ISSN 1188-4169

Canada Communicable Disease Report

Date of Publication: March 2000

Volume 26S2

Supplement

— 2000 —

Canadian recommendations for the prevention and treatment of malaria among international travellers

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2000

Canadian recommendations for the prevention and treatment of malaria among international travellers

prepared by the

COMMITTEE TO ADVISE ON TROPICAL MEDICINE AND TRAVEL (CATMAT)

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PREFACE

The prevention and treatment of malaria have changed considerably over the last decade primarily as a result of the development and spread of drug-resistant parasites and a global resurgence of disease.

The following recommendations are guidelines for health care providers to assist travellers in preventing symptomatic malaria, and in reducing the risk of severe illness or death from this infection.

The Travel Medicine Program at the Laboratory Centre for Disease Control (Health Canada) provides a valuable resource for the traveller and the travel medicine provider. Information is available 24 hours-a-day through the FAXlink service (613-941-3900) or through the internet (www.hc-sc.gc.ca/hpb/lcdc/osh/tmp_e.html).

*CATMAT acknowledges the contribution of Dr. Kain to these guidelines.
Special thanks go to Dr. Phillipa McDonald (HC).

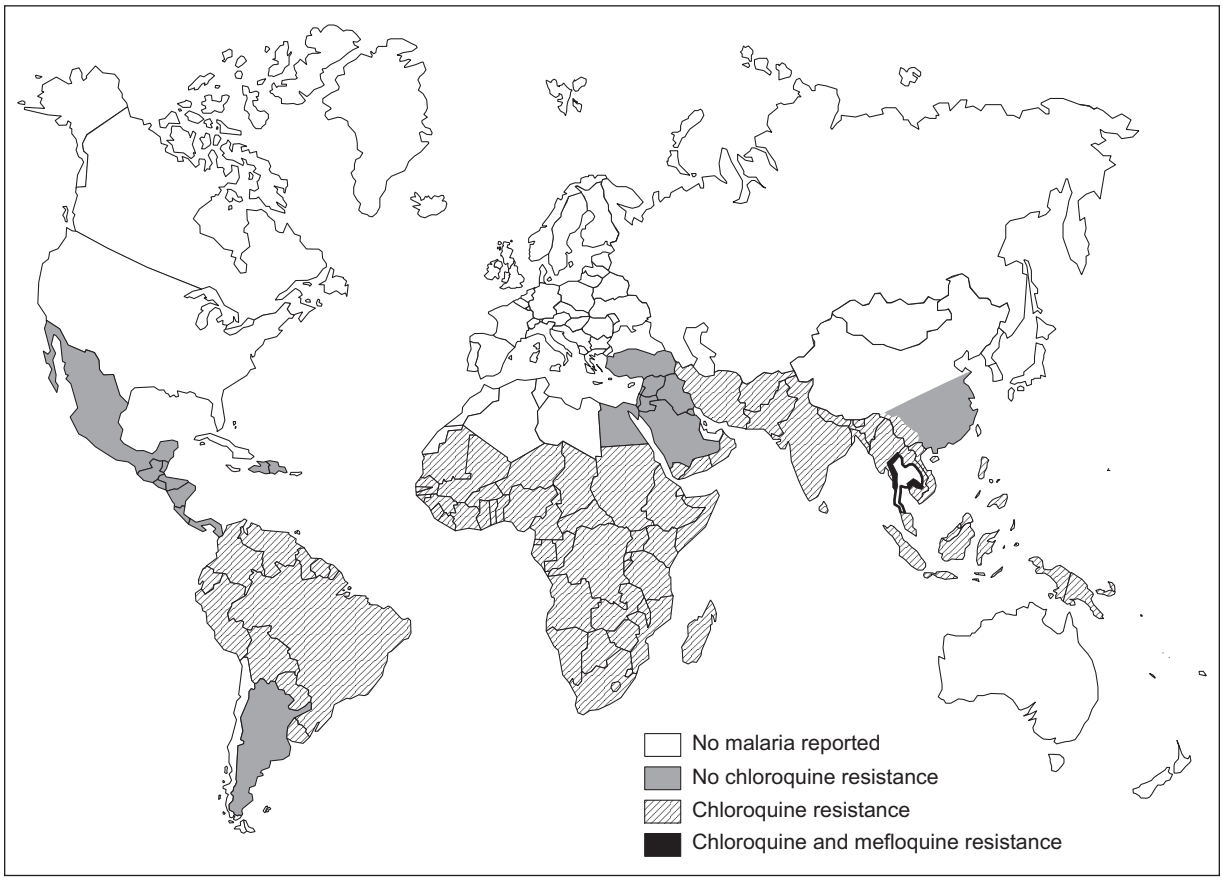
1. Introduction

Malaria is a common and serious infection caused by four species of the genus *Plasmodium: Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale* and *Plasmodium malariae*. Infection with *P. falciparum* can be fatal, and infections caused by *P. vivax* and *P. ovale* can relapse from latent liver stages. All species of malaria are transmitted by the bite of an infected female *Anopheles* mosquito. Rarely, transmission may occur by blood transfusion, by shared needle use, or congenitally from mother to fetus. The disease is characterized by **FEVER** and "flu-like" symptoms such as myalgias, headache, abdominal pain, and malaise. Rigors and chills often occur. The classically described alternate-day fevers or other periodic fevers are often not present. Severe malaria due to *P. falciparum* may cause seizures, coma, and renal and respiratory failure, and may lead to death. **Malaria deaths are frequently the result of delays in the diagnosis and treatment of the infection.**

THE SYMPTOMS OF MALARIA ARE NON-SPECIFIC AND DIAGNOSIS IS NOT POSSIBLE WITHOUT A BLOOD FILM.

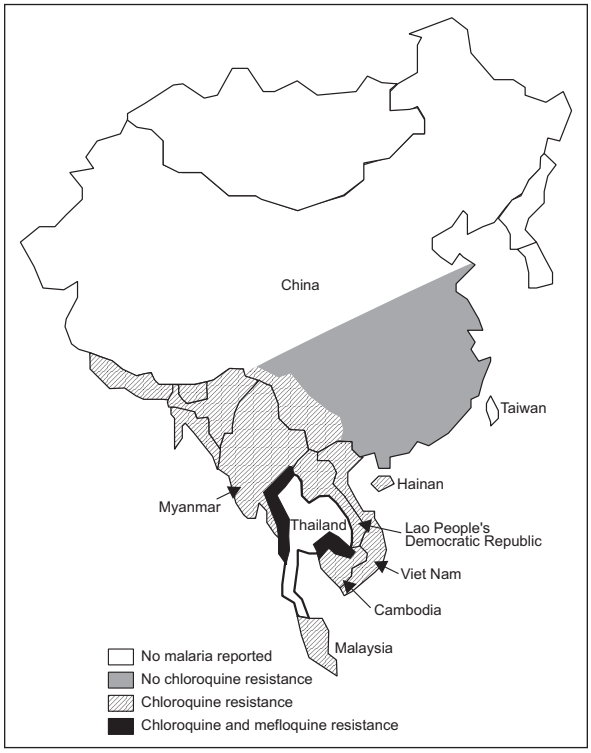
The widespread resistance of *P. falciparum* to chloroquine has complicated the prevention and treatment of malaria. Drug-resistant strains of malaria are now common in much of the world. The maps in Figures 1a and 1b indicate the geographic distribution of *P. falciparum* malaria based on patterns of resistance. These regions require frequent updating as the malaria situation continues to evolve.

Figure 1a
Map showing malaria-endemic zones worldwide*



* Visual aid only, see Appendix I, page 30 for specific country recommendations.

Figure 1b
Enlarged map of China and Thailand showing patterns of malaria resistance*

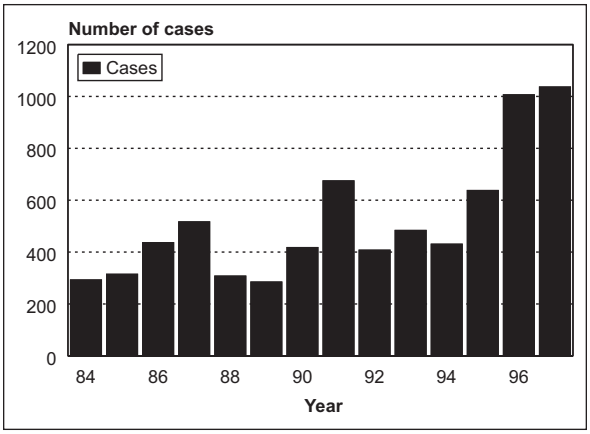


* Visual aid only, see Appendix I, page 30 for specific country recommendations.

As noted in Figure 2 (opposite), the number of reported cases of malaria in Canada has risen more than twofold since 1994, to a peak of 1,036 in 1997. However, it is estimated that only 30% to 50% of cases are reported to public health agencies; therefore the true number of imported cases into Canada is likely to be substantially higher. It is of note that Canada's rate of imported malaria continues to be 3 to 10 times the per capita rate of the United States, which may reflect true differences in risk or may be a reporting artefact.

The majority of imported *P. falciparum* cases in recent years were acquired in sub-Saharan Africa,

Figure 2
Trends in reported malaria cases, Canada, 1984-1997



and the majority of *P. vivax* cases were acquired in the Indian subcontinent. The increased numbers of Canadian malaria cases have been associated with an increased number of malaria deaths: seven from 1997 to 1999. All these deaths were due to *P. falciparum*. Factors contributing to the deaths were noncompliance with or failure to use appropriate chemoprophylactic agents, delay in diagnosis and treatment, and incorrect therapy once a diagnosis had been reached. Almost all malaria deaths in travellers are due to *P. falciparum*.

The overall case-fatality rate of imported *P. falciparum* malaria varies from approximately 1% to 5% and increases to 30% for those over 70 years of age. Progression from asymptomatic infection to severe and complicated malaria can be extremely rapid, with death occurring within 36 to 48 hours. The fatality rate of severe malaria is > 20% even when managed in modern intensive care units. The most important factors that determine patient survival are early diagnosis and appropriate therapy. It should be emphasized that the majority of infections and deaths due to malaria are preventable.

2. PREVENTION

Four components of malaria protection should be discussed with the traveller:

a. the risk of acquiring malaria
b. personal measures to prevent mosquito bites
c. chemoprophylactic drugs (where appropriate)
d. the need to seek early diagnosis and treatment for a febrile illness

a. Risk of Acquiring Malaria

All travellers to malarial areas need to be aware of the risk of malaria infection, how they can best protect themselves, and the need to urgently seek medical advice if they develop a fever. Travellers staying overnight in rural areas may be at highest risk.

Malaria transmission occurs in most of sub-Saharan Africa and New Guinea; in large areas of Southern Asia; in parts of Southeast Asia, Oceania, Haiti, Central and South America; and in limited areas of Mexico, the Dominican Republic, North Africa and the Middle East. Appendix I provides country-specific information on malaria risk and recommended chemoprophylaxis. This information is derived from World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) sources. While this is the most accurate information at the time of publication, many factors such as variations in local reporting rates and surveillance may significantly affect the reliability of these data.

Malaria transmission occurs between dusk and dawn, corresponding to the biting habits of the female *Anopheles* mosquito. The risk of transmission is increased in rural areas and varies seasonally in many locations, being highest at the end of the rainy season. Risk is proportional to the duration of an individual's exposure. Transmission decreases at altitudes above 2,000 metres (6,500 feet).

Travel to urban and tourist areas of Southeast Asia, and Central and South America are considered to entail minimal risk, whereas urban travel in other malaria-endemic regions, such as sub-Saharan Africa, the Indian subcontinent, and New Guinea (Papua New Guinea [PNG] and Irian Jaya) may be associated with significant risk of infection. In recent years, the spread of drug-resistant malaria and the prevalence of infection, especially with *P. falciparum*, have grown steadily. For example, malaria cases are at record levels on the Indian subcontinent, where an increasing proportion are due to drug-resistant *P. falciparum*.

Retrospective studies of large numbers of travellers have provided an approximation of malaria risk during a 1 month stay without chemoprophylaxis: Oceania (PNG, Irian Jaya, Solomon Islands and Vanuatu) 1:30 or higher, sub-Saharan Africa 1:50, Indian subcontinent 1:250, Southeast Asia 1:1,000, South America 1:2,500 and Central America 1:10,000. It is noteworthy that the highest risk areas for malaria are Oceania, Africa and, to a lesser extent, the Indian subcontinent.

b. Personal Measures to Prevent Mosquito Bites

ALL travellers to malaria-endemic regions are advised to use personal protective measures to reduce the risk of bites from *Anopheles* mosquitoes. Any measure that reduces exposure to the evening and night-time feeding female *Anopheles* mosquito will reduce the risk of acquiring malaria. Risk reduction behaviour includes remaining in well-screened or completely enclosed air-conditioned areas, sleeping under insecticide-impregnated mosquito nets, wearing clothing (ideally insecticide-impregnated) that reduces the area of exposed skin, and using insect repellent containing diethyltoluamide (DEET).

The use of insect repellent on exposed skin, particularly between dusk and dawn, is strongly recommended. Of the insect repellents registered in Canada, those containing DEET are the most effective. Although the concentration of DEET varies from product to product, repellency rates are largely equivalent. In general, higher concentrations protect for longer periods of time, but there is little advantage in the duration of repellency with DEET concentrations > 50%, and there may be additional risk of toxicity with higher concentrations. New microencapsulated products

containing 33% DEET are registered in Canada, and they should provide 8 hours of protection. In rare instances, application of insect repellents with DEET has been associated with seizures in young children. Therefore, in children, DEET 10% or less should be applied sparingly to exposed surfaces only and washed off after the children come indoors (see section 4a, page 14, Malaria Prevention in Children).

