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CANADIAN RECOMMENDATIONS FOR THE PREVENTION AND TREATMENT OF MALARIA AMONG INTERNATIONAL TRAVELLERS

Health Canada Santé Canada

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1997
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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Table of Contents

PREFACE

*The prevention and treatment of malaria has changed considerably over the last decade due primarily to 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.*

These recommendations by the Committee to Advise on Tropical Medicine and Travel (CATMAT) were adopted by the Assistant Deputy Minister, Health Protection Branch, Health Canada.

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1. INTRODUCTION

Malaria is a common and serious infection caused by four species of the genus *Plasmodium*: *P. falciparum, P. vivax, P. ovale* and *P. malariae.* Infection with *P. falciparum* can be fatal and infections caused by *P. vivax* and *P. ovale* can relapse from latent liver stages. All types 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, headaches, abdominal pain, and malaise. Rigors and chills often occur. 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 which may lead to death. Malaria deaths are frequently the result of delays in the diagnosis and treatment of the infection.

IMPORTANT NOTE: THE SYMPTOMS OF MALARIA ARE NONSPECIFIC 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. Multidrug-resistant strains of malaria are now common in several regions of the world. Figure 1 indicates the geographic distribution of *P. falciparum* malaria based on patterns of drug resistance. These zones require frequent updating as the malaria situation continues to evolve.

2. PREVENTION

The traveller needs to be informed about four important components of malaria protection:

a. risk of acquiring malaria

b. personal measures to prevent mosquito bites

c. chemosuppressive drugs (where appropriate)

d. early diagnosis and treatment

a. Risk of Acquiring Malaria

Imported malaria is an important problem in Canada. From 1985 to 1996, 5,634 cases of malaria were reported. However, it is estimated that only 30% to 50% of cases are reported to public health agencies. The rate of imported malaria reported in Canada is 5 to 10 times the per capita rate of that of the United States. This may reflect true differences in risk or it may be a reporting artefact. Almost all malaria deaths in travellers are secondary to infection with *P. falciparum* and the great majority of these infections are acquired in sub-Saharan Africa. About 1% to 5% of patients with *P. falciparum* will die; most of these deaths can be prevented by early diagnosis and appropriate therapy. It should be emphasized that the majority of infections are preventable.

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 (See Appendix I). Information on risk in specific countries is derived from the World Health Organization (WHO) and the Centers for Disease Control and Prevention sources. While it is the most accurate information at the time of publication, many factors may have profound effects on local malaria transmission. 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 dependent upon the duration of an individual's exposure. Transmission decreases at altitudes above which the *Anopheles* mosquito cannot easily breed (above 2,000 to 3,000 metres, depending upon location). Travel to urban and tourist areas of Southeast Asia, Central and South America is considered to entail minimal risk, whereas urban travel in other malaria-endemic zones, such as sub-Saharan Africa and the Indian subcontinent, may be associated with significant risk of infection.

b. Personal Measures to Prevent Mosquito Bites

ALL travellers to malaria-endemic zones are advised to use personal insect protective measures to reduce the risk of bites from *Anopheles* mosquitos.

Any measure that reduces exposure to the evening and night-time feeding female *Anopheles* mosquito will reduce the risk of acquiring malaria: remaining in well-screened or completely enclosed air-conditioned areas, sleeping under insecticide-impregnated bed nets and wearing clothing that reduces the amount of exposed skin.

In addition, the use of insect repellent on exposed skin, particularly between dusk and dawn, is strongly recommended. Insect repellents containing diethyltoluamide (DEET®) are the most effective. The concentration of DEET® varies from product to product. Regardless of the concentration, repellency rates are equivalent but higher concentrations protect for longer periods of time. For example, 35% DEET® protects for 4 to 6 hours whereas 95% DEET® protects for 10 to 12 hours. In rare instances, application of insect repellents with high concentrations (> 35%) of DEET® has been associated with seizures in young children. Therefore, in children DEET® (< 35%) should be applied sparingly to exposed surfaces only and washed off after coming indoors. New formulations of DEET®, available in the US, contain a lower concentration (10% to 35%), but protect for longer than 4 to 6 hours.

ALL travellers at risk of acquiring malaria should be strongly encouraged to use insecticide-impregnated bed nets (permethrin or deltamethrin treated) unless their sleeping quarters are well-screened or otherwise protected from mosquitos (**A I – evidence-based medicine recommendations – see Appendix II**). Permethrin or delta-methrin-impregnated nets are significantly more effective at preventing malaria than untreated bed nets and are safe for children and pregnant women **(A I – evidence-based medicine recommendations – see Appendix II**). Impregnated bed nets are available in Canada and should be used in conjunction with the above measures.

c. Chemosuppressive Drugs (where appropriate)

The current CATMAT recommendations for the chemosuppression of malaria are based on the following:

- individual risk assessment
- distribution of drug-resistant malaria
- scientific studies and clinical experience regarding the safety and efficacy of chemosuppressive regimens (See section 3: Chemosuppressive Regimens.)

Individual risk assessment

Several factors need to be assessed when selecting an appropriate chemosuppressive regimen before travel. The travel itinerary should be reviewed in detail and compared to known areas of malaria transmission within a country to determine whether the traveller will actually be at risk of acquiring malaria (see below). The specific **activities** (rural travel, night-time exposure, unscreened accommodations) of the individual in the malaria zone should be considered in estimating the intensity of risk for malaria. The **health factors** of the individual (age, pregnancy, and chronic illness) also need to be known in order to determine the risk of severe disease if malaria were to occur and to choose an appropriate antimalarial drug.

The following factors should also be assessed:

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 blood films prepared with sterile equipment and then properly interpreted) if symptoms of malaria were to occur?
iv. Are there any contraindications to the use of a particular antimalarial drug?

Distribution of drug-resistant malaria (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), 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, Southeast Asia, and occurs sporadically in Africa. 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 negligible risk of malaria in urban centres of Southeast Asia and Central and South America (see section 3a. below). Malaria transmission falls at altitudes exceeding 2,000 metres and is virtually non-existant over 3,000 meters.

d. Early Diagnosis and Treatment

All travellers should be informed that they should suspect malaria if they develop unexplained fever during or after travel. Medical attention should be sought as soon as possible and the traveller should request that a blood sample be examined for malaria parasites.

