Preparing your patients to travel abroad safely
Part 3: Reducing the risk of malaria and dengue fever

Roger E. Thomas, MD, PHD, CCFP, MRCPG

OBJECTIVE To provide evidence-based recommendations for family physicians advising travelers on how to reduce their risk of malaria and dengue fever.

QUALITY OF EVIDENCE A search of MEDLINE from 1990 to November 1998 found 671 articles; randomized controlled trials and systematic reviews were sought. The Cochrane Collaboration was searched for studies relevant to family physicians; meta-analyses of impregnating bed nets with permethrin were found. Health Canada’s evidence-based publications were searched; 10 recommendations based on at least one well-conducted randomized trial were found.

MAIN MESSAGE Good evidence-based advice about the efficacy of mefloquine in chloroquine-resistant areas and for pregnant women and children is available, as is advice on the effectiveness of permethrin-impregnated bed nets.

CONCLUSIONS Family physicians can use evidence-based recommendations to advise their patients on how to prevent malaria. The ways in which patients neglect malaria precautions are well-known. For prevention of both malaria and dengue fever, family physicians should counsel their patients to reduce the risk of being bitten by insects.

This article has been peer reviewed.
Cet article a fait l’objet d’une évaluation externe.
Considerable evidence indicates that travelers are insufficiently aware of the risk of malaria and that they prepare inadequately to avoid it. One study showed that fewer than 50% of British travelers understood the risk of malaria, particularly for children and pregnant women. Only 5% of West Africans living in England, who had visited West Africa and were admitted to the Hospital for Tropical Diseases in London with malaria, had taken antimalarial drugs for 4 weeks after their return. Only 40% of Belgian and 70% of Swiss travelers claimed to have completed 4 weeks of malaria prophylaxis after returning from trips.

Quality of evidence
A search of MEDLINE from 1990 to November 1998 using the MeSH headings “travel” and “malaria” found 671 articles; randomized controlled trials and systematic reviews were sought. The Cochrane Collaboration database of systematic reviews was also searched: meta-analyses relevant to family physicians concerning permethrin-impregnated bed nets were found. Health Canada’s evidence-based publications were searched; 10 recommendations based on at least one well conducted randomized trial relevant to family physicians were found.

Avoiding mosquito bites
Travelers should try to avoid being bitten by mosquitoes by staying indoors between dusk and dawn, by wearing long sleeves and long trousers tucked into socks, by staying in screened buildings, by using diethyltoluamide (DEET) on the skin (35% DEET protects for up to 4 hours, 95% DEET protects for 10 to 12 hours), by using a mosquito bed net, and by using permethrin on bed nets and clothes.

If these precautions are not followed, risk of malaria for a stay of 1 night in a tropical area is 1% if bitten once, 9% if bitten 10 times; and for a stay of 4 weeks is 25% if bitten once and 94% if bitten 10 times.

Use of permethrin-impregnated bed nets
The efficacy of permethrin-impregnated bed nets for preventing malaria in children in areas where malaria is endemic has been shown in a Cochrane Collaboration meta-analysis. The study also concluded that, because mortality from malaria is greatest in the first 3 years of life, children should use preimpregnated bed nets that should be re-impregnated every 3 months. Relative risk of malaria for children using bed nets is 0.82. Risks for children and adults from countries where malaria is not endemic are much higher.

Counseling about specific sources of risk
Physicians should emphasize in their counseling the following factors that affect the efficacy of antimalarial regimens.

Length of exposure increases risk. A visit of 4 to 12 months increases risk 80-fold compared with a visit of 1 week. Male travelers are four times more likely than female travelers to acquire malaria in West Africa: it is not known whether they are outside more or take more risks.

Travelers have inadequate information. Less than 50% of British travelers who went to regions in Africa where malaria is endemic understood the risks, the mosquito vector, or the increased risk to pregnant women and children. Responses to a mailed questionnaire indicated that one third of British general practitioners did not give advice about avoiding insect bites.

Need for compliance. Those least likely to take antimalarial agents and most in need of careful instruction are elderly people traveling to join family abroad; schoolchildren returning to family or school in malarious areas; and those born in malarious areas and now living in the West (not realizing that after 1 to 3 years in the West their immunity is lost).