ALL travellers at risk of acquiring malaria should be strongly encouraged to use insecticide-impregnated mosquito nets (e.g. permethrin, deltamethrin) unless their sleeping quarters are well-screened or otherwise protected from mosquitoes (**A I – evidence-based medicine recommendations –** see Appendix II, page 34). Permethrin or deltamethrin-impregnated nets are significantly more effective in preventing malaria than untreated bed nets and are safe for children and pregnant women (**A I – evidence-based medicine recommendations –** see Appendix II, page 34). Impregnated bed nets are available in Canada for use only by travellers while outside of Canada.

Permethrin treatment of clothing will also reduce the risk of malaria infection. (**A I – evidence based medicine recommendation –** see Appendix II, page 34). Currently, pyrethroid pesticides such as permethrin are not registered in Canada for use on clothing, and travellers should plan to purchase and apply these insecticides at their destination.

c. Chemoprophylactic Drugs (where appropriate)

Recommendations for chemoprophylaxis of malaria should be based on:

- individual risk assessment
- distribution of drug-resistant malaria
- safety and efficacy of chemoprophylactic regimens (See section 3, page 6, Chemoprophylactic Regimens.)

Individual risk assessment

Several factors need to be assessed when selecting an appropriate chemoprophylactic regimen before travel. The travel itinerary should be reviewed in detail and compared with known areas of malaria transmission within a country to determine the likelihood that the traveller will be at risk of acquiring malaria. The specific activities (e.g. rural travel, night-time exposure, unscreened accommodations) of the individual while in the malaria region(s) should be considered in estimating the risk of contracting malaria. The health of the individual (e.g. age, pregnancy, medication, and chronic illness) also needs to be considered in order to determine the risk of severe disease if malaria were to occur and to choose an appropriate antimalarial drug for chemoprophylaxis.

The following should be considered in the individual risk assessment:

i. **Will the traveller be exposed to malaria?**

ii. **Will the traveller be in a drug-resistant *P. falciparum* zone?**

iii. **Will the traveller have prompt access to medical care (including preparation of blood films with sterile equipment and then accurate interpretation) if symptoms of malaria were to occur?**

iv. **Are there any contraindications to the use of a particular antimalarial drug?**

v. **Is the traveller at increased risk for severe disease with malaria, e.g. a young child, asplenic individual, pregnant woman?**

Distribution of drug-resistant malaria (see Figure 1 and Appendix I)

Chloroquine-resistant *P. falciparum* is now widespread in all malaria-endemic areas of the world, except for Mexico, the Caribbean, Central America (north of the Panama Canal), parts of China, and parts of the Middle East. *P. falciparum* malaria resistant to chloroquine AND mefloquine is still rare except in Thailand on the borders with Cambodia and Myanmar (Burma). Resistance to Fansidar® (sulfadoxine-pyrimethamine) is now common in the Amazon basin, parts of sub-Saharan Africa and Southeast Asia. Chloroquine-resistant *P. vivax* is also becoming an important problem, particularly in Papua New Guinea, Irian Jaya, Vanuatu, Myanmar, and Guyana. Strains of *P. vivax* with reduced response to primaquine are now reported from widely divergent areas

including Papua New Guinea, Somalia, and India.

CATMAT considers there to be minimal risk of malaria in urban centres of Southeast Asia and Central and South America. Malaria transmission falls at altitudes exceeding 2,000 metres (6,500 feet) and is virtually non-existent over 3,000 metres (10,000 feet).

d. Early Diagnosis and Treatment

All travellers should be informed that malaria should be suspected if unexplained fever occurs during or after travel. Medical attention should be sought as soon as possible, and the traveller should request that a blood film be examined for malaria parasites. If the initial blood film is negative and the traveller remains symptomatic, then the blood film should be repeated in 12 to 24 hours. ***The most important factors that determine the survival of patients with falciparum malaria are early diagnosis and prompt initiation of appropriate treatment***.

Appendix III (page 35) provides a checklist for the preparation of travellers to malarial areas.

3. CHEMOPROPHYLACTIC REGIMENS

a. Introduction

Medications to reduce the risk of developing clinical malaria should be considered for visitors to the following areas:

URBAN AND RURAL AREAS OF

(**Higher risk**) –sub-Saharan Africa (except most of South Africa), and Oceania (including Papua New Guinea, Irian Jaya, Solomon Islands and Vanuatu).

(**Lower risk**) – Haiti, India, Bangladesh, Pakistan, and Nepal (Terai region).

EVENING OR OVERNIGHT EXPOSURE IN RURAL AREAS OF

Southeast Asia, Central and South America, and certain parts of Mexico, North Africa, and the Dominican Republic (adjacent to Haitian border).

Travellers should be informed that although antimalarials can markedly decrease the risk of acquiring symptomatic malaria, ***NONE OF THESE AGENTS CAN GUARANTEE COMPLETE PROTECTION AGAINST MALARIA***. Personal protection measures are an important adjunct to malaria prevention, even for those taking chemoprophylactic drugs (see section 2, page 3, for prevention).

Symptoms due to malaria may occur as early as 1 week after first exposure, and as late as several years after leaving a malaria region whether or not chemoprophylaxis has been used. In most travellers who acquire *P. falciparum* infection, symptoms develop within 3 months of exposure. Falciparum malaria can be effectively treated early in its course, but delay in therapy may result in a serious and even fatal outcome.

FEVER OCCURRING IN A TRAVELLER WITHIN 3 MONTHS OF DEPARTURE FROM A MALARIA-ENDEMIC AREA IS A MEDICAL EMERGENCY AND SHOULD BE INVESTIGATED URGENTLY WITH THICK AND THIN BLOOD FILMS; THESE SHOULD BE REPEATED 12 TO 24 HOURS LATER IF THE PATIENT REMAINS SYMPTOMATIC.

There is no global consensus on malaria chemoprophylactic regimens. During their travels many individuals will encounter other travellers or health care providers who will counsel them to change or stop their antimalarials (especially mefloquine), leaving them at high risk of acquiring potentially life-threatening malaria. One should warn travellers of this possibility and reinforce the antimalarial guidelines and the risks and benefits of effective chemoprophylaxis. Appendix IV (page 37), entitled "Misconceptions about malaria and mefloquine", may aid the practitioner in answering travellers' questions.

Table 1 (page 7) summarizes the different chemoprophylactic regimens according to regions of drug resistance. This information can be utilized along with Appendix I (page 30) to determine the appropriate antimalarial for an individual traveller.

b. Chloroquine-Sensitive Regions

Chloroquine-sensitive regions are those malarial areas where chloroquine resistance has not been documented or is not widely present. These include Haiti, the Dominican Republic, Central America north of the Panama Canal, North Africa and parts of the Middle East, South America and most of China. See individual countries in Appendix I (page 30) for precise recommendations.

Drug of choice: chloroquine (Aralen®) is the drug of choice for travellers to areas with chloroquine-sensitive malaria. Chloroquine is taken once **weekly**, beginning 1 week before entering a chloroquine-sensitive malarial region, during the period of exposure, and for 4 weeks after leaving the malarial region. (**A I – evidence-based medicine recommendations –** see Appendix II, page 34). Chloroquine is suitable for people of all ages and for pregnant women (see section 3f, page 9, for contraindications and adverse effects). There is insufficient drug excretion in breast milk to protect a breastfeeding infant, and therefore nursing infants should be given chloroquine (adjusted for changing weight, see Table 2, page 11). Since chloroquine overdoses are frequently fatal, instructions for childhood doses should be carefully

TABLE 1
Malaria Chemoprophylaxis Regimens for At-Risk Individuals[a] According to Regions of Drug Resistance

Region	Drug(s) of Choice[b,c]	Alternatives
Chloroquine sensitive	Chloroquine	1st Choice: mefloquine 2nd Choice: doxycycline[d]
Chloroquine resistant	Mefloquine	1st Choice: doxycycline[d] 2nd Choice: primaquine[e] or Malarone[f] 3rd Choice: chloroquine plus proguanil[g]
Chloroquine and mefloquine resistant	Doxycycline[d]	Malarone[f]

[a] IMPORTANT NOTE: Protection from mosquito bites (bed nets, insect repellents, etc) is the first line of defence against malaria for ALL travellers. In the Americas and Southeast Asia, chemoprophylaxis is recommended ONLY for travellers who will be exposed outdoors in rural areas during evening or night time.

[b] (1) Chloroquine and mefloquine are taken weekly, beginning 1 week before entering a malarial region, continued while in that region, and for 4 weeks after departure from the malarial region.
(2) Doxycycline and proguanil are taken daily, starting 1 day before entering a malarial region, continued daily while in that region, and for 4 weeks after departure.
(3) Primaquine and Malarone are taken daily, starting 1 day before entering a malarial region, continued during stay in that region, and for 1 week after departure.

[c] Adult and pediatric dosing information provided in Table 2, page 11.

[d] Contraindicated in pregnancy, during breastfeeding and in those < 8 years.

[e] Contraindicated in G6PD deficiency and in pregnancy.

[f] Limited data, not currently licensed for chemoprophylaxis.

[g] Chloroquine plus proguanil is less effective than mefloquine or doxycycline in these areas.

Note: CATMAT does not recommend proguanil as a single agent for prophylaxis.

followed, and the medication should be kept out of the reach of children.

Alternatives: For individuals unable to tolerate chloroquine, mefloquine or doxycycline should be used (see section 3f, page 9, for contraindications and adverse effects).

c. Chloroquine-Resistant Regions

The chloroquine-resistant regions refer to most of Africa, South America, Oceania and Asia. See individual countries in Appendix I (page 30) for specific recommendations. Note that some border areas of Thailand, Myanmar and Cambodia are also mefloquine-resistant regions (see section 3d, page 8).

Drug of choice: mefloquine is the drug of choice for most travellers to chloroquine-resistant regions. Mefloquine is an effective chemoprophylactic and therapeutic agent against drug-resistant *P. falciparum*. It is significantly more effective than the combination of chloroquine and proguanil for malaria chemoprophylaxis in sub-Saharan Africa (**A I – evidence-based medicine recommendations –** see Appendix II, page 34).

Mefloquine is taken once **weekly**, beginning 1 week before entering a malarial region, continued during the period of exposure, and for 4 weeks after leaving the malarial region. There is no evidence that toxic metabolites of mefloquine accumulate, and long-term (> 1 year) use of mefloquine by Peace Corps volunteers in Africa has not been associated with additional adverse effects. It is recommended, therefore, that the duration of use of mefloquine **NOT** be arbitrarily restricted in individuals who are at risk of acquiring malaria (**B II – evidence-based medicine recommendations –** see Appendix II, page 34).

For travellers who will be at immediate high risk of drug-resistant falciparum malaria, consideration may be given to the use of a loading dose of mefloquine. Data from several trials indicate that mefloquine taken once daily for 3 days before travel followed by a once weekly dose (as above) is a well-tolerated and effective way to rapidly achieve therapeutic blood levels (reaching steady state levels in 4 days compared with 7 to 9 weeks with standard weekly dosing of mefloquine) (**A I – evidence-based medicine recommendations –** see Appendix II, page 34). Only about 1% to 2%

of loading dose recipients discontinued mefloquine, and most of these did so during the first week. The loading dose strategy permits an assessment of drug tolerance before travel and allows a change to a suitable alternative if required. Alternatively, when time permits, mefloquine may be initiated up to 3 weeks before travel in order to assess tolerance and achieve higher blood levels before entry to malaria-endemic areas.

Alternatives: For individuals unable to take mefloquine, alternatives are doxycycline (alternative of choice), primaquine (contraindicated in glucose-6-phosphate dehydrogenase [G6PD] deficiency, see section 9b, page 27), Malarone® (see section 9a, page 26) or, less optimally, chloroquine and proguanil. In comparative trials in Irian Jaya and Africa, doxycycline has been shown to be as effective as mefloquine (**A I – evidence-based medicine recommendations –** see Appendix II, page 34). Chloroquine plus proguanil is approximately 60% more effective in sub-Saharan Africa than chloroquine alone but it is less effective than doxycycline or mefloquine (**A I – evidence-based medicine recommendations –** see Appendix II, page 34).

In some instances, one may need to consider less well-established alternatives. Evidence is accumulating that primaquine is an effective chemosuppressive for *P. falciparum* malaria (**A I – evidence-based medicine recommendations –** see Appendix II, page 34). Recent studies have shown efficacy in semi-immune and non-immune subjects, although data for travellers and for varied geographic regions are limited. Primaquine phosphate is given at adult doses of 30 mg (base) daily and continued for 1 week after exposure. All subjects need to be evaluated for G6PD deficiency before primaquine is initiated. This significantly complicates the prescription process (see section 9b, page 27). Daily Malarone® also shows promise for chemoprophylaxis (**A I – evidence-based medicine recommendations –** see Appendix II, page 34), although there are only limited data regarding its efficacy in non-immune travellers. Malarone® is not currently licensed in Canada for this indication.

In deciding between the alternative drugs, the health care provider must weigh the drug efficacy, risks and character of adverse drug reactions with the likelihood that the traveller will be exposed to chloroquine-resistant malaria. As discussed, such a decision must take into account personal health factors, destination and activities during travel.

d. Chloroquine- and Mefloquine-Resistant Regions

Resistance to both chloroquine and mefloquine is not a significant problem except in rural, wooded regions where Thailand borders with Myanmar (Burma) and Cambodia (areas infrequently visited by tourists). See Figure 1b (page 2) showing map of China and Thailand.

Drug of choice: doxycycline alone is the chemoprophylaxis of choice in these regions. It is taken once daily (100 mg), beginning 1 day before entering a malarial area, continued during the period of exposure and for 4 weeks after exposure. Doxycycline is an effective chemoprophylactic agent against mefloquine-sensitive and mefloquine-resistant falciparum malaria (**AI – evidence-based medicine recommendations –** see Appendix II, page 34) but must be taken DAILY to work. The main reason for doxycycline failure is non-compliance with this daily regimen.