3. CHEMOSUPPRESSIVE REGIMENS (See Tables 1 and 2)

a. Introduction

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

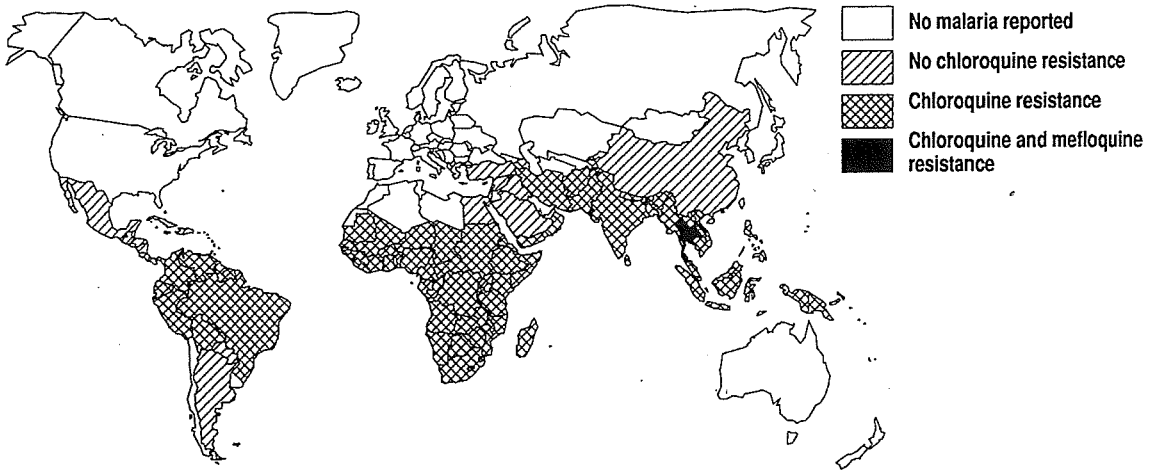
URBAN AND RURAL AREAS OF:

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

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

EVENING OR OVERNIGHT EXPOSURE IN RURAL, NON-RESORT AREAS: of Southeast Asia, Central and South America, and certain parts of Mexico, North Africa, and the Dominican Republic.

Figure 1 Map Showing Malaria-Endemic Zones



Visual aid only, see Appendix I.

Travellers should be informed that although antimalarials can markedly decrease the risk of developing symptomatic malaria, **NONE OF THESE AGENTS CAN GUARANTEE COMPLETE PROTECTION AGAINST MALARIA.** Symptoms due to malaria may occur as early as one week after first exposure, and as late as several years after leaving a malaria zone whether or not chemosuppression has been used.

Most travellers who acquire *P. falciparum* infection will develop symptoms 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 RETURNING FROM A MALARIA-ENDEMIC AREA IS A MEDICAL EMERGENCY AND SHOULD BE INVESTIGATED URGENTLY WITH THICK AND THIN SMEARS FOR MALARIA.

b. Chloroquine-Sensitive Zones

Drug of Choice: For travel to areas where chloroquine resistance has **not** been described, it is recommended that **chloroquine** (Aralen®) be taken alone, once **weekly (A I – evidence-based medicine recommendations – see Appendix II).** It is suitable for people of all ages and for pregnant women. Since insufficient drug is excreted in breast milk, nursing infants should be given chloroquine.

Except for its bitter taste, chloroquine is usually very well tolerated. Other mild side effects (nausea, headache) may be reduced by taking the drug with food or as a split dose twice weekly. Dark-skinned persons may experience generalized pruritis which is not indicative of drug allergy. Transient, minor, visual blurring may occur initially but should not be a reason to discontinue chloroquine. Retinal toxicity, which may occur with long-term high doses of chloroquine (>100 grams total dose) used in the treatment of other diseases, is extremely unlikely with chloroquine given as a weekly chemosuppressive. This type of retinal toxicity would require over 6 years of continuous chemosuppresive use. Chloroquine may worsen psoriasis and rarely is associated with seizures and psychosis. Therefore, chloroquine should be used with caution in individuals with a history of epilepsy or generalized psoriasis **(C III – evidence-based medicine recommendations – see Appendix II).** Doxycycline should be used for individuals who are unable to tolerate chloroquine or for whom the drug is contraindicated (see below). Concurrent use of chloroquine interferes with antibody response to intradermal human diploid rabies vaccine.

Chloroquine is taken once weekly, beginning one week prior to entering a malarial zone, during the period of exposure, and for 4 weeks after leaving the malarial area. Chloroquine is safe for pregnant women and young children. Since overdoses are frequently fatal, instructions for childhood doses should be carefully followed, and the medication should be kept out of the reach of children.

c. Chloroquine-Resistant Zones

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

In chemosuppressive doses, mefloquine is well tolerated. Adverse effects are similar in frequency and severity to those reported with weekly chloroquine use. Approximately 25% of travellers will experience side effects from mefloquine, most of them mild and self-limiting. The most frequent minor side effects reported by mefloquine users are nausea, strange dreams, dizziness, mood changes, insomnia, headache, and diarrhea. Approximately 1% to 4% of mefloquine users may have to discontinue prophylaxis because of adverse effects, a rate which is not significantly different from other chemosuppressive 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 neuropsychologic adverse events (anxiety, depression, nightmares, etc.) requiring drug discontinuation are reported in < 1% of users. In treatment doses (25 mg base/kg), mefloquine is less well tolerated and severe neuropsychiatric reactions are reported to be 10 to 60 times more frequent, occurring in 1/215 to 1/1,700 users. Excessive consumption of ethanol while on mefloquine should be avoided due to a possible enhanced risk of neuropsychiatric reactions (**C III – evidence-based medicine recommendations – see Appendix II**).

In the last decade in vitro or in vivo resistance has been reported sporadically from malaria-endemic areas. At present, however, resistance to mefloquine is not a significant problem except in rural wooded regions of Thailand bordering Myanmar (Burma) and Cambodia (areas infrequently visited by tourists) where **doxycycline** should be used for malaria chemosuppression (see below). Mefloquine may still be used for chemosuppression in other areas of Southeast Asia.

Contraindications to the use of mefloquine:

- Seizure disorder
- History of serious psychiatric illness
- Past severe reaction to mefloquine
- Underlying cardiac conduction disturbances or arrhythmia

Precautions for the use of mefloquine include the following:

- First trimester of pregnancy and children < 5 kilograms (see below)
- 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, see section 8)

There have been concerns regarding the co-administration of mefloquine and agents known to alter cardiac conduction including ß-adrenergic agents, calcium channel blockers, phenothiazines, non-sedating anti-histamines, and tricyclic antidepressants. However, at present these concerns remain theoretic and the concurrent use of these agents is not contraindicated.

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/week for children weighing > 5 kg.

Mefloquine is taken once **weekly**, beginning 1 week prior to entering a malaria zone, continuing during the period of exposure, and for 4 weeks after leaving the malarial area. There is no evidence that toxic metabolites of mefloquine accumulate; long-term use of mefloquine (> 1 year) 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**).

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 (in 4 days compared to 7 to 9 weeks with standard weekly dosing of mefloquine) (**A I – evidence-based medicine recommendations – see Appendix II**). 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, WHO recommends, where possible, that mefloquine be initiated about 3 weeks prior to travel in order to assess tolerance and achieve higher blood levels before entering malaria-endemic areas.

