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

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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

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

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Malaria is caused by the genus *Plasmodium*, of which four species infect humans: *P. falciparum, P. vivax, P. ovale and P. malariae. All 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: myalgias, headaches, abdominal pain, and malaise. Rigors and chills often occur. Severe malaria due to *P. falciparum* may cause seizures, coma, renal failure, and respiratory failure, which may lead to death.

IT IS IMPORTANT TO NOTE THAT MALARIA CANNOT BE DIAGNOSED 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 drug-resistant *P. falciparum* malaria. These zones require frequent updating as the malaria situation changes.

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.

Risk of Acquiring Malaria

Malaria transmission occurs in most of sub-Saharan Africa; in large areas of the Middle East, Southern Asia, Southeast Asia, Oceania, Haiti, Central and South America; and in certain parts of Mexico, North Africa and the Dominican Republic (See Appendix I). Transmission occurs between dusk and dawn, which corresponds to the biting habits of the female *Anopheles* mosquito. The risk of transmission is increased in rural areas, is diminished at altitudes above which the *Anopheles* mosquito does not breed, and is dependent upon the duration of human exposure and activity during exposure. Travel to urban and tourist areas of Southeast Asia, Central and South America is considered to entail minimal risk, although urban travel in the other malaria-endemic zones, especially sub-Saharan Africa, may be associated with significant risk of infection.

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.

Certain factors, such as age, underlying health status, and pregnancy are also important in determining the outcome from acute malaria infection.

General Advice For the International Traveller to a Malaria-Endemic Zone

There are two important components of malaria protection:

1. personal protection against mosquito bites, and
2. chemosuppressive drugs

1. Personal Measures to Avoid Mosquitos

ALL travellers to malaria-endemic zones are advised to use personal insect protective measures to reduce the risk of night-biting mosquitoes.

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

In addition, the use of insect repellant on exposed skin is also recommended. Insect repellents containing N,N diethylmethyltoluamide (DEET) are the most effective. The concentration of DEET varies from product to product, and the higher concentrations protect for longer periods of time. In rare instances, application of insect repellents with high concentrations (> 35%) of DEET has been associated with seizures in young children; therefore, DEET should be applied sparingly to exposed surfaces only and washed off after coming indoors. Thirty-five per cent DEET protects for 4 to 6 hours whereas 95% DEET protects for 10 to 12 hours. New formulations containing a lower concentration of DEET and protecting for longer periods are available.

ALL travellers at risk of acquiring malaria should be strongly encouraged to use permethrin-impregnated bed nets unless their sleeping quarters are air-conditioned, well-screened or otherwise protected from mosquitoes (**AI** - evidence-based medicine recommendations — see Appendix II). Permethrin- or deltamethrin-impregnated nets are significantly more effective at preventing malaria than untreated bed nets and are safe for children and pregnant women (**AI** - evidence-based medicine recommendations — see Appendix II). Impregnated bed nets are available in Canada (1-800-880-TRIP) and should be used in conjunction with the above measures.