Alternatives: there are no proven alternatives for travellers to this region in whom doxycycline is contraindicated or not tolerated. Consultation should be sought from a travel medicine specialist and such travellers should be advised to re-evaluate their travel plans. Limited data suggest that Malarone® may become an alternative chemoprophylaxis in this situation.

e. Primaquine Terminal Prophylaxis for Prevention of Relapses of *P. vivax* and *P. ovale*

P. vivax and *P. ovale* parasites can persist in the liver and cause relapses for as long as 5 years after routine chemoprophylaxis has been discontinued. Since most malarial areas of the world (except Haiti and the Dominican Republic) have at least one species of relapsing malaria, travellers to these areas have some risk of acquiring either *P. vivax* or *P. ovale*, although actual risk for an individual traveller is difficult to define.

Primaquine decreases the risk of relapses by acting against the liver stages of *P. vivax* and *P. ovale*. Primaquine terminal prophylaxis is administered after the traveller has left a malaria-endemic area,

usually during or following the last 2 weeks of chemoprophylaxis. Terminal prophylaxis with primaquine is generally indicated only for persons who have had prolonged exposure in malaria-endemic regions (e.g. long-term travellers or expatriates). Primaquine is contraindicated in pregnant women and individuals deficient in G6PD (see section 3f, below, for adverse effects and precautions).

f. Antimalarial Drug Adverse Effects and Precautions

All antimalarial drugs have the potential to cause side effects and should be prescribed only after completion of an individual risk assessment (as outlined in section 2, page 4) to ensure that only travellers truly at risk of malaria infection receive antimalarial chemoprophylaxis. Any antimalarial drugs utilized for chemoprophylaxis should be used in conjunction with personal protection methods to prevent mosquito bites (see section 2, page 4). Most users of antimalarial chemoprophylaxis will have no or only minor adverse reactions. Careful adherence to dosing guidelines and warnings will decrease the risk of adverse events (see Table 2, page 11).

Chloroquine

Except for its bitter taste, **chloroquine** is usually well tolerated. Other mild side effects, such as nausea and headache, may be reduced by taking the drug with food. African-Canadians may experience generalized pruritus, which is not indicative of drug allergy. Transient, minor visual blurring may occur initially but should not be a reason to discontinue chloroquine. Retinal toxic effects, which may occur with long-term daily doses of chloroquine (>100 g total dose) used in the treatment of other diseases, are extremely unlikely with chloroquine given as weekly chemoprophylaxis. Chloroquine may worsen psoriasis and, rarely, is associated with seizures and psychosis. Therefore, chloroquine should not be used in individuals with a history of epilepsy or generalized psoriasis (**C III – evidence-based medicine recommendations –** see Appendix II, page 34). Concurrent use of chloroquine interferes with antibody response to intradermal human diploid rabies vaccine.

Mefloquine

Mefloquine is generally well tolerated when used for chemoprophylaxis. Approximately 20% to 30% of travellers will experience side effects from either mefloquine or chloroquine; most of these are mild and self-limiting. The most frequent minor side effects reported with mefloquine use are nausea, strange dreams, dizziness, mood changes, insomnia, headache, and diarrhea. Approximately 1% to 4% of mefloquine users discontinue prophylaxis because of adverse effects, a rate not significantly different from other chemoprophylaxis regimens. Severe neuropsychiatric reactions (psychosis, convulsions) are infrequent with prophylactic doses and are reported to occur in approximately 1/10,000 to 1/13,000 individuals. Less severe but nonetheless troublesome neuro-psychologic adverse events (anxiety, depression, nightmares, etc.) requiring drug discontinuation are reported in < 1% of users. In treatment doses (25 mg base/kg), which are not routinely recommended by CATMAT, mefloquine is less well tolerated. Severe neuropsychiatric reactions are reported to be 10 to 60 times more frequent, occurring in 1/215 to 1/1,700 users of treatment doses of mefloquine.

Contraindications for the use of mefloquine include

- known hypersensitivity or past severe reaction to mefloquine
- history of serious psychiatric disorder (e.g. psychosis or severe depression)
- seizure disorder

Precautions for the use of mefloquine include the following:

- children < 5 kg
- occupations requiring fine coordination or activities in which vertigo may be life-threatening, such as flying an aircraft
- concurrent use of chloroquine or quinine-like drugs (halofantrine and mefloquine should not be used concurrently)
- underlying cardiac conduction disturbances or arrhythmia
- first trimester of pregnancy

There have been concerns regarding the co-administration of mefloquine and agents known to alter cardiac conduction, including beta

blockers, calcium channel blockers, phenothiazines, non-sedating antihistamines, and tricyclic antidepressants. However, at present these concerns remain theoretical, and the concurrent use of these agents is not contraindicated. A recent review of available data suggests that mefloquine may be used in persons concurrently receiving beta blockers if they have no underlying cardiac arrhythmia.

Insufficient mefloquine is excreted in breast milk to protect a nursing infant. Although the package insert recommends that mefloquine not be given to children weighing < 5 kg, it should be considered for children at high risk of acquiring chloroquine-resistant *P. falciparum* malaria. There are no pharmacokinetic data upon which to recommend a correct dose for children weighing < 15 kg. The WHO has suggested a chemosuppressive dose of 5 mg base/kg weekly for children weighing > 5 kg.

Doxycycline

Doxycycline is **contraindicated** during pregnancy, in breastfeeding women and in children < 8 years of age. Although the long-term safety (> 3 months) of doxycycline has not been established, historically, tetracycline derivatives have been used at lower doses over many years for skin disorders. However, hepatic necrosis and serum sickness have been associated with prolonged use of minocycline, a tetracyline derivative.

Doxycycline may cause gastrointestinal upset and rarely esophageal ulceration, which are less likely to occur if the drug is taken with food and large amounts of fluid. It should not be taken simultaneously with Pepto-bismol® or antacids. Doxycycline is photosensitizing and may make the skin more susceptible to sunburns. Using a sunscreen that blocks ultraviolet A rays may reduce this problem. Doxycycline may also increase the risk of candidal infections of the vagina; therefore, women should carry antifungal therapy for self-treatment of vaginal candidiasis.

Although tetracyclines and other antibiotics have been cited as a cause of oral contraceptive failure, a recent case-control analysis failed to demonstrate any significant association.

Concurrent use of doxycycline with barbiturates, carbamazapine, or phenytoin may result in decreased doxycycline serum concentration due to induction of microsomal enzyme activity and resulting 50% reduction of the half-life of doxycycline. Adjustment of doxycycline dosage may be necessary with either a twice daily dosing schedule (100 mg bid) or 200 mg daily.

Proguanil

Proguanil should **not** be used as a single agent for chemoprophylaxis. It is well tolerated, and although oral aphthous ulcerations are not uncommon they are rarely severe enough to warrant discontinuing this medication. Proguanil is considered safe during pregnancy and breastfeeding, but insufficient drug is excreted in the milk to protect a nursing infant.

Primaquine

See section 9b (page 27).

Malarone®

See section 9a (page 26).

TABLE 2
Antimalarial Drugs (listed alphabetically), Doses, and Adverse Effects[a]

Generic Name	Trade Name	Packaging	Adult Dose	Pediatric Dose	Adverse Effects
atovaquone/ proguanil	Malarone®	250 mg atovaquone AND 100 mg proguanil	**Prevention:** 1 tablet daily (see text) **Treatment:** 1000 mg atovaquone AND 400 mg proguanil (4 tablets) once daily x 3 days	**Prevention:** 11-20 kg: ¼ tab daily 21-30 kg: ½ tab daily 31-40 kg: ¾ tab daily > 40 kg: 1 tab daily (see text) **Treatment:** 20 mg/kg atovaquone AND 8 mg/kg proguanil once daily x 3 days 11-20 kg: 1 tab daily 21-30 kg: 2 tabs daily 31-40 kg: 3 tabs daily > 40 kg: 4 tabs daily	**Frequent:** nausea, vomiting, abdominal pain, diarrhea, increased transaminases **Rare:** seizures, rash
chloroquine[b] phosphate	Aralen®	150 mg base	**Prevention:** 300 mg base once weekly **Treatment:** 1.5 g base over 3 days[c]	**Prevention:** 5 mg base weekly; maximum 300 mg 5-6 kg or < 4 mo: 25 mg base 7-10 kg or 4-11 mo: 50 mg base 11-14 kg or 1-2 yr: 75 mg base 15-18 kg or 3-4 yr: 100 mg base 19-24 kg or 5-7 yr: 125 mg base 25-35 kg or 8-10 yr: 200 mg base 36-50 kg or 11-13 yr: 250 mg base > 50 kg or ≥ 14 yr: 300 mg base **Treatment:** 25 mg base/kg total over 3 days	**Frequent:** pruritis in African-Canadian individuals, nausea, headache **Occasional:** skin eruptions, reversible corneal opacity, partial alopecia **Rare:** nail and mucous membrane discoloration, nerve deafness, photophobia, myopathy, retinopathy with daily use, blood dyscrasias, psychosis and seizures
clindamycin hydrochloride	Dalacin®	150 mg base	**Prevention:** no indication **Treatment oral:** 300 mg base every 6 hr for 5 days **Treatment IV:** See Table 4 (page 23)	**Prevention:** no indication **Treatment oral:** 5 mg/kg three times per day for 5 days **Treatment IV:** See Table 4 (page 23)	**Frequent:** diarrhea, rash **Occasional:** pseudomembranous colitis **Rare:** hepatotoxicity, blood dyscrasias
doxycycline[d]	Vibramycin®, Vibra-Tabs®, Doryx®	100 mg	**Prevention:** 100 mg once daily **Treatment:** 1 tablet twice daily for 7 days	**Prevention:** 1.5 mg base/kg once daily (max 100 mg) <25 kg or < 8 yr: contraindicated 25-35 kg or 8-10 yr: 50 mg 36-50 kg or 11-13 yr: 75 mg >50 kg or ≥ 14 yr:100 mg **Treatment:** 1.5 mg base/kg twice daily (max 200 mg daily) <25 kg or < 8 yr: contraindicated 25-35 kg or 8-10 yr: 50 mg twice daily 36-50 kg or 11-13 yr: 75 mg twice daily > 50 kg or ≥ 14 yr: 100 mg twice daily	**Frequent:** GI upset, vaginal candidiasis, photosensitivity **Rare:** allergic reactions, blood dyscrasias, azotemia in renal diseases, esophageal ulceration

Generic Name	Trade Name	Packaging	Adult Dose	Pediatric Dose	Adverse Effects
mefloquine	Lariam®	250 mg base	**Prevention:** 250 mg base once weekly **Treatment:** not routinely recommended, see text	**Prevention:** 5 mg/kg weekly < 5 kg: no data 5-9 kg: 1/8 tablet 10-19 kg: ¼ tablet 20-29 kg: ½ tablet 30-45 kg: ¾ tablet > 45 kg: 1 tablet **Treatment:** not routinely recommended, see text	**Common:** transient dizziness, diarrhea, nausea, vivid dreams, nightmares, irritability, mood alterations, headache, insomnia **Rare:** seizures, psychosis, prolonged dizziness
primaquine[e]		15 mg base	**Prevention: primary prophylaxis** 30 mg base daily (see text) **Terminal prophylaxis or radical cure:** 15 mg base/day for 14 days[f]	**Prevention:** **primary prophylaxis** 0.5 mg base/kg daily (see text) **Terminal prophylaxis or radical cure:** 0.3 mg base/kg/day for 14 days[g]	**Occasional:** GI upset, hemolysis in G6PD deficiency, methemoglobinemia
proguanil[h]	Paludrine®	100 mg	**Prevention:** 200 mg daily **Treatment:** see text and atovaquone/proguanil (above)	**Prevention:** 5-8 kg or < 8 mo: 25 mg (1/4 tablet) daily 9-16 kg or 8 mo-3 yr: 50 mg (1/2 tab) daily 17-24 kg or 4-7 yr: 75 mg (3/4 tablet) daily 25-35 kg or 8-10 yr: 100 mg (1 tab) daily 36-50 kg or 11-13 yr: 150 mg (1½ tabs) daily > 50 kg or ≥ 14 yr: 200 mg (2 tabs) daily **Treatment:** see text and atovaquone/proguanil (above)	**Occasional:** anorexia, nausea, mouth ulcers **Rare:** hematuria
pyrimethamine-sulfadoxine	Fansidar®	25 mg pyrimethamine and 500 mg sulfadoxine	**Prevention:** no indication **Treatment:** 3 tablets	**Prevention:** no indication **Treatment:** 2-3 mo: ¼ tablet 4-11 mo: ½ tablet 1-2 yr: ¾ tablet 3-4 yr: 1 tablet 5-9 yr: 1½ tablets 10-11 yr: 2 tablets 12-13 yr: 2½ tablets ≥14 yr: 3 tablets	**Occasional:** headache, nausea, folate deficiency **Rare:** Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis
quinidine gluconate[i]			**Prevention:** no indication **Treatment:** See Table 4 (page 23)	**Prevention:** no indication **Treatment:** See Table 4 (page 23)	**Frequent:** vomiting, cramps, cinchonism (tinnitus, nausea, headache, blurred vision) **Occasional:** widening of QRS complex, cardiac disturbance, fever, delirium, rashes **Rare:** acute hemolytic anemia
quinidine sulphate			**Prevention:** no indication **Treatment:** See Table 4 (page 23) **Note:** this is an intramuscular preparation not recommended for intravenous use	**Prevention:** no indication **Treatment:** See Table 4 (page 23) **Note:** this is an intramuscular preparation not recommended for intravenous use	similar to above

Generic Name	Trade Name	Packaging	Adult Dose	Pediatric Dose	Adverse Effects
quinine dihydrochloride[j]			**Prevention:** no indication **Treatment:** See Table 4 (page 23)	**Prevention:** no indication **Treatment:** See Table 4 (page 23)	**Frequent:** cinchonism (tinnitus, nausea, headache, blurred vision), hypoglycemia **Occasional:** cardiac conduction disturbances, hypersensitivity **Rare:** hemolysis
quinine sulphate	Novoquinine®	250 mg base	**Prevention:** no indication **Treatment[k] oral:** 2 tablets three times daily for 3-7 days (7 days for SE Asia)	**Prevention:** no indication **Treatment[k] Oral:** 7.5 mg base/kg (max 500 mg base) three times daily for 3-7 days (7 days for SE Asia)	similar to above

[a] For more details on adverse events and precautions see section 3f, page 9, and individual drug monographs. For treatment of severe malaria see Table 4 page 23.