Alternatives: For individuals unable to take mefloquine, it is recommended that (1) **doxycycline** be taken, or less optimally (2) **chloroquine and proguanil**. In comparative trials in Irian Jaya and Africa, doxycycline has been shown to have equivalent efficacy to mefloquine (**A I – evidence-based medicine recommendations – see Appendix II**). Chloroquine plus proguanil is more efficacious in sub-Saharan Africa than chloroquine alone but it is considerably less efficacious than doxycycline or mefloquine (**A I – evidence-based medicine recommendations – see Appendix II**). In deciding between (1) doxycycline or (2) chloroquine plus proguanil, 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 above, such a decision must take into account personal health factors, destination and the activities during travel.

Doxycycline is taken **daily** (see below). **Chloroquine** is taken once **weekly** and **proguanil** is taken **daily** (200 mg/day). **It is important to ensure that travellers do not confuse chloroquine (weekly) and proguanil (daily) dosing regimens.**

Proguanil is very well tolerated. Occasionally, oral aphthous ulceration may occur. Rarely this may be severe enough to warrant discontinuing this medication. Proguanil is considered safe during pregnancy and breast feeding but insufficient drug is excreted in the milk to protect a nursing infant.

d. Chloroquine- and Mefloquine-Resistant Zones

Drug of Choice: In these regions **doxycycline** alone is the chemosuppressive of choice. It is taken once **daily** (100 mg), beginning 1 day prior to entering a malarial area, every day during the period of exposure and daily for 4 weeks after exposure. Doxycycline is an efficacious chemosuppressive agent against mefloquine-sensitive and mefloquine-resistant *falciparum* malaria (**A I – evidence-based medicine recommendations – see Appendix II**) but must be taken EVERY DAY to work. Non compliance with this daily regimen is the major reason for doxycycline failures.

Doxycycline is contraindicated during pregnancy, in breast-feeding 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 safely used over many years.

Doxycycline may cause gastrointestinal upset and rarely esophageal ulceration, which is less likely to occur if the drug is taken with food and copious amounts of fluid. It should not be taken simultaneously with Pepto-bismol® or antacids. Because doxycycline is photosensitizing, it may make the skin burn more easily; using a sun screen that blocks ultraviolet A rays may reduce this problem. Doxycycline may also increase the risk of vaginal candidiasis; therefore, women at risk of yeast vaginitis should carry antifungal vaginal suppositories or cream.

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

Zone	Drug(s) of Choice[b]	Alternatives
No Chloroquine Resistance	Chloroquine	Doxycycline
Chloroquine Resistant	Mefloquine	1st Choice: Doxycycline 2nd Choice: Chloroquine plus Proguanil[c]
Chloroquine and Mefloquine Resistant	Doxycycline	

Adult doses

Chloroquine phosphate:	300 mg (base) weekly
Proguanil:	200 mg daily
Doxycycline:	100 mg daily
Mefloquine:	One 250 mg (base) tablet weekly

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 during evening or night time in rural areas.

b All drugs are to be taken 1 week before entering malarial areas, continuing during the stay in malarial areas, and for 4 weeks after leaving malarial areas. Exceptions to this are doxycycline and proguanil which may be started 1 day before entering malarial areas, but must be continued for 4 weeks after departure.

c Chloroquine plus proguanil is less efficacious than mefloquine or doxycycline in these areas.

NB: 100 mg/day of proguanil is no longer recommended in malaria-endemic areas.

TABLE 2

Antimalarial Drugs, Doses[1], and Adverse Effects

Generic Name	Trade Name	Packaging	Adult Dose	Pediatric Dose	Adverse Effects
1. **chloroquine[2] phosphate**	Aralen®	150 mg base	**Prevention:** 300 mg base once weekly **Treatment:** 1.5 g base over 3 days[3]	**Prevention:** < 4 mo: 25 mg base 4-11 mo: 50 mg base 1-2 yr: 75 mg base 3-4 yr: 100 mg base 5-7 yr: 125 mg base 8-10 yr: 200 mg base 11-13 yr: 250 mg base ≥ 14 yr:300 mg base once weekly **Treatment:** 25 mg base/kg total over 3 days	**Frequent:** pruritis, 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
2. **clindamycin hydrochloride**	Dalacin®	150 mg base	**Prevention:** no indication **Treatment oral:** 150-450 mg base every 6 hr for 5 days **Treatment IV:** See Table 4	**Prevention:** no indication **Treatment oral:** 3-7 mg/kg three times per day for 5 days **Treatment IV:** See Table 4	**Frequent:** diarrhea, rash **Occasional:** pseudomembranous colitis **Rare:** hepatotoxicity, blood dyscrasias
3. **doxycycline**	Vibramycin®, Vibra-Tabs®, Doryx®	100 mg	**Prevention:** 100 mg once daily **Treatment:** 1 tablet twice daily for 7 days	**Prevention:** < 8 yr: contraindicated ≥ 8 yr: 1.5 mg salt/kg once daily (max 100 mg daily) **Treatment:** < 8 yr: contraindicated ≥ 8 yr: 1.5 mg salt/kg twice daily (max 200 mg daily)	**Frequent:** GI upset, vaginal candidiasis, photosensitivity **Occasional:** azotemia in renal diseases **Rare:** allergic reactions, blood dyscrasias
4. **halofantrine**	Halfan®	250 mg	**Prevention:** no indication **Treatment:** 2 tablets, three times daily for 1 day. Repeat 1 week later (on an empty stomach under medical supervision).	**Prevention:** no indication **Treatment:** 8 mg/kg three times for 1 day; repeat 1 week later	**Occasional:** cough, pruritis, rash **Rare:** prolonged QT ventricular arrhythmia
5. **mefloquine**	Lariam®	250 mg base	**Prevention:** 250 mg base once weekly **Treatment:** see text	**Prevention:** < 5 kg: not recommended 5-20 kg: 1/4 tablet 20-30 kg: 1/2 tablet 30-45 kg: 3/4 tablet > 45 kg: 1 tablet once weekly **Treatment:** see text	**Common:** dizziness, diarrhea, nausea, strange dreams, headache, insomnia **Rare:** seizures, psychosis

1 Dose for chemosuppression, unless specified for "Treatment".
2 Chloroquine sulfate (Nivaquine®) is not available in Canada, but is available in most malaria-endemic countries in both tablet and syrup form.
3 Generally, 2 tablets twice per day on days 1 and 2, then 2 tablets on day 3 (total of 10 tablets).