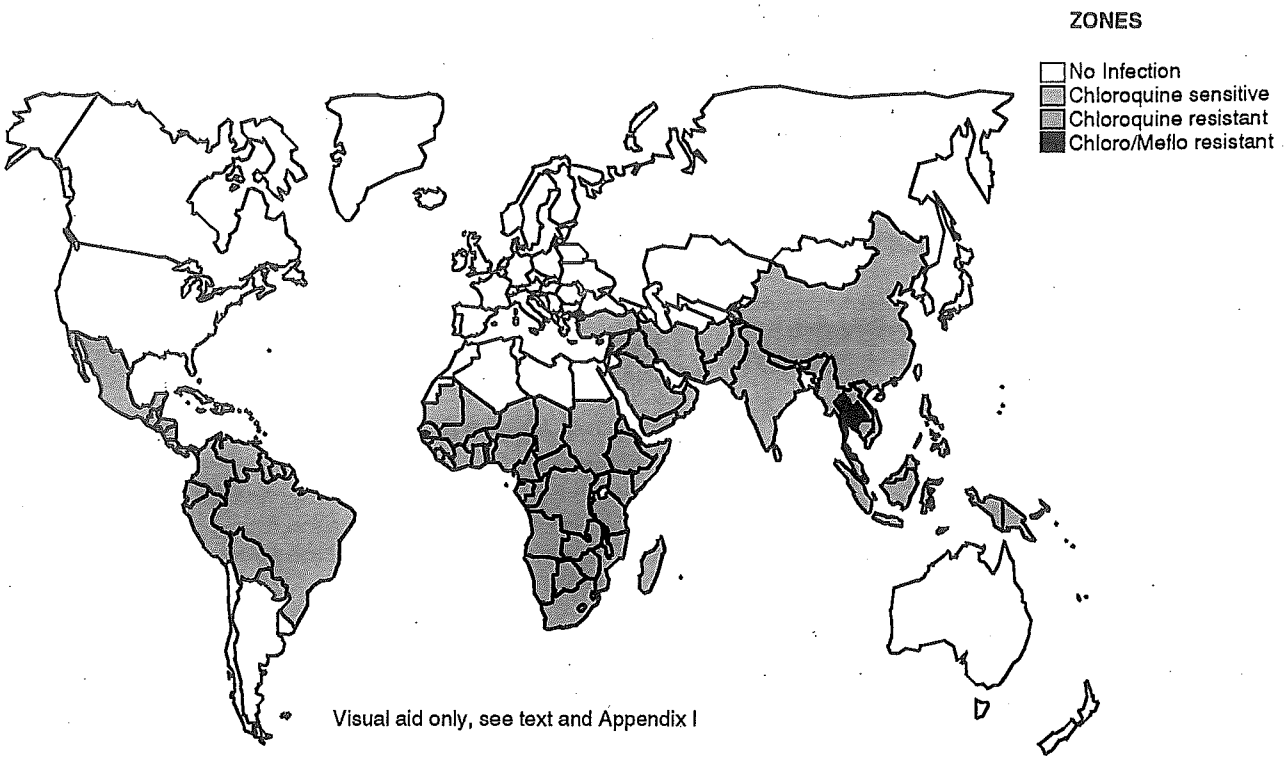
2. Chemosuppressive Drugs

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

1. **URBAN AND RURAL AREAS OF THE FOLLOWING:**

   (**Higher risk**) - sub-Saharan Africa and Oceania (including Papua New Guinea, Irian Jaya, Vanuatu, and the Solomon Islands).

Figure 1 **Map Showing Malaria-Endemic Zones**



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

2. **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.

Travellers should be informed that, although antimalarials 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 chemo-suppression has been used.

Most travellers who acquire *P. falciparum* infection will develop symptoms within 2 to 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 2 TO 3 MONTHS OF RETURNING FROM A *FALCIPARUM*-ENDEMIC AREA IS A MEDICAL EMERGENCY AND SHOULD BE INVESTIGATED WITH URGENT MALARIA THICK AND THIN SMEARS.

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

- geographic distribution of drug-resistant malaria, and
- individual traveller risk assessment.

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 the Caribbean, Central America (west of the Panama canal), and parts of the Middle East. *P. falciparum* malaria resistant to chloroquine AND mefloquine is still rare except on the Thai borders with Laos, Cambodia, and Myanmar. Resistance to Fansidar® (sulfadoxine-pyrimethamine) is now common in the Amazon basin, Southeast Asia and sporadically in Africa.

Within these zones, CATMAT considers there to be negligible risk of malaria in urban centres of Southeast Asia and Central and South America. Malaria is not transmitted above certain altitudes: it is virtually never transmitted at altitudes exceeding 2500 metres.

Individual traveller 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 the "**geography**" of risk. 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, previous splenectomy, 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.

The following factors must also be assessed:

1. Will the traveller be in a drug-resistant *P. falciparum* zone?
2. Would the traveller have prompt access to medical care (including blood smears prepared with sterile equipment and then properly interpreted) if symptoms of malaria were to occur?
3. Are there any contraindications to the use of particular antimalarial drugs?

TABLE 1

Malaria Chemosuppressive Regimens for At-Risk Individuals[a] According to Geographic Areas

Zone	Drug(s) of Choice[b]	Alternatives
Zone A: No Chloroquine Resistance	Chloroquine	Proguanil
Zone B: Chloroquine Resistant	Mefloquine	— Doxycycline — Chloroquine plus Proguanil plus Fansidar® standby[c]
Zone C: Chloroquine and Mefloquine Resistant	Doxycycline	

Adult doses

Chloroquine phosphate:	300 mg (base) weekly
Proguanil:	100 mg daily in Zone A, 200 mg daily in Zone B
Doxycycline:	100 mg daily
Mefloquine:	One 250 mg tablet weekly
Fansidar® (Sulfadoxine-pyrimethamine):	Three 500 mg tablets at one time (for treatment only)

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 chemosuppression is recommended **ONLY** for travellers who will be exposed outdoors during evenings or night time in rural areas.

b All drugs are to be taken 1 to 2 weeks before entering malarial areas, continuing during the stay in malarial areas, and for 4 weeks after leaving malarial areas. The only exception to this is that doxycycline may be started 2 days 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. Single-dose presumptive therapy (3 tabs Fansidar®) **ONLY** when prompt medical attention is **NOT** available.