[b] Chloroquine sulfate (Nivaquine®) is not available in Canada, but is available in most malaria-endemic countries in both tablet and syrup form.

[c] In adults, generally, 2 tablets twice daily on days 1 and 2, then 2 tablets on day 3 (total of 10 tablets).

[d] Contraindicated in pregnancy, during breastfeeding and in those $<$ 8 years.

[e] Contraindicated in G6PD deficiency and pregnancy.

[f] Doses are increased to 30 mg base/day for primaquine-resistant *P. vivax*.

[g] Doses are increased to 0.5 mg base/kg/day for primaquine-resistant *P vivax*.

[h] NOTE: CATMAT does not recommend proguanil as a single agent for prophylaxis. These doses should be taken with weekly chloroquine (see page 11 for chloroquine dosing).

[i] Parenteral quinine is the drug of first choice for severe or complicated malaria. Parenteral quinidine is available through Health Canada's Special Access Program, see text.

[j] Parenteral quinine is available through Malaria Centres of Excellence, see text and Appendix V.

[k] Generally, treatment of chloroquine-resistant strains of *P. falciparum* acquired in Southeast Asia should include a longer course (7 days) of quinine or quinidine and a second drug, as per Table 4, page 23.

4. PREVENTION OF MALARIA IN SPECIAL HOSTS

a. Malaria Prevention in Children

Children are at special risk of malaria since they may rapidly become seriously ill. If travel to malarial areas is unavoidable, babies, including breastfed infants, and children should be well protected against mosquito bites and should receive malaria chemoprophylaxis. Travellers should be clearly advised of the risks involved in taking young children to areas with drug-resistant falciparum malaria.

For ALL children travelling to malarial regions, particular attention should be paid to personal protection measures to reduce contact with mosquitoes (see section 2b, page 3). These include the following: remaining in well-screened areas; wearing clothes that cover most of the body; using insecticide-impregnated mosquito nets (available for cots and small beds); and using insect repellents. The most effective repellents contain diethyltoluamide (DEET), an ingredient in many commercially available products. The actual concentration of DEET varies among repellents and can be as high as 95%; however, repellents with DEET concentrations of 10% are very effective and should last 3-4 hours. Rarely, children exposed to DEET have developed toxic encephalopathy (only 14 cases over 30 years of DEET use and billions of applications every year). The likelihood of adverse reactions can be minimized by the following precautions: apply repellent sparingly and only to exposed skin; avoid applying high concentration products; avoid applying repellents to portions of children's hands that are likely to contact the eyes or mouth; never use repellents on wounds or irritated skin; and wash repellent-treated skin after children come indoors. If a reaction to insect repellent is suspected, wash treated skin and seek medical attention.

In Canada, DEET products are not recommended for use in children < 2 years of age. However, when living in a malaria endemic area, young children are at risk of severe malaria and the risk of severe disease outweighs the risk of **appropriately** applied DEET repellents.

Ensuring that young children take antimalarial agents may be difficult because of the lack of pediatric formulations. Malaria tablets may be crushed and mixed with chocolate syrup, jam, cereal or bananas to mask the taste. Tablets, especially mefloquine, should be protected from sunlight and high humidity once they have been removed from the foil wrapper. All medication, including antimalarials, should be kept out of reach of children and stored in childproof containers to avoid overdose, which may be fatal.

Chloroquine remains the preferred agent for chemoprophylaxis in areas with chloroquine-sensitive malaria. Although it is not available in Canada, chloroquine sulfate (Nivaquine®) is widely available as a syrup in malaria endemic areas. The syrup is often more easily administered than tablets.

Mefloquine remains the drug of choice in chloroquine-resistant regions, although there are no studies that specifically analyze its bioavailability and the rate of metabolism in children. Although the manufacturer recommends that mefloquine not be given to children < 5 kg, it should be considered for prophylaxis of all children at high risk of acquiring chloroquine-resistant *Plasmodium falciparum* at a dose of 5 mg base/kg once weekly (see Table 2, page 12).

There is no safe and effective chemoprophylactic regimen for children < 8 years who travel to mefloquine-resistant areas along the Thai borders with Cambodia and Myanmar (Burma).

Recommendations:

i. If possible, young children should avoid travel to areas with significant transmission particularly of chloroquine-resistant malaria (**C III – evidence-based medicine recommendations –** see Appendix II, page 34).

ii. Personal protection measures should be strongly encouraged for all individuals who travel to malaria-endemic areas (**A I – evidence-based medicine recommendations –** see Appendix II, page 34).

iii. Young children travelling to or residing in chloroquine-sensitive areas should use chloroquine as chemoprophylaxis (**A I – evidence-based medicine recommendations –** see Appendix II, page 34).

iv. For young children travelling to or residing in chloroquine-resistant areas, mefloquine is the drug of choice for chemoprophylaxis (**A I – evidence-based medicine recommendations –** see Appendix II, page 34).

v. The combination of chloroquine and proguanil is safe in children, but is significantly less effective against chloroquine-resistant malaria (**A I – evidence-based medicine recommendations –** see Appendix II, page 34). There is no safe and effective chemoprophylaxis regimen for children < 8 years old who travel to mefloquine-resistant areas where Thailand borders with Cambodia and Myanmar (Burma).

b. Malaria Prevention in Pregnancy

Malaria increases the risk of maternal and neonatal death, miscarriage and stillbirth. Pregnant women should defer travel to malaria-endemic areas whenever possible, particularly to areas with risk of acquisition of drug-resistant falciparum malaria. If travel cannot be avoided, special care should be taken to avoid mosquito bites (see section 2b, page 3), and chemoprophylaxis should be used.

Doxycycline and primaquine are contraindicated during pregnancy, the latter because the G6PD status of the infant cannot be evaluated. Pyrimethamine-sulfadoxine (Fansidar®) is contraindicated in the last month of gestation and in the first 2 months of breastfeeding. Malarone® is not recommended during pregnancy.

According to current data, mefloquine is safe for chemoprophylaxis after the first trimester. When used in **treatment** doses in the first trimester the results of a recent study suggest that mefloqine may be associated with an increased rate of spontaneous abortions. Pregnancy should be avoided for 3 months after completing mefloquine chemoprophylaxis because of melfoquine's long half-life. However, the occurrence of pregnancy while a woman is receiving mefloquine prophylaxis is not an indication for termination of pregnancy.

Chloroquine and proguanil are known to be safe in pregnancy although they are not as effective as mefloquine in preventing chloroquine-resistant *P. falciparum*. This creates a dilemma for women who are, plan to be, or become pregnant while in malaria-endemic areas.

Recommendations:

i. If possible, pregnant women should avoid travel to areas with significant transmission particularly of chloroquine-resistant malaria (**C III – evidence-based medicine recommendations –** see Appendix II, page 34).

ii. Personal protection measures should be strongly encouraged for all individuals who travel to malaria-endemic areas (**A I – evidence-based medicine recommendations –** see Appendix II, page 34).

iii. Pregnant females travelling to or residing in chloroquine-sensitive areas should use chloroquine as chemoprophylaxis (**A I – evidence-based medicine recommendations –** see Appendix II, page 34).

iv. Mefloquine is effective and safe for prophylaxis beyond the first trimester of pregnancy and is recommended where exposure to chloroquine-resistant falciparum malaria is unavoidable (**A I – evidence-based medicine recommendations –** see Appendix II, page 34).

v. Females who plan to travel to areas with chloroquine-resistant falciparum malaria during the first trimester of pregnancy should have an individual risk assessment and counsel from a travel medicine or tropical disease specialist (**A III – evidence-based medicine recommendations –** see Appendix II, page 34).

vi. The combination of chloroquine and proguanil is safe in pregnancy, but is significantly less effective against chloroquine-resistant malaria than mefloquine (**A I – evidence-based medicine recommendations –** see Appendix II, page 34). There is no safe and effective chemoprophylaxis regimen for pregnant women who travel to mefloquine-resistant areas where Thailand borders with Cambodia and Myanmar (Burma).

c. Malaria Prevention in the Immunocompromised Host

The immunocompromised traveller may be at increased risk of severe disease from malaria infections. If travel cannot be avoided, special care should be taken to avoid mosquito bites (see section 2b, page 3), and chemoprophylaxis should be used (see section 3, page 6).

Asplenic individuals are at risk of severe disease with organisms that require splenic clearance, including malaria. Such individuals may become rapidly ill and therefore should seek pretravel consultation from a travel medicine or tropical disease specialist. Consideration should be given to the provision of self treatment for malaria (see section 6, page 19) to be utilized in the event of a febrile illness if medical care is not immediately available.

Those with other forms of immunocompromise, such as HIV or organ transplant recipients, may also be at risk of severe disease from malaria. As well, chemoprophylactic drugs may interfere with other medications required for control of disease or prevention of rejection. Therefore, pretravel consultation with a travel medicine or tropical disease specialist is advised.

Recommendations:

i. Individuals with immunodeficiency, including those with asplenia, HIV infection or transplantation, should have an individual risk assessment and counsel from a travel medicine or tropical disease specialist (**B III – evidence-based medicine recommendations –** see Appendix II, page 34).

ii. Personal protection measures should be strongly encouraged for all individuals who travel to malaria-endemic areas (**A I – evidence-based medicine recommendations –** see Appendix II, page 34).

5. MALARIA PREVENTION IN THE LONG-TERM TRAVELLER OR EXPATRIATE

Modern prevention strategies have had a significant positive impact on the risk of mortality in long-term expatriates, which was reported to be as high as 60% among missionaries in West Africa during the 19th century. However, the effort to develop unique, evidenced-based guidelines for the long-term (> 6 months) traveller or expatriate is severely hampered by a paucity of medical literature in this area.

Concerns encountered when addressing malaria prevention in long-term travellers and expatriates include conflicting counsel regarding appropriate chemoprophylaxis and self-treatment, safety of drugs used for chemoprophylaxis, fear of toxic effects with prolonged use of medication, and lack of adherence to the use of personal protection measures. Confidence but lack of rigour in self-diagnosis coupled with unreliable laboratory diagnosis in many developing countries has resulted in a misrepresentation of drug efficacy by the long-term traveller/expatriate. Data on the incidence of malaria and the effectiveness and tolerance of currently recommended regimens for long-term travellers are limited to the studies of Peace Corps volunteers, in whom mefloquine was well tolerated and was more effective than chloroquine and proguanil in chloroquine-resistant regions.

At present, there is no evidence that long-term use of therapies currently recommended for short-stay travellers have significant adverse reactions. Doxycycline may be an exception, as studies have been confined to short-term travellers and persons using tetracyclines (at lower dosage) for skin therapy.

In general, guidelines for the prevention of malaria in long-term travellers or expatriates should not deviate significantly from standard recommendations for the short-term traveller.

A recent self-reported summary of the malaria prevention strategies of 1,192 long-term expatriates, representing a broad range of government and non-government organizations (NGOs) in sub-Saharan Africa, may provide some assistance in counselling long-term travellers and expatriates. Malaria prophylaxis was taken on a regular basis by 75% of individuals with a compliance rate of 65%. Of those receiving chemoprophylaxis, 54% reported changing their prophylactic regimen, 22% because of adverse effects. The severity of side effects was not associated with any specific drug, but the reported incidence of neuropsychiatric side effects was 10% among persons taking chloroquine and proguanil compared with 17% in the mefloquine group. Mefloquine was the only regimen on which participants reported a change in practice based on media influence (see Appendix IV, page 37, for information on malaria myths and facts). Only a small number indicated that availability and cost were factors in their choice of prophylactic regimens. Participants who did not use prophylaxis cited concerns about adverse reactions and long-term effects as the primary reasons for their choice. Personal protection measures were suboptimal: only 38% had screened doors and windows and 53% used mosquito netting (20% of which were insecticide-treated nets).

There are no data available on self-diagnosis and self-treatment in the long-term traveller or expatriate population. Without training, there is no reason to believe that the efficacy of these interventions will be any better than that demonstrated in the general travel population. However, given that long-term travellers and expatriates represent a reasonably homogeneous group, training on diagnosis and self-treatment (see sections 7, page 21, and 8, page 22), including the use of rapid diagnostic tests for malaria, may prove to be helpful in this population. Self-diagnostic kits that require refrigeration will limit access to this technology in some regions.

Section 3e (page 8) addresses the use of primaquine as terminal prophylaxis to decrease the risk of relapses by acting against the liver stages of *P. vivax* and *P. ovale*. Primaquine terminal prophylaxis is administered after the traveller has left a malaria-endemic area, usually during or after the last 2 weeks of chemoprophylaxis. Terminal pro-

phylaxis with primaquine is generally indicated only for persons who have had prolonged exposure in malaria-endemic regions, such as expatriates or long-term travellers. Primaquine is contraindicated in pregnant women and individuals deficient in G6PD (see section 9b, page 27, for contraindications and precautions).