TABLE 2 *cont'd*

Antimalarial Drugs, Doses[1], and Adverse Effects

Generic Name	Trade Name	Packaging	Adult Dose	Pediatric Dose	Adverse Effects
6. **proguanil**	Paludrine®	100 mg	**Prevention:** 200 mg daily **Treatment:** see text	**Prevention:** < 8 mo: 25 mg 8 mo-3 yr: 50 mg 4-7 yr: 75 mg 8-10 yr: 100 mg 11-13 yr: 150 mg ≥ 14 yr: 200 mg **Treatment:** see text	**Occasional:** anorexia, nausea, mouth ulcers **Rare:** hematuria
7. **primaquine**	—	15 mg base	**Prevention:** see text **Treatment:** 15 mg base/day for 14 days[4]	**Prevention:** see text **Treatment:** 0.3 mg base/kg/day for 14 days	**Occasional:** GI upset, hemolysis in G6PD deficiency, methemoglobinemia
8. **pyrimethamine-sulfadoxine**	Fansidar®	25 mg pyrimethamine and 500 mg sulfadoxine	**Prevention:** no indication **Treatment:** 3 tablets (75 mg pyrimethamine – 1500 mg sulfadoxine)	**Prevention:** no indication **Treatment:** 2-3 mo: 1/4 tablet 4-11 mo: 1/2 tablet 1-2 yr: 3/4 tablet 3-4 yr: 1 tablet 5-9 yr: 1.5 tablets 10-11 yr: 2 tablets 12-13 yr: 2.5 tablets ≥ 14 yr: 3 tablets	**Occasional:** headache, nausea, folate deficiency **Rare:** Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis
9. **quinidine gluconate**	—	10 mL vial	**Prevention:** no indication **Treatment:** See Table 4	**Prevention:** no indication **Treatment:** See Table 4	**Frequent:** nausea, vomiting, cramps, cinchonism **Occasional:** widening of QRS complex, cardiac disturbance, headache, fever, delirium, rashes **Rare:** acute hemolytic anemia
10. **quinidine sulphate**	—	200 mg	**Prevention:** no indication **Treatment:** See Table 4	**Prevention:** no indication **Treatment:** See Table 4	similar to above
11. **quinine dihydrochloride**	—		**Prevention:** no indication **Treatment:** See Table 4	**Prevention:** no indication **Treatment:** See Table 4	**Frequent:** cinchonism (tinnitus, nausea, headache, blurred vision), hypoglycemia with IV **Occasional:** cardiac conduction disturbances, hypersensitivity **Rare:** hemolysis

[1] Dose for chemosuppression, unless specified for "Treatment".
[4] Doses are increased to 30 mg base/day for primaquine-resistant *P. vivax*.

TABLE 2 *cont'd*

Antimalarial Drugs, Doses[1], and Adverse Effects

Generic Name	Trade Name	Packaging	Adult Dose	Pediatric Dose	Adverse Effects
12. **quinine sulphate**	Novoquinine®	250 mg base (300 mg salt)	**Prevention:** no indication **Treatment[5] oral:** 2 tablets three times daily for 3-7 days **Treatment IV:** See Table 4	**Prevention:** no indication **Treatment[5] oral:** 7.5 mg base/kg (max 500 mg base three times daily for 3-7 days) **Treatment IV:** See Table 4	similar to above
13. **atovaquone/ proguanil**	Malarone®	250 mg atovaquone AND 100 mg proguanil	**Prevention:** see text **Treatment:** 1000 mg atovaquone AND 400 mg proguanil once daily x 3 days	**Prevention:** see text **Treatment:** 20 mg/kg atovaquone AND 8 mg/kg proguanil once daily x 3 days	**Frequent:** nausea, vomiting, abdominal pain, diarrhea, increased transaminases **Rare:** seizures, rash

[1] Dose for chemosuppression, unless specified for "Treatment".
[5] Generally, treatment of chloroquine-resistant strains of *P. falciparum* acquired in Southeast Asia should include a longer course (7 days) of quinidine or quinine and a second drug, as per Table 4.

4. 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 some 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, due to 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 are placed on self-treatment protocols.** Travellers should be advised that the clinical presentation of malaria is variable and may mimic other diseases. The most frequent symptoms are fever, headache, 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 to self treat for malaria if they develop **FEVER** and professional medical care is not available within 24 hours. However, they should be made aware that self treatment is only a temporary measure and **MEDICAL ATTENTION SHOULD STILL BE SOUGHT AS SOON AS POSSIBLE.**

a. For individuals in chloroquine-sensitive zones self treatment with chloroquine should be taken (see Table 2).

b. In chloroquine or chloroquine- and mefloquine-resistant *P. falciparum* zones, treatment recommendations for uncomplicated *P. falciparum* include the following (see Table 2):

Begin oral quinine and SEEK MEDICAL HELP AS SOON AS POSSIBLE

OR

Fansidar® 3 x 500 mg tablets taken once only (adult dose) (For sub-Saharan Africa and Asia only; excluding Southeast Asia) and SEEK MEDICAL HELP AS SOON AS POSSIBLE

Notes: Halofantrine is not recommended for self-treatment of malaria (see below). 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.

5. PREVENTION OF MALARIA IN SPECIAL HOSTS

a. Malaria Prevention in Children

Children are at special risk of malaria and may rapidly become ill. Travellers should be clearly advised of the risks involved in taking young children to areas with drug-resistant *falciparum* malaria. Getting young children to take antimalarial agents may be difficult, therefore taking young

children to areas at high risk of malaria should be avoided if possible. Drugs most effective at preventing drug-resistant malaria are not generally recommended in young children. Although the manufacturer recommends that mefloquine not be given to children < 5 kg, it should be considered for prophylaxis of children at high risk of acquiring chloroquine-resistant *P. falciparum* malaria at a dose of 5 mg base/kg/week. The alternative but less efficacious regimen for drug-resistant areas is the combination of chloroquine and proguanil. Doxycycline is contraindicated for children < 8 years of age. In areas with chloroquine-sensitive *falciparum* malaria, chloroquine remains the preferred agent. Chloroquine sulphate (Nivaquine®), while not available in Canada, is widely available as a syrup in malaria-endemic areas; the syrup is often more easily administered than tablets. Malaria tablets may be crushed and mixed with chocolate syrup, cereal or jam to mask the taste. For ALL children travelling to malarial areas particular attention should be paid to personal protection measures such as impregnated bed nets and insect repellents.

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 and chemosuppression should be used. Doxycycline is contraindicated during pregnancy. Fansidar® is contraindicated in the last month of pregnancy, and in the first 2 months of breast feeding. The safety of mefloquine during the first trimester has not been clearly established. Malaria chemosuppressive drugs, such as chloroquine and proguanil, which are safe to take during pregnancy, are not as efficacious as mefloquine or doxycycline in preventing drug-resistant *P. falciparum* malaria. This creates a dilemma for women who are, plan to be, or become pregnant while in malaria-endemic areas.

Recommendations

i. If possible, pregnant females and young children should avoid travel to areas with significant transmission of chloroquine-resistant malaria (**A I – evidence-based medicine recommendations – see Appendix II**).

