliance. Individual risk assessment takes into consideration the duration of stay in the endemic area, the individual exposure, the seasonal transmission rates, and the drug-resistance situation. Methods for prevention of exposure may help reduce the reliance on chemoprophylactic drugs. Exposure–prevention methods may be combined with standby treatment in lower transmission areas if the traveler has been trained to take the antimalarials appropriately. Although suitable for long-term use, chloroquine and chloroquine–proguanil cannot be used as prophylaxis owing to high resistance rates in most endemic regions. Mefloquine is suitable for most malaria-endemic regions, although its use is restricted by neuropsychiatric side effects, particularly in women. Doxycycline is also appropriate; experience with long-term malaria prophylaxis is available for up to 6 months. The use of atovaquone–proguanil is restricted to 28 days in some countries, but clinical studies indicate that its use is suitable for at least 20 weeks. Primaquine is also effective for chemoprophylaxis; experience is limited to 1 year of protection against falciparum and vivax malaria. When giving individual recommendations to a traveler, special considerations for backpackers, expatriates, and frequent travelers may apply.

Principal Considerations

Travel, for business or pleasure, in malaria-endemic regions often lasts for up to only 4 weeks’ duration. Those who travel for longer than 4 weeks are considered long-term travelers, such as backpackers, expatriates who more or less live in one place for months or years, and business travelers who frequently visit tropical areas. In the United Kingdom, long-term travelers are defined as those who are visiting or traveling through malaria-endemic countries for > 6 months.1

There is a negative correlation between compliance of prophylactic measurements and the duration of stay in the endemic area. Long-term travelers tend to adopt a nonchalant attitude toward malaria, as is observed in the local population, and therefore often disregard the recommendations of their physicians back home.

In general, the degree of compliance varies widely. It is by and large accepted that it is more appropriate to individualize rather than to standardize malaria prophylaxis recommendations for long-term travelers; however, expert recommendations are often vague. The German Society of Tropical Medicine, for instance, does not give any specific recommendation but stresses the need for experienced tropical doctors to give appropriate individual advice.2 Publications from the Centers for Disease Control and Prevention (CDC) do not provide any specific recommendation for long-term travelers.3 The World Health Organization (WHO) recommendations on drugs appropriate for long-term application are brief.4 Recently, the Health Protection Agency Advisory Committee on Malaria Prevention for UK Travellers has provided a supplement to the guidelines for malaria prevention in travelers from the United Kingdom for 2003 titled “Malaria Prophylaxis for Long-Term Travellers.”1 This document contains a more complete description of antimalarials and additional preventive measures, together with recommendations for malaria chemoprophylaxis for individual countries, the latter of which are similar to the German guidelines, which also provide country-, region-, and season-specific recommendations for antimalarial drugs.2

Pretravel advice should provide information on individual risk assessment. It is essential to clarify that temporarily exposed travelers are at greater risk than the endemic population since they lack both genetic protective factors and immunity. Moreover, the statistical probability of being infected by sporozoites increases to nearly 100% when, for example, the stay in the endemic area exceeds 4 weeks and 10 bites per night are received, assuming that 1% of the bites are infective.5
An important factor for risk assessment is the drug-resistance situation in the travel area. Drugs that are known to be poorly effective should not be used since a grade 1 or 2 resistance breakthrough might further hamper a differential diagnosis when atypical clinical malaria occurs. This has been shown to be particularly true for travelers developing subclinical forms of falciparum malaria under chloroquine-proguanil prophylaxis. This drug combination has been shown to have an average protective efficacy of < 70%, and it is therefore no longer considered adequate for most malaria-endemic areas.

The Tools

Methods for prevention of exposure, believed to be initiated by armies of the classical era and later by Teutonic tribes, consist of avoiding swamps and staying in higher-altitude camps. Today’s recommendations include the use of window screens, pyrethroid-impregnated bed nets, repellents (on skin, soap, and clothes), and mosquito coils. Conventional formulas of repellents, such as diethyltoluamide, are more effective than plant products such as soybean oil or citronella. Wearing long-sleeved shirts, pants, and socks to cover the skin is usually not acceptable to long-term travelers. Travelers should be encouraged to spray their residences with long-lasting insecticides and to destroy possible mosquito breeding grounds. When explained carefully, these methods are generally well accepted, and when appropriately applied, they are extremely helpful in preventing a reliance on prophylactic drugs.