In conclusion, guidelines for the prevention of malaria in long-term travellers or expatriates should not deviate significantly from recommendations for short-term travellers (**B III – evidence based medicine recommendation –** Appendix II, page 34). The available data indicate that expatriates in high-risk settings have not effectively utilized personal protection measures (**B II – evidence-based medicine recommendations –** see Appendix II, page 34). The majority are using a prophylactic regimen, but sound counsel does not always guide their choice; a significant proportion are influenced by perception of risk rather than documented problems. Therefore, the effectiveness of current recommendations will be affected by the prevailing attitudes in the subculture in which the long-term traveller or expatriate lives (**B II – evidence-based medicine recommendations –** see Appendix II, page 34). At present there is insufficient evidence for the effectiveness of self-diagnosis with rapid malaria test kits to recommend their routine use. Primaquine should be given as terminal prophylaxis (see section 9b for contraindications and precautions) to long-term travellers or expatriates who return from regions with *P. vivax* transmission (**A I – evidence-based medicine recommendations –** see Appendix II, page 34).

6. SELF TREATMENT OF PRESUMPTIVE MALARIA

Most travellers will be able to obtain prompt medical attention when malaria is suspected and therefore **will not require a self-treatment regimen**. Under unusual circumstances, individuals at risk of malaria may be unable to seek medical care within 24 hours and may require self-treatment for presumptive malaria. However, because of the non-specific symptoms of malaria, the potentially serious risk of incorrectly treating another disease and the potential toxicity of malaria therapy, self-treatment should never be undertaken lightly; consultation with a tropical medicine expert is recommended before individuals begin self-treatment protocols.

Travellers should be advised that the clinical presentation of malaria is variable and may mimic other diseases. An alternative diagnosis that requires treatment may be present, particularly in travellers who have been compliant with chemoprophylaxis. The most frequent symptoms of malaria are fever, headache, and generalized aches and pains. Fever, which may or may not be cyclical, is almost always present. Malaria can be misdiagnosed as influenza or another febrile illness, so that an early and accurate diagnosis is essential.

Travellers for whom self-treatment has been recommended should be told that self-treatment is NOT considered definitive treatment but is a temporary, lifesaving measure while they seek medical attention. Self-treatment for malaria should be used only if travellers develop fever and professional medical care is not available within 24 hours. After self-treatment, medical attention should still be sought as soon as possible.

Recommended Regimens* (to be used only if fever develops and medical care is not available within 24 hours):

1. **For individuals in chloroquine-sensitive regions and not receiving chloroquine prophylaxis:** Self-treatment with chloroquine should be taken (see Table 2, page 11). SEEK MEDICAL HELP AS SOON AS POSSIBLE. Chloroquine prophylaxis should be started.
2. **For individuals in chloroquine-sensitive regions and already receiving chloroquine prophylaxis:** Self-treatment with Malarone® should be taken (see Table 2, page 11). SEEK MEDICAL HELP AS SOON AS POSSIBLE. Chloroquine prophylaxis should be resumed.
3. **In chloroquine- or chloroquine- and mefloquine-resistant *P. falciparum* regions, treatment recommendations for uncomplicated *P. falciparum* include the following (see Table 2, page 11):** Begin oral Malarone® (see Table 2). SEEK MEDICAL HELP AS SOON AS POSSIBLE. Mefloquine or other appropriate prophylaxis should be resumed.

OR

Begin oral quinine and doxycycline (see Table 2, page 11). SEEK MEDICAL HELP AS SOON AS POSSIBLE. Mefloquine or other appropriate prophylaxis should be resumed.

OR

Begin oral quinine plus Fansidar® (see Table 2, page 11) (Sub-Saharan Africa or Indian subcontinent only). SEEK MEDICAL HELP AS SOON AS POSSIBLE. Mefloquine or other appropriate prophylaxis should be resumed.

Halofantrine (see section 9e, page 29) and mefloquine are **not** recommended for self-treatment of malaria. In some countries, a combination of mefloquine and Fansidar® is marketed under the name Fansimef®, which should not be confused with mefloquine. Fansimef® is not recommended for the prevention or treatment of malaria. Individuals who are undergoing chemosuppression should never attempt treatment with the same drug, as there is the potential for additive toxicity and reduced efficacy.

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* If vomiting occurs within 30-60 minutes of dose, repeat full dose. If vomiting occurs 1-2 hours after dose, repeat one half dose.

Rapid detection of malaria using a simple dipstick test may be available to some travellers. The sensitivity and specificity of these tests in research laboratories (> 90%) appear promising. However, there are limited data about their accuracy in the hands of non-experienced operators and under non-refrigerated conditions in the tropics. There are no rapid detection kits currently licensed in North America.

7. DIAGNOSIS OF MALARIA

FEVER OCCURRING IN A TRAVELLER WITHIN 3 MONTHS OF DEPARTURE FROM A MALARIA-ENDEMIC AREA IS A MEDICAL EMERGENCY AND SHOULD BE INVESTIGATED URGENTLY WITH THICK AND THIN BLOOD FILMS; THESE SHOULD BE REPEATED 12 TO 24 HOURS LATER IF THE PATIENT REMAINS SYMPTOMATIC.

It is imperative that a travel history be obtained from all patients with a history of fever and that thick and thin blood films for malaria be requested urgently for all individuals who have travelled to or through a malaria-endemic area. *P. falciparum* malaria usually presents within 3 months of last exposure; however, it may be delayed in patients who have taken chemoprophylaxis. In addition, other types of malaria, especially that caused by *P. vivax*, may occur months and occasionally up to 5 years after travel in endemic areas.

The examination of thick and thin blood films by an experienced microscopist is essential for the diagnosis of malaria. The clinical presentation (history and physical examination) of malaria is often non-specific. When malaria is a consideration, especially when the patient may be at risk of *P. falciparum* infection (whether chloroquine-sensitive or not), the laboratory diagnosis and quantification of the level of parasitemia must be considered a medical emergency and be performed as soon as possible (< 24-hour turnaround time).

Not all laboratories are proficient at the diagnosis and speciation of malaria. If appropriate expertise cannot be ensured, then the patient should be treated empirically for chloroquine-resistant falciparum malaria and an immediate referral of the patient or the specimen should be made to a specialized facility. While dipstick methods for the diagnosis of malaria are currently being evaluated in the research setting, none is currently licensed for use in Canada.

Occasionally, a single blood film examination may be falsely negative for malaria parasites. Repeat blood films over 48 hours (e.g. every 12 hours x 3) may be required to exclude the possibility of malaria.

The treatment of malaria depends upon the species of parasite and the level of parasitemia; therefore, every effort should be made to determine these parameters on an urgent basis. Since malaria is a reportable disease in all provinces, physicians are required to report all cases to the local public health authority.

8. TREATMENT OF MALARIA

a. General Principles of Management

This depends on the infecting species of malaria, the severity of infection, the patient's age, the pattern of drug resistance in the area of acquisition, as well as the safety, availability, and cost of antimalarial drugs. Three critical questions need to be addressed in order to initiate effective treatment:

1. **Is this infection caused by *P. falciparum*?** This is critical, as treatment varies according to the species of malaria.
2. **Is this a severe or complicated infection (see Table 3, below)?** Severe or complicated malaria requires parenteral therapy and sometimes an exchange transfusion.
3. **Has the infection been acquired in an area of known drug-resistant malaria (see Appendix I, page 30)?** Therapy will have to be modified accordingly.

When in doubt treat all falciparum malaria as drug resistant.

TABLE 3
Criteria for Severe *Falciparum* Malaria

EITHER
History of recent possible exposure and no other recognized pathology
OR
Asexual forms of *Plasmodium falciparum* on blood smear
AND
Any one or more of the following 11 features:
1) Impaired consciousness or coma
2) Severe normocytic anemia
3) Renal failure
4) Pulmonary edema
5) Hypoglycemia
6) Circulatory collapse, shock
7) Spontaneous bleeding/disseminated intravascular coagulation
8) Repeated generalized convulsions
9) Acidemia/acidosis
10) Hemoglobinuria
11) Parasitemia of > 5% in non-immune individuals
Adapted from *Severe and complicated malaria*. 2nd ed. Trans Roy Soc Trop Med Hyg 1990;84(Suppl 2).

b. Management of *Falciparum* Malaria

The following guidelines have been derived, in part, from the World Health Organization Division of Control of Tropical Diseases (*Severe and complicated malaria*. 2nd ed. Trans Roy Soc Trop Med Hyg 1990;84[Suppl 2]). The interested reader is referred to this document for a more detailed discussion of these issues.

A detailed geographic history is essential to the management of malaria. *P. falciparum* malaria acquired in areas where drug resistance is known to occur should be treated as chloroquine resistant.

Severe *P. falciparum* infections, as defined by the criteria in Table 3 may have a mortality rate of 20% or higher. These patients require immediate hospitalization, and urgent, intensive medical management. As a general rule, all non-immune patients with *P. falciparum* malaria, whether severe or not, should be considered for admission to hospital in order to ensure tolerance of antimalarial drugs and to detect complications or early treatment failure. All patients with severe *P. falciparum* infections and those who are unable to tolerate drugs orally should receive intravenous quinine or, less optimally, quinidine (see Table 4, page 23). In the treatment of severe malaria, parenteral preparations of quinine and quinidine are equivalent. Quinine is preferred by CATMAT because of the cardiotoxicity of quinidine. Patients treated with intravenous quinidine should receive electrocardiographic monitoring, and infusion rates should be decreased if the corrected QT interval is prolonged by more than 25% of baseline. Intravenous quinine and quinidine are no longer readily available in Canada.

Because of the potential for adverse outcome with delays in acquiring parenteral malaria therapy, every effort has been made to ensure that parenteral quinine is available throughout Canada for the treatment of severe malaria. A nation-wide network of **Malaria Centres of Excellence** (see Appendix V, page 39) is being established to facilitate the storage and rapid distribution of parenteral quinine for the treatment of severe *P. falciparum* infections.

TABLE 4
Chemotherapy of Severe *Falciparum* Malaria

NOTE: Quinine is the drug of choice. The four quinine and quinidine protocols listed below are equally efficacious and in all cases a switch to oral therapy should be made as soon as possible.

A. If an infusion pump is available:

1. **Quinine[a] (base) 5.8 mg/kg** loading dose[b] [quinine dihydrochloride (salt) 7 mg/kg] intravenously by infusion pump over 30 minutes followed immediately by **8.3 mg base/kg** [quinine dihydrochloride (salt) 10 mg/kg] diluted in 10 mL/kg isotonic fluid by intravenous infusion **over 4 hour**s, repeated 8 hourly (maintenance dose)[c] for up to 72 hours or until the patient can swallow, then quinine tablets to complete 3-7 days of treatment (7 days for SE Asia).

OR

2. **Quinidine[d,e] (base) 6.2 mg/kg** loading dose[b] [quinidine gluconate (salt) 10 mg/kg] by intravenous infusion **over 1 to 2 hours**, followed by quinidine **(base) 0.0125 mg/kg/min** [quinidine gluconate (salt) 0.02 mg/kg/min] by infusion pump (maintenance dose)[c] for up to 72 hours or until the patient can swallow, then quinine tablets to complete 3-7 days of treatment (7 days for SE Asia).

B. Without an infusion pump:

1. Quinine[a] **(base) 16.7 mg/kg loading dose**[b] [quinine dihydrochloride (salt) 20 mg/kg], by intravenous infusion **over 4 hours**, then **8.3 mg base/kg** [quinine dihydrochloride (salt) 10 mg/kg] diluted in 10 mL/kg isotonic fluid by intravenous infusion **over 4 hours**, repeated 8 hourly (maintenance dose)[c] for up to 72 hours or until the patient can swallow, then quinine tablets to complete 3-7 days of treatment (7 days for SE Asia).

OR

2. Quinidine[d,e] **(base) 15 mg/kg loading dose**[b] [quinidine gluconate (salt) 24 mg/kg] in a volume of 250 mL of normal saline infused **over 4 hours** followed by a maintenance dose[c], beginning 8 hours after the beginning of the loading dose, of quinidine **(base) 7.5 mg/kg** [quinidine gluconate (salt) 12 mg/kg] infused **over 4 hours**, every 8 hours for up to 72 hours or until the patient can swallow, then quinine tablets to complete 3-7 days of treatment (7 days for SE Asia).

PLUS (either concurrently with quinine/quinidine or immediately after)

1. Doxycycline: 100 mg orally twice daily for 7 days; pediatric dose 2 mg/kg (to a maximum of 100 mg) twice daily; contraindicated: pregnancy, breastfeeding or age < 8 years.

OR

2. Fansidar®: 3 tablets at one time (see Table 2 for pediatric dosage).

OR

3. Clindamycin: 10 mg/kg (loading dose) intravenously, followed by 5 mg/kg every 8 hours until blood is clear of asexual parasites (ONLY IF UNABLE TO TAKE DOXYCYCLINE, TETRACYCLINE OR FANSIDAR®).

[a] Loading dose should not be used if patient received quinine, quinidine or mefloquine within the preceding 24 hours.

[b] Parenteral quinine dihydrochloride may be obtained through the Malaria Centres of Excellence (see Appendix V for contact information).

[c] Switch to oral quinine as soon as possible. In patients requiring more than 48 hours of parenteral therapy, reduce the quinine or quinidine maintenance dose by one-third to one-half.

[d] Parenteral quinidine gluconate may be obtained on a patient-by-patient basis with authorization from the Special Access Program, Therapeutic Products Programme, Finance Building, 2nd Floor, Tunney's Pasture, Ottawa, Ontario K1A 1B9, Address Locator 0202C1. (613) 941-2108 (08:30-16:30 hours EST), (613) 941-3061 (after hours), (613) 941-3194 (fax), web site: www.hc-sc.gc.ca/hpb-dgps/therapeut

[e] Quinidine should be used only if parenteral quinine is unavailable, see text. Cardiac monitoring is required.