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®	1 50 mg base	Prevention: 300 mg base once weekly **Treatment:** 1.5 g base over 3 days[3]	**Prevention:** < 1 yr: 37.5 mg base 1-3 yr: 75 mg base 4-6 yr: 100 mg base 7-10 yr: 150 mg base 11-16 yr: 225 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 & mucous membrane discoloration, nerve deafness, photophobia, myopathy, retinopathy with daily use, blood dyscrasias, psychosis and seizures
2. **clindamycin hydrochloride**	Dalacin®	150 mg base	**Treatment oral:** 150-450 mg base every 6 hr for 5 days **Treatment IV:** See Table 4	**Treatment oral:** 3-7 mg/kg three times daily **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: 2mg/kg once daily (max 100 mg daily) **Treatment:** < 8 yr: contraindicated ≥ 8 yr: 2 mg/kg twice daily (max 200 mg daily) for 7 days	**Frequent:** GI upset, vaginal candidiasis, photo-sensitivity **Occasional:** azotemia in renal diseases **Rare:** allergic reactions, blood dyscrasias
4. **halofantrine**	Halfan®	250 mg	**Treatment:** 2 tablets, three times daily for one day. Repeat one week later	**Treatment:** 8 mg/kg three times for one day; repeat one week later	**Occasional:** cough, pruritis, rash **Rare:** prolonged QT, ventricular arrhythimia
5. **mefloquine**	Lariam®	250 mg base	**Prevention:** 250 mg base once weekly	**Prevention:** < 15 kg: unknown 15-19 kg: 1/4 tablet 20-30 kg: 1/2 tablet 31-45 kg: 3/4 tablet	**Common:** dizziness, nausea, diarrhea, headache, insomnia, strange dreams

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 & 2, then 2 tablets on day 3 (total of 10 tablets).

TABLE 2 *(Continued)*

Antimalarial Drugs, Doses[1], and Adverse Effects

Generic Name	Trade Name	Packaging	Adult Dose	Pediatric Dose	Adverse Effects
6. proguanil	Paludrine®	100 mg	**Prevention:** 100 mg once daily; 200 mg daily in chloroquine-resistant areas	**Prevention:** ≤ 2 yr: 25 mg 3-6 yr: 50-75 mg 7-10 yr: 100 mg once daily; double dose in chloroquine-resistant areas	**Occasional:** anorexia, nausea, diarrhea, mouth ulcers **Rare:** hematuria
7. primaquine	—	15 mg base	**Treatment:** 15 mg base/day for 14 days[4]	**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	**Treatment:** 3 tablets (75 mg pyrimethamine and 1500 mg sulfadoxine)	**Treatment:** 2-11 mos: 1/4 tablet 1-3 yr: 1/2 tablet 4-8 yr: 1 tablet 9-14 yr: 2 tablets > 14 yr: 3 tablets as a single dose	**Occasional:** headache, nausea, vomiting, folate deficiency **Rare:** Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis
9. quinidine gluconate	—	10 mL vial	See Table 4	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	See Table 4	See Table 4	Similar to above
11. quinine dihydrochloride	—		See Table 4	See Table 4	**Frequent:** cinchonism (tinnitis, nausea, headache, blurred vision) hypoglycemia with IV **Occasional:** Cardiac conduction disturbances, hypersensitivity **Rare:** hemolysis
12. quinine sulphate	Novoquinine®	250 mg base	**Treatment[5] oral:** 2 tablets three times daily for 3-7 days **Treatment IV:** See Table 4	**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

4 Doses are increased to 22.5 mg - 30 mg base/day for primaquine-resistant *P. vivax*.

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.

Chemosuppressive Regimens
(See Tables 1 and 2)

Zone A
Chloroquine-Sensitive Regions Only

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** (**AI** - evidence-based medicine recommendations — see Appendix II). It is suitable for people of all ages and for pregnant women. Since insufficient chloroquine is excreted in breast milk to protect nursing infants, they should be given antimalarial drugs.

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 at bedtime, or as a split dose twice weekly. Dark-skinned persons may experience generalized itchiness, which is not indicative of drug allergy. Difficulty focusing the eyes may occur initially but should not be a reason to discontinue chloroquine because the problem usually resolves in a few weeks. This problem should not be confused with the more serious risk of retinal toxicity that may occur with long-term high dose chloroquine (> 100 g) used in the treatment of other diseases. This type of retinal toxicity is extremely unlikely with the weekly chemosuppressive doses of chloroquine used to prevent malaria. Chloroquine may worsen psoriasis and rarely is associated with seizures and psychosis. Chloroquine should not be used in individuals with a history of epilepsy. In chloroquine-sensitive areas, individuals with epilepsy should use proguanil (see below).

Chloroquine is taken once **WEEKLY**, beginning 1 to 2 weeks prior to entering a malaria zone, continuing during the period of exposure, and for 4 weeks after leaving the malarial area. Chloroquine is safe for pregnant women and young children, but overdoses are frequently fatal. Instructions for childhood doses should be carefully followed, and the medication should be kept out of the reach of children.