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

iii. Pregnant females and young children travelling to or residing in chloroquine-sensitive areas should use chloroquine as a chemosuppressive (**A I – evidence-based medicine recommendations – see Appendix II**).

iv. Data indicate that mefloquine is effective and safe in pregnancy beyond 16 weeks gestation. Therefore, mefloquine may be used for prophylaxis of pregnant women (> 16 weeks gestation) **where exposure to chloroquine-resistant *falciparum* malaria is high and unavoidable** (**A I – evidence-based medicine recommendations – see Appendix II**). Pregnant females (< 16 weeks gestation) at high risk of *falciparum* malaria should be referred for individual risk assessment and counselling by a tropical disease expert. The combination of chloroquine and proguanil is safe in pregnancy but is significantly less efficacious against drug-resistant malaria (**A I – evidence-based medicine recommendations – see Appendix II**). There is no safe and effective chemosuppressive regimen available for pregnant women and children (< 8 years old) who travel to mefloquine-resistant areas on the Thai borders with Cambodia and Myanmar (Burma).

6. DIAGNOSIS OF MALARIA

Current travel destinations and immigration policies combined with escalating drug-resistant malaria have resulted in an increase in the number of cases of imported malaria, particularly that caused by drug-resistant parasites. In 1996, 744 cases of malaria were reported in Canada, representing a 73% increase from the 432 cases recorded in 1994. The reported rate may underestimate the true number of cases by 40% to 70% because of failure to take into account those who are diagnosed and treated abroad, and the prevalence of underreporting.

The overall case-fatality rate of imported *P. falciparum* malaria varies from 0.6% to 4.2% 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 ≥ 30% even when managed in modern ICU settings. ***The most important factors that determine patient survival are early diagnosis and appropriate therapy.***

TRAVELLERS AND HEALTH-CARE PROVIDERS ALIKE MUST CONSIDER THE DIAGNOSIS OF MALARIA IN ANY FEBRILE ILLNESS THAT OCCURS DURING OR AFTER TRAVEL TO A MALARIA-ENDEMIC AREA.

It is imperative that a travel history be obtained from all patients with a history of fever and that thick and thin films for malaria be requested urgently for all individuals who have travelled to or through a malaria-endemic area. *Falciparum* malaria usually presents within 3 months of last exposure; however, it may be delayed in patients who take chloroquine or mefloquine prophylaxis. In addition, other types of malaria, especially that caused by *P. vivax*, may occur months and occasionally 1 to 2 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). If facilities are not available to make the diagnosis, then an immediate referral of the patient or the specimen should be made to a facility which has expertise to do so.

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 is dependent on the species of parasite and the parasitemia; therefore, every effort should be made to determine the species of malaria and the level of parasitemia 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. Physicians should also be aware that the current case definition of malaria includes "foreign cases", defined as "a history of malaria acquired and treated abroad and confirmed in Canada by examination of a blood smear prepared abroad" or a traveller with a history of fever who responded to antimalarials but for whom a blood smear was never examined.

7. TREATMENT OF MALARIA

a. General Principles of Management

Management 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, 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*?
   Treatment varies according to the species of malaria.
2. Is this a severe or complicated infection (see Table 3)?
   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 (Appendix I)?
   Therapy will have to be modified accordingly.

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 infections.**

Severe *P. falciparum* infections, as defined by the criteria in Table 3, may have a mortality rate of 30% or higher. These patients require immediate hospitalization, and urgent and 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 antimalarials and to detect complications and early treatment failure.

All patients with severe *P. falciparum* infections (and those who are unable to tolerate oral drugs, regardless of the severity of infection) should receive intravenous quinine or quinidine (see Table 4). In the treatment of severe malaria, parenteral preparations of quinine and quinidine are equivalent, and either drug is acceptable for treatment. Although equally active, quinidine is more cardiotoxic than quinine and patients treated with intravenous quinidine should receive electrocardiographic monitoring. Infusion rates should be decreased if the corrected QT interval is prolonged by more than 25% of baseline. Intravenous quinine and quinidine are emergency release drugs that can be obtained through the Emergency Drug Release Program, Health Canada, telephone 613-941-2108, 24 hr/day. In at least three recent cases of imported malaria, delays in acquiring IV quinine or quinidine contributed to fatal

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).

TABLE 4

Chemotherapy of Severe *Falciparum* Malaria[a]

NOTE: The four quinine and quinidine protocols listed below are equally efficacious.

A. If an infusion pump is available:

1. Quinidine **(base) 6.2 mg/kg loading dose**[a,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 for 72 hours or until the patient can swallow, then quinine tablets to complete 7 days of treatment.

OR

2. Quinine[c] **(base) 5.8 mg/kg loading dose**[a,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 hours, repeated 8 hourly (maintenance dose) until the patient can swallow, then quinine tablets to complete 7 days treatment.

B. Without an infusion pump:

3. Quinidine **(base) 15 mg/kg loading dose**[a,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, 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 7 days or until oral quinine can be instituted.

OR

4. Quinine[c] **(base) 16.7 mg/kg loading dose**[a,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) until the patient can swallow, then quinine tablets to complete 7 days treatment.

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 if age < 8 years.

OR

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

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®).

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[a] 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.

[b] Loading dose should not be used if patient received quinine, quinidine or mefloquine within the preceding 12 to 24 hours.

[c] Parenteral quinine dihydrochloride and quinidine gluconate may be obtained on a patient-by-patient basis with authorization from the Bureau of Pharmaceutical Assessment, Health Protection Branch, Health Canada, Tower B, 1600 Scott Street, Ottawa, Ontario, K1A 1B6, (613) 941-2108.

outcomes. Directors of hospital pharmacies must ensure that they have ready access to either parenteral quinine or quinidine for the treatment of severe malaria.

Uncomplicated *P. falciparum* infections unequivocally acquired in a chloroquine-sensitive zone may be treated with chloroquine alone (as per Table 2). Those infections that were possibly or definitely acquired in drug-resistant zones should be treated with 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), or if necessary parenterally (as per Table 4). The base-salt equivalents of selected antimalarials are shown in Table 5.

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.

TABLE 5

Base/Salt Equivalents of Selected Antimalarial Drugs

Drugs	Base	Salt
Chloroquine phosphate	150 mg	250 mg
Chloroquine sulfate[1]	100 mg	136 mg
Clindamycin hydrochloride	150 mg	225 mg
Mefloquine	250 mg	274 mg
Quinidine gluconate	5.0 mg 7.5 mg 10 mg 15 mg	8 mg 12 mg 16 mg 24 mg
Quinidine sulfate	7.5 mg 10 mg 15 mg	9 mg 12 mg 18 mg
Quinine dihydrochloride	5 mg 7.5 mg 15 mg 16.7 mg	6 mg 9 mg 18 mg 20 mg
Quinine sulfate	250 mg	300 mg

[1] not available in Canada

c. Ancillary Treatment for 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)**. In cases of complicated *P. falciparum* infection (Table 3) or hyperparasitemia (> 5% parasitemia in non-immune individuals), exchange transfusion has been used on an experimental basis as a potentially life-saving procedure. ***If this situation arises, consultation with a tropical disease expert is strongly recommended.***

d. Management of Non-*Falciparum* Malaria

Outside of New Guinea (Papua New Guinea and Irina Jaya), chloroquine remains the treatment of choice for malaria other than *falciparum* (as per Table 2).