The Centres will also provide expertise in the management of malaria cases. As well, each Centre will provide surveillance data to LCDC on cases treated with parenteral quinine.

Parenteral quinidine gluconate dosing is provided in Table 4. It is as effective as parenteral quinine in the treatment of severe malaria, but the risk of cardiotoxicity necessitates cardiac monitoring. Parenteral quinidine gluconate can be obtained on a patient-by-patient basis with authorization from Health Canada's Special Access Program, see footnote, Table 4, for contact information. Parenteral quinidine sulfate is an intramuscular preparation that is not recommended for intravenous use.

Uncomplicated *P. falciparum* infections unequivocally acquired in a chloroquine-sensitive zone may be treated with chloroquine alone (as per Table 2, page 11). Those infections that were possibly or definitely acquired in drug-resistant regions should be treated with Malarone® or quinine and a second drug. If the patient can tolerate oral quinine, then it and the second drug – either doxycycline, Fansidar®, or clindamycin – may be administered simultaneously or sequentially (start quinine first), either orally (as per Table 2, page 11) or, if necessary, parenterally (as per Table 4). The base-salt equivalents of selected antimalarials are shown in Table 5 (page 24).

When quinine is administered to a patient who has taken mefloquine or halofantrine in the previous 2 weeks, there is a risk of drug-induced cardiac arrhythmia; if possible, such patients should be monitored electrocardiographically.

Approximately 5% or more of patients may fail treatment for falciparum malaria. Most patients fail within 1 month of treatment. To ensure that patients are cured, it is important to repeat a thick and thin blood film on day 7 and day 28 after therapy, and at any time there is recurrence of symptoms.

TABLE 5
Base/Salt Equivalents of Selected Antimalarial Drugs

Drugs	Base (mg)	Salt (mg)
Chloroquine phosphate	150	250
Chloroquine sulfate[a]	100	136
Clindamycin hydrochloride	150	225
Mefloquine	250	274
Quinidine gluconate	5.0 7.5 10 15	8 12 16 24
Quinidine sulfate[b]	7.5 10 15	9 12 18
Quinine dihydrochloride	5 7.5 15 16.7	6 9 18 20
Quinine sulfate	250	300

[a] Not available in Canada
[b] Intramuscular preparation, should not be used intravenously.

c. Ancillary Treatment of Severe Malaria

Many ancillary treatments have been suggested for the treatment of severe malaria, but few have been objectively shown to improve outcome. Only antipyretics (acetaminophen) and anticonvulsants (prophylactic phenobarbitol) have been supported by sufficient evidence to warrant their use. The use of steroids to treat severe or cerebral malaria has been associated with worse outcomes and should be avoided (**E I – evidence-based medicine recommendations** – see Appendix II, page 34). In cases of complicated *P. falciparum* infection (Table 3, page 22) or if there is high parasitemia (≥ 10%), exchange transfusion has been used on an experimental basis as a potentially life-saving procedure.

When managing a patient with severe or complicated falciparum malaria, consultation with an infectious or tropical disease expert is strongly recommended (see Appendix V, page 39, for contact information).

d. Management of Non-Falciparum Malaria

Outside of New Guinea (Papua New Guinea and Irian Jaya), chloroquine remains the treatment of choice for malaria other than falciparum (as per Table 2, page 11). Recent reports have confirmed the presence and high prevalence (80%) of chloroquine-resistant *P. vivax* in Irian Jaya. Sporadic cases of chloroquine-resistant *P. vivax* malaria have been reported elsewhere (e.g. in Indonesia, Papua New Guinea, the Solomon Islands, Myanmar, and Guyana). At present, chloroquine can no longer be relied upon either for chemoprophylaxis or treatment of *P. vivax* acquired in New Guinea, and the optimal treatment is unknown. Although effective, a prolonged course of quinine (> 3 days) is often required to cure *P. vivax* infection from New Guinea and is poorly tolerated.

Mefloquine and halofantrine have been shown to be efficacious in small clinical trials, but each is limited by safety issues associated with therapeutic doses (see sections 3f, page 9, and 9e, page 29). Standard chloroquine doses (25 mg base/kg/72 hours) combined with high dose primaquine (2.5 mg base/kg/48 hours) have been suggested as treatment for chloroquine-resistant *P. vivax* acquired in Irian Jaya, but have failed in cases from Guyana. Expert advice from an infectious or tropical disease specialist should be sought for the management of these cases.

As with falciparum malaria, response to treatment should be documented with repeat of thick and thin blood films on day 7 and day 28 after therapy, and at any time there is recurrence of symptoms. A recurrence of parasitemia less than 30 days after treatment suggests chloroquine-resistant *P. vivax*; recurrence after more than 30 days suggests primaquine resistance.

e. Prevention of Relapses of Malaria Due to *P. vivax* or *P. ovale*

P. vivax and *P. ovale* have a persistent liver phase that is responsible for relapses and is susceptible only to treatment with primaquine or related drugs. None of the currently recommended chemoprophylaxis regimens will prevent relapses due to these two species of malaria. In order to reduce the risk of relapse following the treatment of symptomatic *P. vivax* or *P. ovale* infection, primaquine is indicated to provide "radical cure". Primaquine is not routinely recommended to prevent relapsing malaria in asymptomatic returning travellers (terminal prophylaxis). However, terminal prophylaxis with primaquine is generally indicated for persons with prolonged exposure in malaria-endemic areas (e.g. long-term travellers or expatriates, see section 5, page 17). For terminal prophylaxis primaquine is administered after the traveller has departed from a malaria-endemic area, usually during or following the last 2 weeks of chemoprophylaxis. (See Table 2, page 11 for dosage recommendations).

Primaquine use is contraindicated in pregnancy. *P. vivax* or *P. ovale* infections occurring during pregnancy should be treated with standard doses of chloroquine (Table 2, page 11). Relapses can be prevented by weekly chemoprophylaxis with chloroquine until after delivery, when primaquine can be safely used for mothers with normal G6PD levels.

Primaquine is generally well tolerated but may cause nausea and abdominal pain; this may be diminished by taking the drug with food. More importantly, primaquine may cause oxidant-induced hemolytic anemia in those with a deficiency of G6PD, as well as methemoglobinemia. Those of Mediterranean, African, and Asian ethnic origin or those receiving > 15 mg base/day have a greater risk of hemolysis. All individuals should have their G6PD level measured before primaquine therapy is initiated.

Primaquine is contraindicated in those with severe G6PD deficiency. In mild variants of G6PD deficiency, primaquine has been used safely at a lower dose (0.8 mg base/kg/week; adult dose 45 mg base once weekly for 6 weeks) for radical cure of *P. vivax* or *P. ovale* malaria. Primaquine should be initiated for radical cure after chloroquine therapy has been completed and the acute febrile illness is over (about 1 to 2 weeks). Patients should be advised to stop their medication and report to a physician immediately if jaundice or abnormally dark or brown urine is noted.

f. *P. vivax* Resistance to Primaquine

P. vivax isolates with a decreased responsiveness to primaquine are well documented in Southeast Asia and, in particular, Papua New Guinea and Irian Jaya. Recently, primaquine radical treatment failure has been reported from Thailand and Somalia.

When *P. vivax* malaria relapses following primaquine therapy there are two issues to be considered: (1) the treatment of the acute vivax malaria (see section 8d, page 24), and (2) prevention of further relapses by doubling the standard dose of primaquine, i.e. 30 mg (0.5 mg/kg/day) of primaquine base daily for 14 days (**B I – evidence-based medicine recommendations –** see Appendix II, page 34).

Response to treatment should be documented with repeat of thick and thin blood films on day 7 and day 28 after therapy, and at any time there is recurrence of symptoms. A recurrence of parasitemia less than 30 days after treatment suggests chloroquine-resistant *P. vivax*; recurrence after more than 30 days suggests primaquine resistance.

9. NEW DRUGS FOR THE PREVENTION AND TREATMENT OF MALARIA

a. Atovaquone/Proguanil (Malarone®) for the Treatment and Prevention of Malaria

Atovaquone (ATQ), a hydroxynapthaquinone, is a member of a novel class of antimalarials first described in the 1920s. ATQ is an analog of ubiquinone, which selectively inhibits parasite mitochondrial electron transport. ATQ has similar activity against both chloroquine-sensitive and chloroquine-resistant *P. falciparum* isolates. However, when ATQ is used as monotherapy, resistance develops rapidly. ATQ displays *in vitro* antagonism with artemisinin compounds and quinolines but synergy with proguanil and tetracycline. Proguanil displays its synergistic activity with ATQ even in the context of documented proguanil resistance.

The fixed drug combination Malarone® (tablet: 250 mg ATQ and 100 mg proguanil) is licensed in Canada for the treatment of uncomplicated malaria, but it is not currently licensed for chemoprophylaxis.

Compared with other standard antimalarial regimens, the ATQ/proguanil combination has demonstrated excellent safety and tolerance with fewer reported adverse events than mefloquine and quinine plus tetracycline. During treatment, the most frequent adverse events are those associated with the gastrointestinal tract. Approximately 8% to 15% of adults and children will experience nausea, vomiting, abdominal pain or diarrhea, and in 5% to 10% there will be transient, asymptomatic elevations in transaminases and amylase. Serious adverse events associated with ATQ/proguanil are rare. One episode of anaphylaxis has been attributed to this combination. Three patients experienced convulsions 2 to 5 days after initiation of therapy, each with a history of seizure disorders. ATQ has been associated with fever and rash in HIV-infected patients, requiring discontinuation of therapy. It has been shown to be teratogenic in rabbits but not in rat models (FDA category C drug). Pregnancy and hypersensitivity to either component are the only contraindications to ATQ/proguanil.

In clinical trials of treatment of acute uncomplicated *P. falciparum* malaria conducted in Southeast Asia, South America, and Africa, the efficacy of the combination of ATQ and proguanil (dosed once daily for 3 days) has exceeded 95%. As well, published case reports have documented that this combination drug successfully treated multidrug-resistant malaria that had failed to respond to other therapies. (**AI – evidence-based medicine –** see Appendix II, page 34).

ATQ/proguanil combination therapy has also been effective in pediatric populations at a dose of 20 mg/kg/day of ATQ and 8 mg/kg/day of proguanil for 3 days.

Three placebo-controlled studies have demonstrated a greater than 95% efficacy of ATQ/proguanil as a chemoprophylactic agent against *P. falciparum* malaria in semi-immune adults and children at an adult dose of 1 tablet per day. Mounting evidence indicates that ATQ/proguanil is effective as a causal (acting at the liver stage) as well as suppressive (acting at the blood stage) prophylactic agent and can therefore be discontinued 1 week after departure from a malaria-endemic area. Additional studies in non-immune adults and children are required in order to satisfy regulatory agencies of its safety and effectiveness as a chemoprophylactic agent.

Recommendations

i. ATQ combined with proguanil (Malarone®), an effective and well-tolerated therapy, can now be considered as first line therapy (with attention to contraindications and precautions) for uncomplicated multidrug-resistant *P. falciparum* malaria. (**A I – evidence-based medicine recommendations –** see Appendix II, page 34).

ii. There are insufficient data at present to recommend its use for malaria caused by other *Plasmodium* species (*vivax, ovale, malariae*). (**C – evidence-based medicine recommendations –** see Appendix II, page 34).

iii. ATQ/ proguanil may be considered for the treatment of falciparum malaria that fails standard drug regimens (**A I – evidence-based medicine recommendations –** see Appendix II, page 34).

iv. At present ATQ/proguanil (Malarone®) is not licensed for prophylaxis use in Canada; however, there may be limited use for ATQ/ proguanil as a prophylactic agent (with attention to contraindications and precautions) when other recommended options are either inappropriate or contraindicated. (**B I – evidence-based medicine recommendations –** see Appendix II, page 34).

b. Primaquine and Tafenoquine for the Prevention of Malaria

Primaquine is an 8-aminoquinolone that has been used for decades to prevent relapses of *P. vivax* and *P. ovale* infections (radical cure) and as a gametocidal agent to decrease the transmission of *P. falciparum* in malaria-endemic areas. Because primaquine has activity against both blood and tissue (liver) stages of malaria, it can eliminate *P. vivax* and *P. falciparum* infections that are developing in the liver (causal prophylaxis) and prevent symptomatic or clinical infection.

Recent randomized double blind, placebo-controlled studies have examined the efficacy of primaquine as a prophylactic agent in partially immune Kenyan children and non-immune Indonesian and Colombian men. Given at a dose of 0.5 mg/kg base per day (adult dose 30 mg base per day) for 11 to 50 weeks, primaquine had a protective efficacy of 85% to 95% against both *P. falciparum* and *P. vivax* infections. Primaquine was better tolerated than other standard chemoprophylactic regimens in persons who were not G6PD deficient.

Primaquine is generally well tolerated but may cause nausea and abdominal pain, which can be decreased by taking the drug with food. More importantly, primaquine may cause oxidant-induced hemolytic anemia with methemoglobinemia, particularly among individuals with G6PD deficiency. Primaquine is **contraindicated** in patients with severe G6PD deficiency. In mild variants of G6PD deficiency, primaquine has been used safely at a lower dose for radical cure to prevent *P. vivax* and *P. ovale* relapses (0.8 mg base/kg/week; adult dose 45 mg base weekly for 6 weeks); however, this reduced dose is insufficient for chemoprophylactic activity. When used at prophylactic doses (0.5 mg base/kg/day) in children and men with normal G6PD activity, mean methemoglobin rates (5.8%) were below those associated with toxicity (>10%).