Alternatives: In chloroquine-sensitive malaria areas, when chloroquine cannot be taken, **PROGUANIL** (Paludrine®) in a single daily dose of 100 mg may be taken, beginning 1 week prior to exposure, once **DAILY** during the period of exposure, and once **DAILY** for 4 weeks after leaving the malarial area.

Proguanil is not known to cause harm to the developing fetus and is safe for infants and young children. Insufficient proguanil is excreted in the breast milk to protect a nursing infant. Proguanil is very well tolerated. Occasionally, oral aphthous ulceration may occur. Rarely, this may be severe enough to warrant discontinuing the medication. Proguanil resistance may occur independently of chloroquine resistance. Doses of chloroquine and proguanil should be reduced in renal failure.

Zone B
Chloroquine-Resistant Regions

Drug of Choice: MEFLOQUINE is the drug of choice for most travellers to chloroquine-resistant regions (**AI** - evidence-based medicine recommendations — see Appendix II). 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.

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-limited. The most frequent minor side effects from mefloquine are nausea, strange dreams, dizziness, mood changes, insomnia, headache, and diarrhea. Only about 1% of mefloquine users have to discontinue prophylaxis because of adverse effects. Severe neuropsychiatric reactions (psychosis, convulsions) are infrequent with prophylactic doses and occur in approximately 1/10,000 to 1/13,000 individuals. In treatment doses, however, neuropsychiatric reactions are reported to be 10 to 60 times more frequent and are estimated to occur in 1/215 to 1/1,700 users. Mefloquine is not suitable for those with liver impairment. Excessive consumption of alcohol while on mefloquine should be avoided due to a possible enhanced risk of neuropsychiatric reactions (**CIII** - evidence-based medicine recommendations — see Appendix II).

Resistance to mefloquine was first described in Thailand in 1982 and, in the last decade, in vitro or in vivo resistance has been reported sporadically from other 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. **Doxycycline** should be used for malaria chemosuppression along the border areas with Cambodia and Myanmar (see below). Mefloquine may still be used for chemosuppression for other areas of Southeast Asia.

Contraindications to the use of mefloquine:
- Seizure disorder or history of serious psychiatric illness

Precautions for the use of mefloquine include the following:
- Pregnancy (especially 1st trimester) and children < 15 kg (see below)
- Occupations or activities in which vertigo may be life-threatening, such as airline pilots
- Concurrent use of chloroquine or quinine-like drugs including halofantrine
- Underlying cardiac conduction disturbances

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 < 15 kg, it should be considered for children at high risk of chloroquine-resistant *P. falciparum* malaria. There are no pharmacokinetic data upon which to

recommend a correct dose for children weighing < 15 kg; however, the World Health Organization has suggested a chemosuppressive dose of 5 mg/kg/week in children weighing > 5 kg.

Mefloquine is taken once **WEEKLY**, beginning 1 to 2 weeks prior to entering a malaria zone, continuing during the period of exposure, and then once **WEEKLY** for 4 weeks after leaving the malarial area. For travellers who have < 1 week before departure, consideration may be given to the use of a loading dose of mefloquine. Limited data suggest that mefloquine taken once daily for 3 days before travel followed by once weekly (as above) is a well tolerated and effective way to rapidly achieve therapeutic blood levels. There is no evidence that toxic metabolites of mefloquine accumulate and long-term use of mefloquine (> 1 year) by Peace Corp Volunteers in Africa has not been associated with additional adverse effects. It is recommended, therefore, that the use of mefloquine **NOT** be arbitrarily restricted to 6 months in individuals who are at risk of acquiring malaria in mefloquine-sensitive areas (**BII** - evidence-based medicine recommendations — see Appendix II).

Alternatives: For individuals unable to take mefloquine, it is recommended that (1) **DOXYCYCLINE** be taken, or less optimally (**2**) **CHLOROQUINE PLUS PROGUANIL**, with the provision of **FANSIDAR®** (pyrimethamine-sulfadoxine) for presumptive self-treatment when appropriate (see below). In deciding between (1) doxycycline versus (2) chloroquine plus proguanil and back-up Fansidar®, the physician must weigh the drug efficacy, risks and character of adverse drug reactions versus 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, geographic destination and the activities during travel. Chloroquine plus proguanil is less efficacious than doxycycline. It is more efficacious in sub-Saharan Africa than chloroquine alone but its efficacy elsewhere is largely unknown. **Fansidar® resistance is widespread in Southeast Asia and the Amazon basin and this regimen is not recommended in these areas.** Because of the long half-life of sulfadoxine, Fansidar® is contraindicated in the last month of pregnancy, due to the potential risk of kernicterus in the newborn. Since sulphonamides are transmitted in breast milk, breast-feeding mothers should not take Fansidar® for the first 2 months after delivery.