Delay in diagnosis might result in death. In a United States study, 86% of cases of falciparum malaria presented within 1 month of return, 10% within 1 to 2 months, 3% within 3 to 5 months, and only 1.4% after 12 months. In the United Kingdom, 28% developed symptoms abroad, but 95% of the remainder developed symptoms within 3 weeks of return. About 100 travelers returning to Europe die of malaria each year due to delay in developing symptoms (usually 2 to 4 weeks after returning); delay in seeking diagnosis; and delay in physicians’ offices when doctors do not ask for a travel history, are unaware of the delay in symptoms of malaria, or wait for test results through routine channels.

Inadequate avoidance of insect bites. A large on-board survey of passengers traveling to Africa on a Swiss airline (with a follow-up mailed questionnaire...
Concerning their compliance with malaria prevention found that 90% took their prophylactic medication regularly, but only 1% used all four physical preventive measures (mosquito net, insect repellents, insecticides, and long clothing in the evening).6 Permethrin is the greatest nonpharmacologic advance in mosquito control, and travelers should buy treated nets or treat their own bed nets and clothing.

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**Advising on malaria prophylaxis**
Travelers should begin antimalarial medications 2 weeks before departure in order to detect potential allergies and to build up good levels in the tissues. For antimalarial drugs taken weekly, travelers should be advised to take them on the same day of the week, every week, while in malarious areas, and for 4 weeks after return to Canada.

Patients can be advised that mefloquine prophylaxis is highly effective. A MEDLINE search of randomized controlled trials of mefloquine found 37 trials, of which 10 met the inclusion criteria for systematic review. Withdrawal due to side effects was higher in the treatment arm than in the placebo arm of the studies (odds ratio [OR] 3.49; 95% confidence interval [CI] 1.42 to 8.56). The OR for withdrawal compared with trials of other prophylaxis was 1.33 (95% CI 0.75 to 2.36).7

The evidence-based Health Canada publication 1997 Canadian Recommendations for the Prevention and Treatment of Malaria among International Travelers8 rates as A1 the following prophylactic regimens: in chloroquine-sensitive areas, chloroquine; in chloroquine-resistant areas, mefloquine or doxycycline (or, less optimally, chloroquine plus proguanil) for people unable to take mefloquine; and, in chloroquine- and mefloquine-resistant areas, doxycycline8 (Table 1).

**Pregnant women and children**
For pregnant women and children, the following recommendations are rated A1:8 avoid travel to areas with strong resistance to chloroquine; use personal protective measures in malarious areas; use chloroquine in the few chloroquine-sensitive areas (Haiti, Dominican Republic, Central America, and the Middle East; use mefloquine in chloroquine-resistant areas when exposure is high; use mefloquine beyond 16 weeks of pregnancy; and refer pregnant women at high risk of falciparum malaria for individual risk assessment and counseling by a tropical disease expert (Table 2).8 Travelers should be advised that there is no safe and effective chemosuppressive for pregnant women and children younger than 8 years traveling to the borders of Thailand with Myanmar and Cambodia.

Pregnant women should use extra diligence in avoiding insect bites. They should use DEET on their skin in concentrations of 25% or less and wash it off when not needed. Permethrin should be used on clothing and bed nets: there are no known harmful effects during pregnancy.14

In general, travel to areas of chloroquine-resistant Plasmodium falciparum (CRPF) should be avoided during the first 3 months of pregnancy. If patients have to travel, mefloquine should be used, because the risks of CRPF are greater than the risks of side effects from mefloquine.14,15 Women in Malawi and on the Thai-Myanmar border have used it without adverse effects.15

Although chloroquine and proguanil are safe during pregnancy (proguanil is not known to cause harm to fetuses), an, the combination in chloroquine-resistant areas is only 50% effective (significantly less effective than mefloquine) and is thus not an adequate choice.