Collectively, these data indicate that primaquine appears to be a safe and effective prophylactic agent in semi-immune children and non-immune adults. Theoretically, because primaquine is a causal agent, individuals should be required to take it only during periods of exposure and for 1 week after departure from the malaria-endemic area. This would avoid the requirement to complete 4 weeks of chemoprophylaxis following exposure (a common reason for non-adherence with standard regimens) and may be particularly useful for travellers with short exposures (2 to 7 days) in high-risk areas such as sub-Saharan Africa and New Guinea. Primaquine should be taken daily starting 1 day before entering a malaria-endemic area, continued while in the area and for 1 week after departure.

Tafenoquine (WR 238605) is a long acting 8-aminoquinoline with a half-life measured in weeks rather than hours. Initial research has shown efficacy with weekly chemoprophylaxis and evidence of causal prophylaxis. Phase 2 studies are ongoing in semi- and non-immune people. In the future, tafenoquine may provide another option for chemoprophylaxis in those without G6PD deficiency.

Recommendations

i. Primaquine chemoprophylaxis is **contraindicated** in individuals with G6PD deficiency and during pregnancy (**E II – evidence-based medicine recommendations –** see appendix II, page 34).

ii. Although not a first line chemoprophylactic agent, primaquine may be considered an alternative chemoprophylactic agent (with attention to contraindications and precautions) for those **without** G6PD deficiency when other regimens are either inappropriate or contraindicated (**AI – evidence-based medicine recommendations –** see appendix II, page 34).

c. Artemisinin Derivatives (Qinghaosu) for the Treatment of Drug-Resistant Malaria

Artemisinin (qinghaosu) is a naturally occurring sesquiterpene lactone peroxide structurally unrelated to any known antimalarial. Qinghaosu, derived from cultivated *Artemisia annua*, is available as the parent compound artemisinin (oral, parenteral, and suppository formulations) and as three semisynthetic derivatives: a water-soluble hemisuccinate salt (artesunate) for parenteral or oral administration; and two oil-soluble compounds (artemether and arteether) for intramuscular injection. All are metabolized to a biologically active metabolite, dihydroartemisinin. Artesunate is a prodrug for dihydroartemisinin and as such is the most rapidly active of the derivatives examined to date. All compounds have their antiparasitic effects on the younger ring-form parasites, thereby decreasing the numbers of late parasite forms that can obstruct the host's microvasculature.

All artemisinin preparations have been studied and used only for treatment. They are recommended **for treatment use only and not for prophylaxis**. All compounds are at least as efficacious as quinine in the treatment of severe and complicated malaria. Qinghaosu and its derivatives lead to faster parasite (mean: 32% faster) and fever (mean: 17% faster) clearance times than do any other antimalarials. In spite of the more rapid antiparasitic action of qinghaosu compounds, these agents have not been shown to decrease mortality compared with quinine.

Artemisinin-related compounds act rapidly against drug-resistant *P. falciparum* strains but have high recrudescence rates (about 10% to 50%) when used as monotherapy for less than 5 days. Recent studies have examined longer durations of therapy (7 days) and combinations of qinghaosu derivatives and mefloquine in order to prevent recrudescence. *In vitro* synergy has been demonstrated between artemisinin derivatives, mefloquine, and tetracycline. In Thailand, treatment with oral artesunate (over 3 to 5 days) combined with mefloquine (15 to 25 mg/kg) was more effective than mefloquine or artesunate alone. Combination therapy results in > 90% cure rates of primary and recrudescent *P. falciparum* infections.

Artemisinin derivatives have been used by over 1 million patients and are well tolerated. To date, there have been two human cases of complete heart block associated with their use, but most volunteer and clinical studies have found no evidence of cardiac or other toxicity. Neurologic lesions involving the brainstem have been seen in rats, dogs, and primates given repeated doses of artemisinin derivatives. To date, no clinical neurologic events have been observed in humans; however, studies addressing cumulative toxicity in humans have not been performed. The safety of qinghaosu derivatives in pregnancy has not been established. Because of their short half-life artemisinin and its derivatives should not be used for prophylaxis.

Artemisinin and its derivatives are now available and increasingly used in Southeast Asia and Africa; none is licensed in Canada. Combinations of artesunate and mefloquine appear to be the most active drug regimens for treatment of multidrug-resistant falciparum malaria in Southeast Asia. The quality of artemisinin derivatives available in developing countries is questionable, as they may not be produced in accordance with the good manufacturing production standards required in North America. Although there is good evidence that therapy with artemisinin compounds is safe, questions about cumulative neurologic toxicity require resolution.

Recommendations

i. Artemisinin compounds are effective alternative therapies for multidrug-resistant malaria (complicated and uncomplicated). However, at present, there are insufficient toxicity data or evidence of clinical superiority over standard therapy to routinely recommend these as first-line agents, particularly for *P. falciparum* infections acquired in Africa (**A I – evidence-based medicine recommendations –** see Appendix II, page 34).

ii. Artemisinin compounds should not be used for chemoprophylaxis. (**C III – evidence-based medicine recommendations** – see Appendix II, page 34).

iii. Artemisinin compounds may be considered for the treatment of laboratory-confirmed severe falciparum malaria acquired in areas where *P. falciparum* is known to be multidrug-resistant

OR for the treatment of falciparum malaria that fails standard drug regimens. In such cases, they should be used in combination with mefloquine or tetracycline (**A I – evidence-based medicine recommendations** – see Appendix II, page 34).

Artemisinin derivatives are not currently available in North America or Europe.

d. Azithromycin for the Prevention of Malaria

Azithromycin (Zithromax®) is a macrolide antibiotic that has been shown to have only limited effectiveness in the prevention of malaria (**A II – evidence-based medicine recommendations** – see Appendix II, page 34). Studies performed to date are small and suggest that azithromycin is less effective than mefloquine or doxycycline. Azithromycin should be considered for chemoprophylaxis only in highly selected groups. It is considered to be safe in pregnancy and in children, and is available in suspension. However, in view of the serious consequences of malaria in pregnancy, utilization of this suboptimal antimalarial would not routinely be recommended. If used, azithromycin requires daily dosing (adult dose of 1 tablet per day) starting the day before exposure, continued during exposure and for 4 weeks after departure from the malarial region.

Recommendations

There is insufficient evidence to recommend azithromycin as an alternative antimalarial except in circumstances in which other, more effective and safer medications are not available or are contraindicated. (**CI – evidence-based medicine recommendations –** see Appendix II, page 34).

e. Halofantrine for the Treatment of Malaria

Halofantrine is a phenanthrene methanol derivative related to mefloquine and quinine. It is available only in an oral formulation, which is limited by variable bio-availability. Halofantrine is not licensed in Canada and has recently been withdrawn from the market because of concerns about cardiotoxicity. It remains widely available in the tropics, and **travellers should be made aware of the danger of this drug**. The World Health Organization has reported cardiac deaths associated with the use of halofantrine and no longer recommends its use.

UNTIL THERE IS A CLEARER UNDERSTANDING OF THE FREQUENCY AND DETERMINANTS OF HALOFANTRINE CARDIOTOXICITY, ESTABLISHED ALTERNATIVES ARE PREFERRED

Recommendations

i. Halofantrine should **not** be used for self-directed therapy (**D II – evidence-based medicine recommendations –** see Appendix II, page 34).

ii. Halofantrine is **not** indicated for the treatment of multidrug-resistant malaria (combined resistance to mefloquine and chloroquine) or for the treatment of recrudescent malaria (**D II – evidence-based medicine recommendations –** see Appendix II, page 34).

iii. Travellers who inquire about halofantrine or who are likely to encounter its use (e.g. West Africa) should be informed of its potential cardiotoxicity (**C III – evidence-based medicine recommendations –** see Appendix II, page 34).

f. Pyronaridine for the Treatment of Malaria

Pyronaridine is a benzonaphthyridine, synthesized in China in 1970, which has been used for the treatment of *P. vivax* and *P. falciparum* for more than 20 years. The drug has been shown to be very effective in the treatment of falciparum malaria in children in Cameroon. It has more gastrointestinal side-effects than chloroquine. There are insufficient data at present to recommend the use of pyronaridine for the treatment of malaria in non-immune travellers.

APPENDIX I[†]

Malaria Risk by Geographic Areas in Countries with Endemic Malaria

Country	Areas of risk within country	Recommended Regimens
Afghanistan	All	Mefloquine
Algeria	Very limited in Sahara region	None
Angola	All	Mefloquine
Argentina	*P vivax* in rural areas near Bolivian and Paraguay borders	Chloroquine
Armenia	Risk limited to western borders areas: Masis, Ararat, and Artashat regions in Ararat district. No risk in tourist areas.	Chloroquine
Azerbaijan	Southern border areas and Khachmas region in north	Chloroquine
Bangladesh	All, except no risk in city of Dhaka	Mefloquine
Belize	Rural areas including resort areas, off shore islands, and forest preserves, except no risk in central coastal Belize District	Chloroquine
Benin	All	Mefloquine
Bhutan	Rural areas, in districts bordering India	Mefloquine
Bolivia	Rural areas < 2500 metres only, except no risk in Oruro Department and Province of Ingavi, Los Andes, Omasuyos, Pacajes, Southern and Central Potosi Department.	Mefloquine
Botswana	Northern part of country (North of 21° South) from November to June	Mefloquine
Brazil	Risk in Acre and Rondonia states, territories of Amapa and Roraima, and in rural areas of Amazonas, Maranhao, Mato Grosso, Para, and Tocantins. The outskirts of Manaus and Porto Velho are risk areas. Note: No risk for travellers to coastal states from the horn to Uruguay border and Iguassu Falls.	Mefloquine
Burkina Faso	All	Mefloquine
Burma: see Myanmar		
Burundi	All	Mefloquine
Cambodia	All, except no risk in Phnom Penh and around Tonle Sap. Malaria risk exists in Angkor Wat.	Mefloquine (doxycycline on western borders)
Cameroon	All	Mefloquine
Cape Verde	Limited risk exists on Sao Tiago Island from September to November	None
Central African Republic	All	Mefloquine
Chad	All	Mefloquine
China	Rural areas only in Anhui, Fujian, Guangdong, Guangxi, Guizhou, Hainan, Hubei, Hunan, Jiangsu, Jiangxi, Shandong, Shanghai, Sichuan, Xinjiang, Xizang, Yunnan and Zhejiang provinces/autonomous regions. Transmission occurs < 1500 metres from July to November north of 33° North, from May to December between 33° North and 25° N and throughout the year below 25° North. Note: Travellers visiting cities and popular rural tourist routes are generally not at risk and require no prophylaxis.	Chloroquine (mefloquine for Hainan Island and southern provinces bordering Myanmar, Lao People's Democratic Republic and Vietnam)
Colombia	In general, rural areas only, no risk in Bogota and vicinity	Mefloquine
Comoros	All	Mefloquine
Congo	All	Mefloquine
Costa Rica	Rural areas only (including tourist areas). No risk in central highlands. Limited risk in rural areas of Alajuela, Guanacaste, Limon, Heredia and Los Chiles provinces.	Chloroquine
Côte d'Ivoire (formerly Ivory Coast)	All	Mefloquine

[†] Adapted from *CDC Health Information for International Travel 1999-2000* and WHO *International Travel and Health 2000*.

Country	Areas of risk within country	Recommended Regimens
Democratic Republic of Congo	All	Mefloquine
Djibouti	All	Mefloquine
Dominican Republic	All rural areas. Highest risk in areas bordering Haiti. Travellers visiting resort areas are generally not at risk and require no prophylaxis.	Chloroquine
Ecuador	All provinces along eastern border and Pacific coast: Canar, Cotopasi, El Oro, Esmeraldas, Guayas, Los Rios, Manabi, Morona-Santiago, Napo, Pastaza, Pinchincha, Sucumbios, Zamora, Chinchipe. (No risk in Quito and vicinity, the central highland tourist areas or the Galapagos Islands.)	Mefloquine
Egypt	Limited risk in El Faiyum area and part of Southern (upper) Egypt. (No risk in main tourist areas including cruises.)	Chloroquine
El Salvador	Rural areas only	Chloroquine
Equatorial Guinea	All	Mefloquine
Eritrea	All, except no risk in Asmara and above 2,000 metres	Mefloquine
Ethiopia	All, except no risk in Addis Ababa and above 2,000 metres	Mefloquine
French Guiana	All	Mefloquine
Gabon	All	Mefloquine
Gambia	All	Mefloquine
Ghana	All	Mefloquine
Guatemala	Rural areas only, except no risk in central highlands above 1,500 metres	Chloroquine
Guinea	All	Mefloquine
Guinea-Bissau	All	Mefloquine
Guyana	High risk in rural areas of all interior regions including Rupununi, North West Regions and along Pomeroon River. The risk in Georgetown and New Amsterdam is low.	Mefloquine
Haiti	All	Chloroquine
Honduras	High risk of predominantly *P. vivax* in rural areas only	Chloroquine
India	All areas below 2,000 metres including Delhi and Bombay, except no transmission in parts of the states of Himachal Pradesh, Jammu, Kashmir, and Sikkim	Mefloquine
Indonesia	In general, rural areas only, except high risk in all areas of Irian Jaya (western half of island of New Guinea). No risk in cities of Java and Sumatra or resort areas in Java or Bali. Note: Transmission is largely confined to rural areas not visited by most tourists.	Mefloquine
Iran, Islamic Republic of	Limited risk in rural areas only (March to November) in the provinces of Sistan-Baluchestan, Kermany and Hormozgan, the southern parts of Fars, Kohgiluyeh-Boyar, Lorestan and Chahar Mahai-Bakhtiani and the north of Khuzestan.	Mefloquine
Iraq	All areas in northern region (May to November): Duhok, Erbil, Basrah, Tamim, Ninawa and Sulaimaniya province.	Chloroquine
Ivory Coast: see Côte d'Ivoire		
Kenya	All areas including game parks except low risk in city of Nairobi and above 2,500 metres	Mefloquine
Korea, Democratic People's Republic of (North)	Limited malaria risk from *P. vivax* exists in some southern areas.	None
Korea, Republic of (South)	Risk of *P. vivax* in and along demilitarized zone, areas not visited by travellers. Antimalarial drugs are not recommended for tourists.	None
Lao People's Democratic Republic	All areas, except no risk in city of Vientiane	Mefloquine
Liberia	All	Mefloquine
Libyan Arab Jamahiriya	Limited risk in two small foci in southwest of country from February to August	None
Madagascar	All, highest risk in coastal areas	Mefloquine
Malawi	All	Mefloquine
Malaysia	Remote rural areas of peninsular Malaysia and Sarawak (NW Borneo), urban and coastal areas are malaria free. All areas of Sabah (NE Borneo).	Mefloquine
Mali	All	Mefloquine
Mauritania	All areas, except no risk in the northern areas of Dakhlet-Nouadhibou and Tiris-Zemour. In Inchiri and Adrar, risk from July to October.	Mefloquine
Mauritius	Risk of *P. vivax* in rural areas only, except no risk in Rodrigues Island	Chloroquine