CHLOROQUINE is taken once **WEEKLY** plus **PROGUANIL** (2 tablets **DAILY**); in addition, the traveller should carry a self-treatment course of **SULFADOXINE-PYRIMETHAMINE** (Fansidar®) for use if symptoms of malaria develop and immediate medical assessment is not available. Fansidar® contains a sulphonamide and is, therefore, not suitable for those who are allergic to sulpha drugs. Self-treatment with Fansidar® must be considered only a temporary measure, and follow-up medical assessment should still be sought as soon as possible. Weekly chloroquine should be continued even if Fansidar® has been self-administered.

Note: In some countries, a combination of mefloquine plus Fansidar® is marketed under the name Fansimef®, which should not be confused with mefloquine. Fansimef® is not recommended for the prevention of malaria.

Zone C
Chloroquine AND Mefloquine-Resistant Regions

Agent of Choice: In these regions **DOXYCYCLINE** (Vibramycin®) alone is the chemosuppressive of choice. It is taken once **DAILY** (100 mg), beginning 2 days prior to entering a malarious area, every day during the period of exposure and **DAILY** for 4 weeks after exposure.

Doxycycline is contraindicated during pregnancy, in breast-feeding women and in children < 8 years. The long-term safety (> 3 months) of doxycycline has not been established.

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 is therefore recommended. Doxycycline may also increase the risk of vaginal candidiasis; therefore, it may be prudent for women to carry antifungal vaginal suppositories or cream.

Self-Treatment of Presumptive Malaria

Although **MOST INDIVIDUALS WILL NOT REQUIRE A SELF-TREATMENT REGIMEN**, under some circumstances individuals at risk of malaria may find themselves in a situation requiring self-treatment for presumptive malaria. However, **self-treatment should never be undertaken lightly and consultation with a Tropical Medicine expert is recommended before individuals are placed on self-treatment protocols.** Due to the non-specific nature of malaria symptoms, the potentially serious risk of mistreating another disease, and the potential toxicity of malaria therapy, travellers should be advised of the clinical presentation of malaria, which can be very variable and mimic many other diseases. The most frequent symptoms are fever, headache, generalized aches and pains; cough, abdominal pain and diarrhea occur less commonly. **FEVER**, which may or may not be cyclical, **IS ALMOST ALWAYS PRESENT**. Malaria can be easily misdiagnosed as "influenza" or other febrile illnesses so that an early and accurate diagnosis is essential. If professional medical care is not available, travellers with **FEVER** should be told to self-treat for malaria. However, they should be made aware that self-treatment of a possible malarial infection is only a temporary measure following which medical attention should be sought as soon as possible. All travellers should continue their recommended chemosuppression after self-treatment.

(a) For individuals in chloroquine-sensitive regions (Zone A) on no chemosuppressive agents, self-treatment with chloroquine should be taken (see Table 2).

(b) In drug-resistant *P. falciparum* areas (Zones B and C), treatment recommendations for uncomplicated *P. falciparum* include the following (see Table 2):

Individuals on chloroquine and proguanil

For sub-Saharan Africa and Asia only (excluding Southeast Asia): Fansidar® 3 x 500 mg tablets taken once only (adult dose)

OR

- Oral quinine **PLUS** doxycycline or tetracycline

OR

- Quinine **PLUS** clindamycin (only for those unable to take doxycycline, tetracycline or Fansidar®)

Individuals on mefloquine or doxycycline

- Oral quinine **PLUS** doxycycline or tetracycline

OR

- Quinine **PLUS** clindamycin (only for those unable to take doxycycline or tetracycline)

Individuals on no chemosuppressive agent

- Oral quinine **PLUS** doxycycline or tetracycline

OR

- Quinine **PLUS** Fansidar® (with the exception of Southeast Asia and the Amazon basin of Brazil where Fansidar® is not recommended for treatment)

OR

- Quinine **PLUS** clindamycin (only for those unable to take doxycycline, tetracycline or Fansidar®)

Halofantrine for self-treatment

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. Absorption is increased when halofantrine is taken with food. The main use proposed for halofantrine is in the treatment of mild or moderately severe falciparum malaria, known or suspected to be resistant to chloroquine and possibly to other established anti-malarial drugs, such as pyrimethamine/sulfadoxine. Halofantrine has also been effective against *P. vivax* and small numbers of cases of *P. malariae* and *P. ovale*. Halofantrine has also been suggested as an alternative drug for "presumptive" or self treatment of malaria in travellers.

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 has not confirmed this. In Thailand, cure rates with halofantrine (24 mg/kg) varied from 65% to 70% as primary treatment to 40% in retreatment of recrudescent infections. The high recrudescent rates after standard halofantrine therapy have led to a recommendation to re-treat patients, particularly non-immune individuals, on day 7.