Women pregnant with a first child develop higher levels of parasitemia. For pregnant women, CRPF is a medical emergency, and quinine (or quinidine) followed by pyrimethamine should be used.14

Other antimalarial agents have been shown to be safe during pregnancy (pyrimethamine is used for toxoplasmosis and dapsone for leprosy). Doxycycline inhibits bone growth, and artemisinin has been shown to be embryotoxic in animal studies.14

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**Table 1. Evidence-based statements about malaria chemosuppressives**

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                                        |                | 2nd choice: chloroquine + proguanil |
| Chloroquine- and mefloquine-resistant     | Doxycycline    | None         |

Data from Health Canada.8

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Balancing mefloquine’s side effects and benefits

A Swiss study found that mefloquine had 100% prophylactic efficacy (but caused nausea and dizziness in 30% of those taking it). In Peace Corps volunteers in sub-Saharan Africa, mefloquine was 94% (95% CI 86% to 97%) more effective than chloroquine and 86% (95% CI 67% to 94%) more effective than chloroquine plus proguanil. A summary of a range of studies concluded that the prophylactic efficacy of mefloquine was 91% compared with 82% for pyrimethamine plus sulfadoxine; 72% for chloroquine plus proguanil; and 10% to 40% for chloroquine.

Although concerns have been raised about mefloquine’s side effects, most people do not have side effects. Falciparum malaria can be fatal. Those at risk of CRPF should take mefloquine: it has been used safely for years by Peace Corps volunteers.

The main concern is the (rare) risk of seizures (1/13,000 for short-term prophylactic use; 1/1200 to 1/1700 for therapeutic use). Patients with an established history of hypersensitivity to mefloquine or with neuropsychiatric disorders are counseled not to take mefloquine and, therefore, should strongly consider not going to malarious areas. Mefloquine lowers the serum level of valproic acid: doses of valproic acid might need to be adjusted for patients with seizures.

Another concern has been that mefloquine might produce dizziness and imbalance. A double-blind placebo-controlled study of mefloquine in 23 Swiss trainee airline pilots, however, found no differences in flying performance, psychomotor function, or body sway. A study of 420 travelers to Africa found that 11% reported adverse effects, mostly neurologic and psychiatric, but there were no changes in the results of computerized performance tests.

Self-treatment

Experts discourage patients from self-treatment, except in isolated areas where help is not available. Thick and thin smears are required for diagnosis of malaria, and a series of smears can confirm that the medication is clearing malaria from the bloodstream. A copy of the Health Canada dosages for self-treatment of malaria should be given to every traveler who might go to areas where medical help is unavailable. There is an excellent discussion of self-treatment in Schlagenhauf and Phillips-Howard.

Avoiding dengue fever

Dengue is the most frequent arbovirus infection among travelers in the tropical regions of Africa.
South America, Central America, the Caribbean, Asia, and Oceania. Dengue fever has been seen considerably more frequently since 1980 in Central and South America and the Caribbean. There is no vaccine to prevent it. It is transmitted by the day-biting Aedes genus of mosquitoes, which is adapted to living in water receptacles in urban areas. Similar precautions to those taken for malaria will reduce the likelihood of contracting dengue fever.19

Symptoms are myalgias, arthralgias, headache, and a rash (similar to measles, or small red spots, or small bleeding spots under the skin). Dengue fever is usually mild and self-limited. Diagnosis might not be straightforward: of 130 German tourists with clinical symptoms, only 7% had the confirmatory rise in dengue IgG and IgM.20

Dengue fever can present in a severe form, dengue hemorrhagic fever, which is rare in travelers from the developed world but more common among those younger than 15 years or having a second attack. Its symptoms include hemorrhage, shock, high fever, intense muscle aches (“breakbone fever”), and headaches.21

Conclusions
• Family physicians can give good, evidence-based advice to their patients traveling to the tropics.
• Avoiding being bitten by mosquitoes is an important way to avoid malaria and dengue fever.
• Meta-analyses support the efficacy of permethrin-impregnated bed nets in preventing malaria.
• Meta-analyses strongly endorse the effectiveness of mefloquine in chloroquine-resistant areas.
• Health Canada has published detailed, evidence-based recommendations for chemoprophylaxis for travelers, including pregnant women and children.

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References