Country	Areas of risk within country	Recommended Regimens
Mayotte	All	Mefloquine
Mexico	Rural areas including rural resort areas of the following states: Campeche, Chiapas, Chihauhua, Durango, Guerrero, Hidalgo, Jalisio, Michoacan, Nayarit, Oaxaca, Quintana Roo, Sinaloa, Sonora and Veracrus.	Chloroquine
Morocco	Very limited risk of *P. vivax* in rural areas of some provinces	None
Mozambique	All	Mefloquine
Myanmar (formerly Burma)	Rural areas. Note: Travellers to Yangon (Rangoon) and Mandalay are not at risk and need no prophylaxis.	Mefloquine (doxycyline for Thai borders)
Namibia	All areas of Ovamboland and Caprivi Strip	Mefloquine
Nepal	Rural areas in Terai District and hill districts below 1,200 metres. No risk in Kathmandu.	Mefloquine
New Hebrides: see Vanuatu		
Nicaragua	Rural areas and outskirts of Bluefields, Bonanza, Chinandega, Leon, Puerto Cabeza, Rosita and Siuna	Chloroquine
Niger	All	Mefloquine
Nigeria	All	Mefloquine
Oman	All	Mefloquine
Pakistan	All areas below 2,000 metres including cities	Mefloquine
Panama	Rural areas north and west of Canal Rural areas south and east of Canal No risk in the Canal Zone or in Panama City	Chloroquine Mefloquine
Papua New Guinea	All	Mefloquine
Paraguay	In general, only rural areas bordering Brazil. *P. vivax* predominates.	Chloroquine
Peru	Rural areas only. Note: no risk for travellers visiting only Lima and vicinity, coastal areas south of Lima, or the highland tourist areas (Cuzco, Machu Picchu, Lake Titicaca) and no prophylaxis needed.	Chloroquine Mefloquine for borders with Brazil and Ecuador
Philippines	Rural areas only, except no risk in Manila and province of Bohol, Catanduanes and Cebu. Chloroquine resistance in rural areas of Luzon, Basilian, Mindoro, Palawan, Mindanao and Sulu-Archipelago.	Chloroquine Mefloquine for chloroquine-resistant areas.
Rwanda	All	Mefloquine
Sao Tome and Principe	All	Mefloquine
Saudi Arabia	All areas in Western province, except no risk in the high altitude areas of Asir province (Yemen border), and the urban areas of Jeddah, Mecca, Medina and Taif	Mefloquine
Senegal	All	Mefloquine
Sierra Leone	All	Mefloquine
Solomon Islands	All	Mefloquine
Somalia	All	Mefloquine
South Africa	Rural areas (including game parks) in the northern, eastern and western low altitude areas of the Transvaal and the Natal Coast north of 28° south.	Mefloquine
Sri Lanka	All rural areas except no risk in Colombo, Kalutara, Nuwara Eliya.	Mefloquine
Sudan	All	Mefloquine
Suriname	Rural areas only, except no risk in Paramaribo district and coastal areas north of 5° North.	Mefloquine
Swaziland	All lowland areas	Mefloquine
Syrian Arab Republic	Rural areas only (May to October) especially along northern border. No risk in districts of Damascus, Deir-es-zor and Sweida.	Chloroquine
Tajikistan	Risk predominantly in southern border areas (Khatlon region); risk in some central (Dushanbe), western (Gorno-Badakhshan) and northern (Leninabad) areas. Chloroquine resistance suspected in some areas.	Chloroquine
Tanzania, United Republic of	All	Mefloquine
Thailand	Malaria risk exists throughout the year in rural, especially forested and hilly, areas of the whole country, mainly towards the international borders (not visited by most travellers). There is no risk in cities and the main tourist resorts (e.g. Bangkok, Chiangmai, Pattaya, Phuket, Samui). Mefloquine resistance reported from areas on borders with Myanmar and Cambodia.	Doxycycline for overnight exposure in rural areas on border with Myanmar and Cambodia.
Togo	All	Mefloquine

Country	Areas of risk within country	Recommended Regimens
Turkey	Cukurova/Amikova areas and southeast Anatolia (April to October). No risk in main tourist areas in west and south-west.	Chloroquine
Uganda	All	Mefloquine
United Arab Emirates	Risk in foothills and valleys in the mountainous regions of northern Emirates. No risk in cities of Dubai, Sharjah, Ajman, Umm al Qaiwain and Emirate of Abu Dhabi.	Chloroquine
Vanuatu (formerly New Hebrides)	All, except no risk on Futuna Island.	Mefloquine
Venezuela	Rural areas only, in all border states and territories and the states of Barinas, Merida, and Portugesa	Mefloquine
Viet Nam	Rural areas only, no risk in Red Delta and coastal plain north of Nha Trang.	Mefloquine
Yemen	All except no risk in Aden and airport areas.	Mefloquine
Zaire: see Democratic Republic of Congo		
Zambia	All	Mefloquine
Zimbabwe	All except no risk in cities of Harare and Bulawayo.	Mefloquine

Countries not listed are considered free of malaria.

APPENDIX II

Strength and Quality of Evidence Summary Sheet*

Categories for the strength of each recommendation	
CATEGORY	**DEFINITION**
A	Good evidence to support a recommendation for use.
B	Moderate evidence to support a recommendation for use.
C	Poor evidence to support a recommendation for or against use.
D	Moderate evidence to support a recommendation against use.
E	Good evidence to support a recommendation against use.
Categories for the quality of evidence on which recommendations are made	
GRADE	**DEFINITION**
I	Evidence from at least one properly randomized, controlled trial.
II	Evidence from at least one well designed clinical trial without randomization, from cohort or case-controlled analytic studies, preferably from more than one centre, from multiple time series, or from dramatic results in uncontrolled experiments.
III	Evidence from opinions or respected authorities on the basis of clinical experience, descriptive studies, or reports of expert committees.

* From: Macpherson DW. *Evidence-based medicine*. CCDR 1994;20:145-47.

APPENDIX III

Checklist for Travellers to Malarial Areas

The following is a checklist of key issues to be considered in advising travellers. The numbers in parentheses refer to those pages in the text where these issues are discussed in detail.

a) Risk of malaria (see section 2a, page 3, section 4, page 14, and Appendix I, page 30)

Travellers should be informed about their individual risk of malaria infection and the presence of drug-resistant *P. falciparum* malaria in their areas of destination. Pregnant women and adults taking young children should question the necessity of the trip.

b) Anti-mosquito measures (see section 2b, page 3)

Travellers should be instructed on how to protect themselves against mosquito bites.

c) Chemoprophylaxis (see section 3, page 6)

Travellers should be:

1. advised to start chemoprophylaxis before travel, to use prophylaxis continuously while in malaria-endemic areas and for 4 weeks after leaving such areas (except for Malarone® and primaquine, which are taken for 1 week after leaving such areas).
2. questioned about drug allergies and other contraindications for drug use.
3. informed that antimalarial drugs can cause side effects; if these side effects are serious, medical help should be sought promptly and use of the drug discontinued. Mild nausea, occasional vomiting or loose stools should not prompt discontinuation of chemoprophylaxis, but medical advice should be sought if symptoms persist.
4. warned that they may acquire malaria even if they use malaria chemoprophylaxis.
5. warned that they may receive conflicting information regarding antimalarial drugs overseas, but that they should continue their prescribed medication unless they are experiencing moderate to severe adverse effects.

d) In case of illness (see section 7, page 21)

Travellers should be:

1. informed that symptoms of malaria may be mild, and that they should suspect malaria if they experience a fever or flu-like illness (unexplained fever).
2. informed that malaria may be fatal if treatment is delayed.
3. informed that medical help should be sought promptly if malaria is suspected, and a blood film should be taken and examined for malaria parasites on one or more occasions (if possible, blood films should be brought home for review).

4. reminded that self treatment (if prescribed) should be taken only if prompt medical care is not available within 24 hours and that medical advice should still be sought as soon as possible after self-treatment (see section 6, page 19).
5. reminded to continue to take chemoprophylaxis in cases of suspected or proven malaria.

e) Special hosts (see section 4, page 14)

Pregnant women, young children and immunocompromised individuals require special attention because of the potential effects of malaria illness and inability to use some drugs.

(Adapted from *International Travel and Health*, World Health Organization, Geneva, 1999).

APPENDIX IV

Misconceptions about Malaria and Mefloquine

1. Myth: Malaria is not a serious infection for healthy people.

Fact: Malaria is a major killer worldwide and is the principal life-threatening infectious disease that Canadian travellers face when travelling to high-risk areas of the world. In recent years there has been a dramatic increase in malaria cases in Canadian travellers, including several deaths.

2. Myth: All travellers to the developing world need malaria prophylaxis.

Fact: Many destinations in the developing world are either free of malaria or the risk is so low that malaria prophylaxis is not needed. Furthermore, some travellers to countries with known malaria risk may not need to take malaria prophylaxis because malaria transmission is often confined to particular areas of a country (usually rural) and may be seasonal. For example, most individuals travelling only to urban centres or resort areas in Central and South America or Southeast Asia do not require malaria prophylaxis. However, **ALL** travellers (adults and children) to any area with any risk of malaria should use personal protection measures, such as treated mosquito nets and insect repellents, to avoid mosquito bites.

3. Myth: Pregnant women, babies and children should not receive malaria prophylaxis.

Fact: On the contrary, pregnant women, babies and small children are at particular risk for serious malaria; if they must go to high-risk areas they should take malaria prophylaxis. Several effective prophylaxis regimens are known to be safe in these groups.

4. Myth: Most people who take mefloquine have serious side effects.

Fact: For travellers to high-risk areas, the risk of acquiring malaria and dying is significantly greater than the risk of experiencing a serious side effect from mefloquine. Over 11 million travellers have used mefloquine prophylaxis, and severe reactions (seizure, psychosis) to this drug are rare (reported from 1 in 10,000 to 1 in 13,000 users). The great majority of mefloquine users (95-99%) have either no side effects or only mild and temporary ones. Occasionally, a traveller will experience a less severe but still troublesome neuropsychological reaction (e.g. anxiety, mood change) to mefloquine (1 in 250 to 500 users) requiring a change to an alternative drug. These reactions are almost always reversible. Death from malaria, however, is not.

5. Myth: Drugs that are safer than mefloquine are available either in Canada or abroad.

Fact: For high-risk regions of the world, mefloquine is the most effective drug to prevent malaria. Alternatives typically offered to travellers to Africa (e.g. chloroquine, proguanil [Paludrine®], amodiaquine, pyrimethamine [Daraprim®], pyrimethamine plus sulfadoxine [Fansidar®], pyrimethamine plus dapsone [Maloprim®]) are significantly less effective and often more toxic than mefloquine. Doxycycline is an effective alternative but may occasionally have troublesome side effects and must be taken each and every day in order to prevent malaria.

6. Myth: If I take prophylaxis, the malaria I get will be more resistant to treatment.

Fact: The prevention of malaria in travellers using prophylactic drugs (including mefloquine) does not promote the development of resistant malaria parasites. Appropriately used prophylaxis can actually reduce resistance by lowering the burden of malaria disease.

7. Myth: There is only a limited period in which one can take prophylaxis safely.

Fact: There is no absolute time limit on how long one can take any antimalarial prophylactic drug. The small number of individuals who will experience significant side effects from antimalarial drugs usually do so within the first few weeks of use. Many mild side effects decrease with continued use of prophylaxis.

8. Myth: Some malaria cannot be treated.

Fact: If identified early and treated appropriately, almost all malaria can be completely cured. However, even short delays in the diagnosis of malaria can make treatment more difficult and less successful.

9. Myth: Once infected with malaria, you are infected for life.

Fact: Appropriate treatment and follow-up can ensure complete cure of malaria.

10. Myth: Individuals born and raised in a malarial country are immune for life.

Fact: Over time, individuals raised in areas where malaria is common either die from the disease or become partially immune to its most serious manifestations. However, this immunity is short lived once an individual leaves a malarious area.

Although avoidance of mosquito bites is important for protection (e.g. appropriate clothing, screens and mosquito nets, repellents), anti-malarial prophylactic drugs are essential for optimal protection in most settings. Any individual who has travelled to malarial areas and subsequently develops fever should urgently seek medical advice (even if the fever appears many months after returning to Canada) and request blood films to rule out malaria.

Appendix V

Contact Information for Malaria Centres of Excellence

The following hospital centres across Canada have been identified as Centres of Excellence for Malaria. Each Centre will have depositories of parenteral quinine for the treatment of severe malaria and can provide expertise in the management of malaria infections.

To obtain parenteral quinine, please contact the listed pharmacy in your area. Please refer to Table 4 for dosing information.

The designated physician for each Centre can be used as a resource for any questions you may have with regard to the treatment of malaria.

For after-hours assistance please contact the infectious disease consultant on call.

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