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

Increased doses of halofantrine (4.5 g over 6 days or 72 mg/kg over 3 days) are more effective than "standard doses" (24 mg/kg) especially in the treatment of recrudescent infections but are more cardiotoxic (see below).

Halofantrine is generally well tolerated with low rates of gastrointestinal side effects. It is better tolerated by patients than quinine, and is as well or better tolerated than mefloquine. Pruritus can occur in African patients as with chloroquine, but appears to be milder.

Recently, there has been increasing concern about halofantrine cardiotoxicity. High-dose halofantrine (72 mg/kg) induced consistent dose-related prolongation of the QT interval, 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 World Health Organization has reported multiple cardiac deaths associated with the use of halofantrine.

Recommendation

UNTIL THERE IS A CLEARER UNDERSTANDING OF THE FREQUENCY AND DETERMINANTS OF CLINICAL CARDIOTOXICITY WITH HALOFANTRINE USE, 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 (**DII** - 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 (**DII** - evidence-based medicine recommendations — see Appendix II).

iii. There may be limited use for halofantrine (with attention to contraindications and precautions) in physician-directed situations for patients with normal QT intervals, where other recommended treatment options are

inappropriate or contraindicated (**DII** - evidence-based medicine recommendations — see Appendix II).

An ECG should be performed to assess whether there are conduction abnormalities or a prolonged QT interval in individuals who are likely to receive halofantrine. Halofantrine is contraindicated in patients with congenital or acquired QT interval prolongation and probably should be avoided in patients with severe electrolyte abnormalities, concurrent use of drugs with effects on cardiac conduction, recent prophylaxis or treatment with mefloquine (within 4 weeks) or quinine, 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 (**DII** - 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 (**CIII** - 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.

Chemosuppression for Children

Children are at special risk of malaria and may become ill rapidly. Travellers should be clearly advised of the risks involved in taking young children to areas with drug-resistant falciparum malaria. Travel with young children to malarious areas should be avoided unless absolutely necessary. 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 < 15 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 would be 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. Chloroquine tablets may be crushed and mixed with cereal or jam to mask the taste. For **ALL** children travelling to malarious areas particular attention should be paid to personal protection measures.

Chemosuppressive Regimens for Women Who Are or May Become Pregnant or Children While in Malaria-Endemic Areas

Malaria causes greater morbidity and mortality during pregnancy for both the mother and the fetus. Doxycycline is contraindicated during pregnancy. Fansidar® is contra-indicated in the last month of pregnancy, and in the first 2 months of breast feeding. The safety of mefloquine throughout pregnancy has not been clearly established. Malaria chemoprophylaxis 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. Pregnant females and young children should avoid travel to areas with significant transmission of chloroquine-resistant malaria (**BII** - evidence-based medicine recommendations — see Appendix II).

ii. Personal protection measures should be strongly encouraged for all individuals who do travel (**AI** - 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 (**AI** - evidence-based medicine recommendations — see Appendix II).

iv. There are insufficient data to support the routine use of mefloquine in pregnancy. Limited data suggest that it is effective and safe in pregnancy beyond 20 weeks gestation. Therefore, mefloquine can be considered for prophylaxis of pregnant women (> 20 weeks gestation) **where exposure to chloroquine-resistant falciparum malaria is high and unavoidable** (**BII** - evidence-based medicine recommendations — see Appendix II). Pregnant females (< 20 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 plus proguanil is safe in pregnancy but is significantly less efficacious against drug-resistant malaria (**BII** - evidence-based medicine recommendations — see Appendix II).

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, which is available on prescription in Canada. 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 returning travellers. Primaquine use is contraindicated in pregnancy.

Most people tolerate primaquine very well, but individuals with glucose 6-phosphate dehydrogenase deficiency (G6PD) may experience serious hemolysis when using it. Patients of Mediterranean, African, and Asian ethnic origin or those receiving > 15 mg dose per day of primaquine have a greater risk of hemolysis. These individuals, in particular, should have G6PD levels measured. In cases where G6PD levels are very low, an infectious or tropical disease expert should be consulted. 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.

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, resistance has been confirmed in Thailand and Somalia. When *P. vivax* malaria relapses following primaquine therapy, the dose of primaquine should be increased to 1.5 to 2 times standard therapy, i.e., 22.5 mg to 30 mg of primaquine base daily for 14 days for adults. Since the tablet is not scored, the lower dose must be given as 15 mg alternating with 30 mg daily for 14 days.

Diagnosis of Malaria

The changing character of malaria worldwide has been reflected in the type and severity of malaria cases seen in Canada; an increasing portion of Canadian cases are due to *P. falciparum* and are severe. This has been documented at two large Canadian tropical disease clinics; in addition, five Canadians died of *falciparum* malaria acquired in Africa during a 5-month period in 1989.