Recent reports have confirmed the presence and high prevalence (80%) of chloroquine-resistant *P. vivax* in Irian Jaya. Sporadic cases of chloroquine-resistant *vivax* malaria have been reported from elsewhere in Indonesia, Papua New Guinea, the Solomon Islands, Myanmar, and Guyana, South America. At present, chloroquine can no longer be relied upon either for chemosuppression or treatment of *P. vivax* acquired in New Guinea. The optimal treatment for *vivax* malaria acquired in New Guinea is unknown. Although effective, quinine is often required in prolonged course (> 3 days) 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. 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.

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. None of the currently recommended chemosuppressive 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 recommended for routine use to prevent relapsing malaria in asymptomatic returning travellers. 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). Relapses can be prevented by weekly chemosuppression with choloroquine until after delivery when primaquine can be safely used for mothers with normal glucose 6-phosphate dehydrogenase (G6PD) levels.

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

Primaquine resistance in the radical cure of *P. vivax* malaria is well documented in Southeast Asia and, in particular, Papua New Guinea and Irian Jaya. Recently, primaquine treatment failure has been reported from

Thailand and Somalia. When *P. vivax* malaria relapses following primaquine therapy, the dose of primaquine should be increased to two times standard therapy, i.e. 30 mg of primaquine base daily for 14 days for adults.

8. NEW DRUGS FOR PREVENTION AND TREATMENT OF MALARIA

a. Halofantrine

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. The main use previously proposed for halofantrine was in the treatment of mild to moderately severe *falciparum* malaria, known or suspected to be resistant to chloroquine, and as an alternative drug for "presumptive" self-treatment of malaria in travellers. Halofantrine has also been demonstrated to be effective as therapy for chloroquine-resistant *P. vivax* infections.

Although initial studies of halofantrine (24 mg/kg; adult dose 500 mg every 6 hours x 3 doses) showed it to be effective against *P. falciparum* in Thailand and Africa, more recent experience in Southeast Asia has not confirmed this. In Thailand, cure rates with halofantrine (24 mg/kg) varied from 65% to 70% as primary treatment to 40% in re-treatment of recrudescent infections. The high recrudescent rates after standard halofantrine therapy have led to a recommendation to re-treat patients, particularly non-immune patients, on day 7.

Halofantrine has reduced efficacy in malaria occurring after failure of mefloquine prophylaxis and there is in vivo and in vitro evidence demonstrating cross resistance between halofantrine and mefloquine.

Halofantrine is generally well tolerated with low rates of gastrointestinal side effects. It is better tolerated by patients than quinine or mefloquine but concerns about cardio-toxicity (see below) limit its use for therapy and chemosuppression.

Halofantrine treatment results in concentration-dependant delays in ventricular depolarization and atrio-ventricular conduction. High-dose halofantrine (72 mg/kg) induced consistent dose-related prolongation of the corrected QT interval (QTc), similar to the effect induced by quinidine. Even standard dose halofantrine (24 mg/kg) is associated with QTc prolongation in about 80% of patients. The likelihood of significant QTc prolongation was greater when halofantrine was used as re-treatment following mefloquine failure. Published reports have described proven cases of torsades de pointes ventricular tachycardia associated with standard dose halofantrine use in individuals with familial prolongation of the QT interval. The WHO has reported cardiac deaths associated with the use of halofantrine and no longer recommends its use.

Recommendations

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

i. It is recommended that halofantrine not be used for self-directed therapy in situations of self diagnosis of malaria (**D II – evidence-based medicine recommendations – see Appendix II**).

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**).

iii. There may be limited use for halofantrine (with attention to contraindications and precautions) for physician-directed treatment for patients with normal QT intervals, where other recommended treatment options are inappropriate or contraindicated (**D II – evidence-based medicine recommendations – see Appendix II**).

Individuals who are likely to receive halofantrine should have an ECG performed to assess whether there are conduction abnormalities or a prolonged QT interval. Halofantrine is contraindicated in patients with congenital or acquired QT interval prolongation and should be avoided in patients with severe electrolyte abnormalities, recent prophylaxis or treatment with mefloquine (within 4 weeks), concurrent use of drugs with effects on cardiac conduction (quinine, quinidine, chloroquine, tricyclic antidepressants, neuroleptic drugs, terfenadine, or astemizole), or thiamine deficiency. If used, the dosage should be limited to 24 mg/kg (8 mg/kg q6h x 3 doses) and repeated at 1 week. Halofantrine should NOT be taken with food (**D II – evidence-based medicine recommendations – see Appendix II**).

iv. 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**).

Halofantrine is licensed in the United States and Canada, but has not been marketed. It is widely available in Africa and Europe.

b. 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 semi-synthetic 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 to quinine.

Artemisinin-related compounds act rapidly against drug-resistant *P. falciparum* strains but have high recrudescent rates (about 10% to 50%) when used as monotherapy for ≤ 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 in 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.

Artemisinin and its derivatives are now available and increasingly used in Southeast Asia and Africa. Combinations of artesunate and mefloquine appear to be the most active drug regimens for treatment of multidrug-resistant *falciparum* malaria in Southeast Asia. However, present pre-clinical and toxicity data are insufficient to meet current drug registration requirements necessary for these drugs to be licensed and distributed in Canada. Although there is good evidence (**A I – evidence-based medicine recommendations – see Appendix II**) that short-term 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 and evidence of clinical superiority over standard therapy to recommend these agents, particularly for *P. falciparum* infections acquired in Africa (**A I – evidence-based medicine recommendations – see Appendix II**).

ii. Artemisinin compounds may be considered for the treatment of 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 (**A I – evidence-based medicine recommendations – see Appendix II**).

iii. The use of artemisinin compounds should be restricted and these agents should not be used for chemoprophylaxis. They should be used only for laboratory-confirmed *falciparum* infections and in combination with mefloquine or tetracycline (**C III – evidence-based medicine recommendations – see Appendix II**).

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

c. Atovaquone/Proguanil (Malarone®) for Treatment and Chemosuppression

Atovaquone (ATQ), a hydroxynapthaquinone, is a member of a novel class of antimalarials first described in the 1920s. ATQ was developed as a metabolically stable derivative by Wellcome Laboratories during the 1970s.

Although first identified for its antimalarial activity, ATQ was subsequently found to have broad spectrum anti-protozoal activity and is now licensed for the treatment of mild to moderate *Pneumocystis carinii* pneumonia. In addition, it is active against *Toxoplasma gondii* and *Babesia* sp.

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 used as monotherapy, ATQ resistance develops rapidly. Because of high recrudescent rates (about 30%), subsequent studies examined ATQ combination therapy. Based on in vitro studies indicating that ATQ displays synergy with proguanil and tetracycline and in vitro antagonism with artemisinin compounds and quinolines, combinations of ATQ/proguanil and ATQ/tetracycline have been examined. Based on its demonstrated safety and synergism with ATQ, proguanil has been formulated with ATQ as a fixed drug combination with the trade name Malarone® (tablet: 250 mg ATQ and 100 mg proguanil).