It is more difficult to give standardized recommendations for chemoprophylaxis. Moreover, the compliance with malaria chemoprophylaxis is extremely poor, particularly in long-term, occupational travelers and backpackers. The main reasons for this reluctance seem to be fear of long-term side effects and conflicting advice on prophylaxis. One option is to convince the traveler to take prophylactic drugs at least temporarily when the local transmission rate increases seasonally. For the rest of the year, standby treatment may be sufficient. Unfortunately, medical facilities capable of producing a qualified diagnosis are not common in hyper- and holoendemic malaria areas, where the patients sometimes seem more experienced than their physicians. Thus, the appropriate application of standby treatment is currently more or less unverifiable in long-term travelers. In any case, travelers should be encouraged to use good manufacturing practice (GMP) drugs from home since the rate of counterfeit drugs is high in some developing countries.

Long-term malaria chemoprophylaxis is generally believed to have been implemented for the first time in 1854, when Dr. William Balfour Baikie effectively put his staff on quinine while exploring the Niger River in West Africa. Reports of the US Sanitary Commission, however, provide evidence that quinine was added as early as 1840 to the whiskey of the military post staff at Tampa Bay, Florida, successfully preventing “miasmatic disease” or “African fever.”

Today the indications for various short-term prophylaxis measurements are well established, whereas the use of long-term chemoprophylaxis is still open for extensive modification. During recent decades the majority of malaria drugs have been tested for long-term use. Some of these drugs are no longer considered useful for travelers, such as sulfadoxine-pyrimethamine, mefloquine-sulfadoxine-pyrimethamine, and dapsone-pyrimethamine.

Drugs for Long-Term Use

WHO recommendations for chloroquine are generally accepted among physicians as the standard. The drug is appropriate for long-term use, and the risk of serious side effects associated with long-term prophylactic use is low. Retinopathy associated with long-term use of chloroquine is a rare event, even if a cumulative chloroquine dose in excess of 300 g is used, although it has been known to occur at lower doses. Therefore, chloroquine requires screening for retinal changes every 2 years when taken for more than 3 (700 mg/wk) or 5 (300 mg/wk) years. With increasing drug resistance, however, indications for such chemoprophylaxis are decreasing. In Germany, for example, chemoprophylaxis is no longer recommended for travelers going to any endemic area, with or without proguanil (which is usually combined with chloroquine). Using daily proguanil in addition to chloroquine has not always been shown to provide additional protection.

Because of increasing drug resistance in the past 15 years, chloroquine and proguanil have been gradually replaced by mefloquine for both short- and long-term prophylaxis. Major studies of mefloquine tolerability, as well as worldwide monitoring, have shown that serious adverse events are rare, and it is usually safe and well tolerated for long-term prophylaxis, particularly in males. There is no measurable accumulation of mefloquine in the serum, even when every-other-week dosing is replaced by weekly dosing, the latter which is more effective as shown in the 1990s. Mefloquine-resistant parasites, however, have been isolated from military, long-term travelers since the early 1990s. Female travelers should be informed of an increased risk of neuropsychiatric side effects during long-term prophylaxis. Mefloquine plasma levels do not show substantial gender-specific differences; thus, recommendations on dose reduction for female travelers under long-term mefloquine prophylaxis so far lack scientific support.

Both mefloquine and doxycycline are appropriate prophylactic drugs for chloroquine-resistant infections,
which now occur in nearly all of the *Plasmodium falciparum*-endemic areas. There is little information regarding long-term (> 6 mo) use of doxycycline; however, available data are reassuring.\(^2\) There is considerable information regarding its use in long-term therapy for acne, Q fever endocarditis,\(^3\) and small, asymptomatic, abdominal aortic aneurysms.\(^3\) As for malaria chemoprophylaxis, the drug has predominantly been tested by military personnel, and the incidence of adverse events as well as the effectiveness were acceptable.\(^2\) The major side effects are episodes of cutaneous photosensitivity reactions, tooth discoloration, yeast infection, and gastrointestinal symptoms,\(^3\) including esophageal perforation. National regulations, such as those regarding the patient’s formal or informal consent, should be considered when the drug is not specifically licensed for malaria prophylaxis. There is no general limitation or restriction for the use of doxycycline in the CDC recommendations.\(^2\) The monohydrate formula of doxycycline is better tolerated than the hyclate formula.\(^3\)