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.

To assist in the diagnosis and management of malaria a travel history must be sought and a clearly-defined geographic exposure obtained. *Falciparum* malaria usually presents clinically within 2 months of last exposure; however, it may be delayed in patients who take mefloquine prophylaxis. In addition other types of malaria, especially that caused by *P. vivax*, may occur months to several years after travel in endemic areas.

The examination of thick and thin blood films 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 must be considered a medical emergency and be performed as soon as possible. If facilities are not available to make the diagnosis at the time of presentation of the patient, then a referral should be made immediately to a facility that has expertise to do so.

Occasionally, a single blood film examination may be falsely negative for malaria parasites. Repeat blood films may need to be examined frequently during the first several days of investigation to exclude the possibility of malaria.

As the treatment of malaria is dependent on the species of parasite, every effort should be made on an urgent basis to speciate the infection by thin blood film. 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 with a history of fever that responded to antimalarials but for whom a blood smear was never examined".

Management of Non-*Falciparum* Malaria

For over 40 years chloroquine has been the treatment of choice for malaria other than *falciparum*. Outside of New Guinea, chloroquine remains the treatment of choice for malaria other than falciparum (as per Table 2). The use of primaquine for *P. vivax* and *P. ovale* malaria has been discussed previously.

Recent reports have confirmed the presence and high prevalence (22%) of chloroquine-resistant *P. vivax* in Irian Jaya (New Guinea). Sporadic cases of chloroquine-resistant vivax malaria have been reported from elsewhere in Indonesia, Papua New Guinea, the Solomon Islands, Brazil, and Myanmar. 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 higher doses to cure *P. vivax* infection from New Guinea. Mefloquine and halofantrine may be useful agents but adequate clinical trials evaluating their effectiveness have not been performed. Expert advice from an infectious or tropical disease specialist should be sought for the management of these cases.

Management of *Falciparum* Malaria

The following guidelines have been derived 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)(update 1995; in press)]. The interested reader is referred to this document for a more detailed discussion of this subject.

A detailed geographic history is essential to the management of malaria infections. ***P. falciparum* malaria acquired in areas with drug resistance must be considered to be chloroquine-resistant and, therefore, should be treated as such.**

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, consideration should be given to admit all patients with *P. falciparum* malaria, whether severe or not, to allow for monitoring of the patient during initiation of therapy. In the treatment of complicated malaria, results following use of parenteral preparations of quinine and quinidine are equivalent. Although equally active,

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 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). (Update 1995). In press.

TABLE 4

Chemotherapy of Severe *Falciparum* Malaria[a]

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. 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** or until oral quinine can be instituted.

   OR

3. 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 hydrochloride [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.

   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 hydrochloride [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

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

   OR

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

   OR

3. Clindamycin: 10 mg base/kg (loading dose) intravenously, followed by 5 mg base/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 may be obtained on a patient-by-patient basis with authorization from the Bureau of Human Prescription Drugs, Health Protection Branch, Health Canada, Tower B, Holland Cross, 1600 Scott Street, Ottawa, Ontario, K1A 1B8 (613) 941-2108.

quinidine is more cardiotoxic than quinine and patients treated with intravenous quinidine should be monitored electrocardiographically. Quinidine is licensed and widely distributed in Canada, but intravenous quinine is an emergency release drug and is not readily available. Therefore, to emphasize its availability parenteral quinidine is placed first in the recommendations. However, either drug is acceptable for treatment. Parenteral quinidine is marketed by several drug companies as listed in the *Canadian Compendium of Pharmaceuticals and Specialties*.

Uncomplicated *P. falciparum* infections unequivocally acquired in a chloroquine-sensitive zone (Zone A) may be treated with chloroquine alone, as per Table 2. Uncomplicated *P. falciparum* infections that were possibly or definitely acquired in Zones B or C should be treated with quinine and a second drug, as described in the next paragraph. If the patient can tolerate oral quinine, then it and the second drug should be administered as per Table 2.

All patients with severe *P. falciparum* infections, and those who are unable to tolerate oral quinine, regardless of the severity of the infection, should receive intravenous quinidine or quinine. At this time, parenteral quinine is an emergency drug that can be obtained through the Emergency Drug Release Program, Health Canada, telephone 613-993-3105. Parenteral quinidine, which is equally effective in the treatment of malaria, is available in most hospital pharmacies. The recommended dosing schedule is given in Table 4. For drug-resistant *P. falciparum* malaria, another agent, in addition to quinine or quinidine, is recommended. The second drug - either doxycycline, Fansidar®, or clindamycin - may be administered simultaneously or sequentially, either orally (as per Table 2) or, if not possible, then 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 during the last 2 weeks, there is a risk of drug-induced cardiac arrhythmia; if possible, such patients should be monitored electrocardiographically.