Compared to other standard antimalarial regimens such as mefloquine and quinine/tetracycline, the ATQ/proguanil combination has demonstrated excellent safety and tolerance. In excess of 200,000 courses of ATQ/proguanil have been prescribed worldwide and only 122 adverse

events have been reported in post-marketing surveillance, suggesting that the drug is well tolerated. 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 5% to 10% will develop 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. Convulsions occurred 2 to 5 days after initiation of therapy in three patients with a past 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).

In clinical trials conducted in Southeast Asia, South America, and Africa, the combination of ATQ and proguanil was highly efficacious in the treatment of acute uncomplicated *falciparum* malaria. Cure rates following ATQ/proguanil once daily for 3 days have exceeded 95% even in areas of multidrug resistance (**B II – evidence-based medicine recommendations – see Appendix II**). Adverse events were similar to mefloquine and better than quinine plus tetracycline. 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.

Field trials have also demonstrated the efficacy of ATQ/proguanil as a suppressive agent against *P. falciparum* malaria in semi-immune adults in Kenya. Additional studies in children and non-immune adults are required in order to satisfy regulatory agencies of its safety and effectiveness as a chemosuppressive agent.

Recommendations

i. ATQ combined with proguanil or tetracycline is an effective and well tolerated alternative therapy for multidrug-resistant malaria (uncomplicated) acquired in Southeast Asia, Africa, or South America (**B II – evidence-based medicine recommendations – see Appendix II**). However, at present there is insufficient evidence of clinical superiority over standard agents to routinely recommend this combination therapy.

ii. There may be limited use for ATQ/proguanil (with attention to contraindications and precautions) in situations where other recommended therapeutic options are either inappropriate or contraindicated. ATQ/proguanil may be considered for the treatment of *falciparum* malaria that fails standard drug regimens. Re-treatment of ATQ failures with ATQ/proguanil is not indicated (**D II – evidence-based medicine recommendations – see Appendix II**).

iii. The use of ATQ/proguanil should be restricted and, at present, this combination should not be used for chemosuppression. ATQ should be used only for the treatment of laboratory-confirmed *P. falciparum* infections in combination with proguanil, tetracycline, or doxycycline (**B II – evidence-based medicine recommendations – see Appendix II**). There are insufficient data at present to recommend its use for malaria caused by other *Plasmodium* species.

ATQ is available as 250 mg tablets and as a suspension in Canada and proguanil as 100 mg tablets. The standard adult treatment course is 1,000 mg ATQ and 400 mg proguanil once daily for 3 days. The fixed drug combination Malarone® (1,000 mg ATQ and 400 mg proguanil) is currently available in England for the treatment of *P. falciparum* malaria but is not yet marketed in Canada.

d. Primaquine for Chemoprophylaxis

Primaquine is an 8-aminoquinoline 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 and double blind placebo-controlled studies have examined the efficacy of primaquine as a prophylactic agent in partially immune Kenyan children and Indonesian men. Given at a dose of 0.5 mg/kg base per day (adult dose approximately 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 as well or better tolerated than other standard chemosuppressive regimens.

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 methemaglobinemia, particularly in individuals with G6PD deficiency. Primaquine is contraindicated in patients with severe 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 weekly for 6 weeks) for radical cure to prevent *P. vivax* or *P. ovale* relapse. However, this reduced dose is insufficient for prophylactic activity. When used at the higher dose (0.5 mg base/kg/day) in prophylactic studies in children and men with normal G6PD activity, it was well tolerated. Mean methemoglobin rates (5.8%) were below those associated with toxicity (> 10%).

Collectively, these data indicate that primaquine is a safe and effective prophylactic agent in semi-immune children and adults. If it is demonstrated to be a causal prophylaxtic agent, primaquine would only need to be taken during periods of exposure and for a few days after departure from malarial areas. This would avoid the requirement to complete 4 weeks of chemosuppression following exposure (a common reason for non-compliance with standard regimens) and would be particularly useful for travellers with short exposure (2 to 7 days) in high-risk areas such as

sub-Saharan Africa and Papua New Guinea. **However, at present, there are insufficient data demonstrating its effectiveness in non-immune travellers.**

Recommendations

i. Primaquine is an effective alternative chemosuppressive agent to prevent *P. vivax* and *P. falciparum* malaria (**A I – evidence-based medicine recommendations – see Appendix II**). However, at present there is insufficient evidence of effectiveness in non-immune travellers to recommend it over standard regimens.

ii. There may be limited use for primaquine as a prophylactic agent (with attention to contraindications and precautions) in situations where other recommended chemosuppressive options are either inappropriate or contraindicated. Primaquine should not be used in individuals with G6PD deficiency or during pregnancy (**E II – evidence-based medicine recommendations – see Appendix II**).

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	Rural areas near Bolvian and Paraguay borders.	Chloroquine
Azerjaijan	Souther border areas and Khachmas region in north.	Chloroquine
Bangladesh	All, except no risk in 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 meters) 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	Rural areas of Acre, Amazonas, Goias, Maranhao, Mato Grosso and Para States; and territories of Tocantins, Amapa, Rondonia, Roraima and urban areas of Amazon River Basin. **Note:** No risk for travellers to coastal states from the horn to Uruguay border and Iguassu Falls.	Mefloquine
Burkina Fasa	All	Mefloquine
Burma: see Myanmar		
Burundi	All	Mefloquine
Cambodia	All, except no risk in Phnon Penh and around Tonle Sap. Malaria risk exists in Angkor Wat.	Mefloquine (Doxycycline on western borders)
Cameroon	All	Mefloquine
Cape Verde	September to November Sao Tiago Island.	None
Central African Republic	All	Mefloquine
Ceylon: see Sri Lanka		
Chad	All	Mefloquine
China	Rural areas only in Anhui, Hainan, Fujian, Guangdong, Guangxi, Buizhou, Jiangsu, Jiangxi, Shandong, Sichuan, Yunnan and Zhejiang Provinces/autonomous regions. Transmission occurs < 1500 meters 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 southern provinces bordering Myanmar, Laos 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

† Adapted from *CDC Health Information for International Travel 1996-97* and WHO Malaria Recommendations, 1997. Countries not listed are considered free of malaria.