In some countries (not the United States), the use of atovaquone-proguanil is restricted to 28 days plus 1 to 2 days before and 1 week after the stay in the endemic area. However, in single observations as well as in clinical studies, the drug has proved to be appropriate for long-term prophylaxis. For example, in Indonesia over a 20-week duration, the daily dose of 250 mg atovaquone plus 100 mg proguanil (1 adult tablet of Malarone) prevented most of the 148 transmigrants from contracting vivax or falciparum malaria with a protective efficacy of 84 and 96%, respectively.\(^3\) A 6-month safety study in Danish soldiers showed that the drug was well tolerated and effective.\(^3\) A recent postmarketing surveillance showed atovaquone-proguanil to be well tolerated by long-term travelers taking the drug for up to 34 weeks.\(^3\) Since the drug is considered causal prophylaxis, that is, acting on the plasmodial liver stage, it may be discontinued after 1 week, as compared with 4 weeks after departure from the malarious area in the case of mefloquine. It is particularly useful for a subset of long-term travelers, namely, those who travel frequently to and from endemic areas, to provide them some relief from continuous drug consumption. Atovaquone-proguanil has been well accepted by the travel community because of its lower rate of severe and neuropsychiatric side effects compared with mefloquine.\(^3\)

Primaquine is used for relapse prevention against vivax and ovale malaria. It is also effective for causal chemoprophylaxis. In order not to risk severe hemolysis, those with glucose-6-phosphate dehydrogenase deficiency should be excluded. Recently, Javanese transmigrants were protected against falciparum and vivax malaria at an efficacy of 93% when they took daily doses of 30 mg for 20 weeks.\(^3\) An earlier study in Javanese men showed primaquine to be 94.5% effective for prevention of *Plasmodium falciparum* infection and 90.4% for *Plasmodium vivax* infection when used for 1 year.\(^3\) In both studies the drug was well tolerated. Primaquine is usually not licensed for long-term malaria chemoprophylaxis. The CDC recently added it to their list of approved drugs but did not stipulate whether it should be used for short or long terms.\(^3\)

In clinical phase 2 studies, another 8-aminoquinoline, tafenoquine, has been shown to be effective in 86 or 89% when given in 200 or 400 mg weekly doses, respectively, for up to 13 weeks in Kenya.\(^3\) Apparently, the drug will not be released for marketing in the near future.

### Special Considerations for Frequent Travelers

Travelers who frequently visit malaria-endemic area to another are not usually familiar with local medical facilities, and they are unable to estimate the laboratory quality of malaria testing. Continuous chemoprophylaxis should therefore be encouraged when indicated. Priority should be given to drugs that may be used for both chemoprophylaxis and standby, such as mefloquine and atovaquone-proguanil.

### Special Considerations for Expatriates

Expatriates who live where malaria is hyper- or holoendemic should be encouraged to take continuous chemoprophylaxis during the high-transmission periods and to be on standby for the rest of the season. They should rely on local malaria testing and treatment only if there is external quality control of test results.

### Special Considerations for Backpackers

Backpackers and other travelers who move from one malarious area to another are not usually familiar with local medical facilities, and they are unable to estimate the laboratory quality of malaria testing. Continuous chemoprophylaxis should therefore be encouraged when indicated. Priority should be given to drugs that require the minimum period of application.
recommendation and the compliance to be expected from the traveler. When accompanied with appropriate information on the respective malaria situation, more general prophylaxis methods are easily accepted, whereas the long-term use of drugs is not. Thus, even for high-transmission areas, it may be indicated to recommend chemoprophylaxis at intervals, for example, in periods of high malaria transmission during the rainy season or during trips from low- to high-transmission areas. In summary, the following issues should be considered for long-term travelers to hyper- and holoendemic malaria regions:

- Give appropriate information on the respective malaria situation.
- Encourage exposure prophylaxis including spraying of the residence and control of mosquito breeding grounds.
- Give information on the drugs appropriate for the individual case.
- Encourage chemoprophylaxis for periods of high transmission.
- Encourage standby treatment for periods without chemoprophylaxis.
- Make sure that GMP drugs are used for chemoprophylaxis and standby treatment.
- Take caution in recommending local clinics for malaria testing if there is no information on the quality standard.

References