APPENDIX I† *(continued)*

Malaria Risk by Geographic Areas in Countries with Endemic Malaria		
Country	**Areas of risk within country**	**Recommended Regimens**
Côte d'Ivoire (formerly Ivory Coast)	All	Mefloquine
Dijbouti	All	Mefloquine
Dominican Republic	All rural areas. Highest risk in areas bordering Haiti. No risk in tourist areas.	Chloroquine
Ecuador	All provinces along eastern border and Pacific coast: Esmeraldas, Guayas, Manabi, El Oro. Rural areas in provinces of Canar Cotopasi, Los Rios, Morona, Santiago, Napo, Pastaza, Zamora, Sucumbios, Chinchipe and Pinchincha. (No risk in Quito and vicinity, the central highland tourist areas or the Galapagos Islands). Chloroquine resistance in Guayaquil.	Mefloquine
Egypt	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 over 2,000 metres. No risk in Asmara.	Mefloquine
Ethiopia	All, 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 for no risk in central highlands (> 1,500 metres).	Chloroquine
Guinea	All	Mefloquine
Guinea-Bissau	All	Mefloquine
Guyana	Rural, in all interior regions including Rupununi, North West Regions and along Pomeroon River. Only Georgetown and New Amsterdam are transmission free.	Mefloquine
Haiti	All	Chloroquine
Honduras	Rural areas only.	Chloroquine
India	All areas below 2,000 metres including Delhi and Bombay, except no transmission in Himachal Pradesh, Jammu, Kashmir, and Sikkim.	Mefloquine
Indonesia	In general rural areas only, except high risk in all areas of Irian Jaya. 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	Rural areas only (March to November) in the provinces of Sistan-Baluchestan, Kermany and Hormozgan, the southern parts of Fars, Kohgiluyh-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 Sulaymaniya province.	Chloroquine
Ivory Coast: see Côte d'Ivoire		
Kenya	All except low risk in city of Nairobi and above 2,500 metres.	Mefloquine

† Adapted from *CDC Health Information for International Travel 1996-97* and WHO Malaria Recommendations, 1997. Countries not listed are considered free of malaria.

APPENDIX I† *(continued)*

Malaria Risk by Geographic Areas in Countries with Endemic Malaria

Country	Areas of risk within country	Recommended Regimens
Lao People's Domestic Republic	All areas, except no risk in city of Vientiane.	Mefloquine
Liberia	All	Mefloquine
Libyan Arab Janahiriya	Limited risk in two small foci in Southwest of country from February to August.	None
Madagascar	All, highest in coastal areas.	Mefloquine
Malawi	All	Mefloquine
Malaysia	In general, rural areas only including Sarawak (NW Borneo), but throughout Sabah (NE Borneo). Otherwise, none in urban and coastal areas.	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	Rural areas only, except no risk in Rodrigues.	Chloroquine
Mayotte	All	Mefloquine
Mexico	Rural areas only including Oaxaca, Chiapas, Sinaloa, Michoacan, Quintana Roo, Guerrero, Campeche, Tabasco, Nayarit, Chihauhua and Hidalgo. No risk in resort areas.	Chloroquine
Morocco	Very limited risk 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 including cities in areas below 2,000 metres.	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.	Chloroquine
Peru	In general, all rural areas, except no risk in Lima and vicinity and coastal areas South of Lima. **Note:** travellers to Lima and vicinity and to highland tourist areas (Cuzco, Machu Picchu) are not at risk and need no prophylaxis.	Chloroquine Mefloquine for borders with Brazil and Ecuador

† Adapted from *CDC Health Information for International Travel 1996-97* and WHO Malaria Recommendations, 1997. Countries not listed are considered free of malaria.

APPENDIX I† *(continued)*

Malaria Risk by Geographic Areas in Countries with Endemic Malaria

Country	Areas of risk within country	Recommended Regimens
Philippines	Rural areas only, except no risk in Manila and province of Bohol, Catanduanes and Cebu.	Chloroquine
	Rural areas of Luzon, Basilian, Mindoro, Palawan, Mindanao and Sulu-Archipelago.	Mefloquine
Rwanda	All	Mefloquine
Sao Tome and Principe	All	Mefloquine
Saudi Arabia	All areas except the Eastern, Northern and Central provinces, the high altitude areas of Asir province, and the urban areas of Jeddah, Mecca, Medina and Taif.	Chloroquine
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 (formerly Ceylon)	All areas except 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.	Chloroquine
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	In southern border areas.	Mefloquine
Tanzania, United Republic of	All	Doxycycline
Thailand	Rural border areas only (not visited by most travellers), no risk in Bangkok, Chiangmai, Pattaya or beach resort areas. Mefloquine resistance. Doxycycline recommended on borders with Myanmar and Cambodia for overnight exposure in rural areas.	Mefloquine
Togo	All	Chloroquine
Turkey	Cukurova/Amikova areas and southeast Anatolia (April to October). No risk in main tourist areas in west and south-west.	Mefloquine
Uganda	All	Chloroquine
United Arab Emirates	Risk in foothills and valleys in the mountanous regions of northern Emirates. No risk in cities of Dubai, Sharjah, Ajman, Umm al Qaiwain and Emirate of Abu Dhabi.	Mefloquine
Vanuatu (formerly New Hebrides)	All, except no risk on Futuna Island.	Mefloquine
Venezuela	Rural areas of all border states and rural areas of the states of Barinas, Monagas, Sucre, Tachira, Amazonas, Delta Amacuro, Apure, and Bolivar.	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 (Republic of Congo)	All	Mefloquine

† Adapted from *CDC Health Information for International Travel 1996-97* and WHO Malaria Recommendations, 1997. Countries not listed are considered free of malaria.

Malaria Risk by Geographic Areas in Countries with Endemic Malaria		
Country	**Areas of risk within country**	**Recommended Regimens**
Zambia	All	Mefloquine
Zimbabwe	All except no risk in cities of Harare and Bulawayo.	Mefloquine

† Adapted from *CDC Health Information for International Travel 1996-97* and WHO Malaria Recommendations, 1997. Countries not listed are considered free of malaria.

APPENDIX II

Categories for 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 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 of respected authorities on the basis of clinical experience, descriptive studies, or reports of expert committees.

APPENDIX III

Checklist for Travellers to Malarious 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 (Appendix I)

Travellers should be informed about the 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 (page 1)

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

c) Chemosuppression (page 2)

Travellers should be:

1. *advised to start chemosuppression before travel, and to use prophylaxis continuously while in malaria endemic areas and for 4 weeks 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 chemosuppression, 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

Travellers should be:

1. *informed that symptoms of malaria may be mild, and that they should suspect malaria if they experience unexplained fever.*
2. *informed that malaria may be fatal if treatment is delayed. Medical help should be sought promptly if malaria is suspected, and a blood sample should be taken and examined for malaria parasites on one or more occasions (if possible, blood smears should be brought home for review).*
3. *reminded that self-treatment (if prescribed) should be taken only if prompt medical care is not available and that medical advice should still be sought as soon as possible after self-treatment.*
4. *reminded to continue to take chemosuppression in cases of suspect or proven malaria.*

e) Special categories (page 8)

1. *Pregnant women and young children require special attention because of the potential effects of malaria illness and inability to use some drugs (for example, doxycycline).*

(Adapted from *International Travel and Health*, World Health Organization, Geneva, 1997).