In cases of complicated *P. falciparum* infection (Table 3), or hyperparasitemia (> 5% 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 hematologist and an expert in tropical diseases is strongly recommended.

TABLE 5

Base 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	8 mg
	7.5 mg	12 mg
	10 mg	16 mg
	15 mg	24 mg
Quinidine sulfate	7.5 mg	9 mg
	10 mg	12 mg
	15 mg	18 mg
Quinine dihydrochloride	5 mg	6 mg
	7.5 mg	9 mg
	15 mg	18 mg
	16.7 mg	20 mg
Quinine sulfate	250 mg	300 mg

[1] not available in Canada

Artemisinin (Qinghaosu) for the treatment of drug-resistant malaria

Artemisinin is a naturally occurring sesquiterpene lactone peroxide, structurally unrelated to any known anti-malarial. 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 preparations have been studied and utilized only for treatment. They are recommended for treatment use only and not for chemosuppression.

Artemisinin compounds are at least as efficacious as quinine and chloroquine 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 anti-malarials. However, it has not been shown that the more rapid anti-parasitic action of qinghaosu compounds will decrease mortality associated with severe malaria.

Artemisinin-related compounds act rapidly against drug-resistant *P. falciparum* strains but have high recrudescent rates (approximately 10% to 50%) when used as monotherapy for ≤ 5 days. Recent studies have examined longer durations of therapy 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 (600 mg over 5 days) followed by mefloquine (1250 mg) was more effective than mefloquine or artesunate alone. Combination therapy resulted in 100% cure rates of primary and recrudescent *P. falciparum* infections.

Artemisinin derivatives have been used in over 1 million patients and are well tolerated. Animal studies suggest toxicity in the liver, kidney, bone marrow, heart and central nervous system. To date, there have been two human cases of complete heart block associated with the use of artemisinin but most volunteer and clinical studies have

found no evidence of cardiotoxicity. Neurologic lesions involving the brainstem have been seen in rats, dogs, and more recently in primates [unpublished] given repetitive doses of artemisinin derivatives. To date no clinical neurologic events have been observed in humans but no studies have addressed cumulative toxicity in humans. The safety of qinghaosu derivatives in pregnancy has not been established.

Artemisinin and its derivatives are now available and being increasingly utilized in Southeast Asia and Africa. Combinations of artesunate and mefloquine appear to be the most active drug regimens against 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. Only artemether and arteether are made under Good Manufacturing Procedures (GMP) and are being submitted for approval by drug regulatory authorities. Although there is good evidence (**AI** - evidence-based medicine recommendations — see Appendix II) that short-term therapy with artemisinin compounds is safe, questions about cardiac and neurologic toxicity and long-term 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 (**AI** - 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 (**AI** - evidence-based medicine recommendations — see Appendix II).

iii. The use of artemisinin compounds should be regulated and these agents should not be used for chemo-suppression. They should be used only for laboratory-confirmed falciparum infections and in combination with mefloquine or tetracycline (**CIII** - evidence-based medicine recommendations — see Appendix II).

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

APPENDIX I†

Malaria Risk by Geographic Areas in Countries with Endemic Malaria		
Country	**Areas of risk within country**	**Recommended Regimen(s)**
Afghanistan	All	Mefloquine
Algeria	Sahara region	None
Angola	All	Mefloquine
Argentina	Rural areas near Bolivian border	Chloroquine
Azerbaijan	Southern border areas	Chloroquine
Bangladesh	All, except no risk in city of Dhaka	Mefloquine
Belize	Rural areas, except no risk in Belize District	Chloroquine
Benin	All	Mefloquine
Bhutan	Rural areas in districts bordering India	Mefloquine
Bolivia	Rural areas 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)	Mefloquine
Brazil	Rural areas of Acre, Amazonas, Goias, Maranhao, Mato Grosso and Para States; and territories of Amapa, Rondonia, Roraima and urban areas of Amazon, River Basin	Mefloquine
Burkina Fasa	All	Mefloquine
Burma: see Myanmar		
Burundi	All	Mefloquine
Cambodia	All, no risk in Phnom Penh Doxycycline on Western borders	Mefloquine
Cameroon	All	Mefloquine
Central African Republic	All	Mefloquine
Ceylon: see Sri Lanka		
Chad	All	Mefloquine
China	Rural areas only in Anui, Fujian, Guangdong, Guangxi, Guizhou, Hebei, Henan, Hubei, Hunan, Jiangsu, Jiangxi, Liaoning, Shanxi, Shandong, Sichuan, Yunnan, Xignjiang and Zhejiang Provinces/autonomous regions	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	None in central highlands Limited risk in rural areas of Alajuela, Guanacaste, Limon and Puntarenas Provinces	Chloroquine
Cote d'Ivoire (formerly Ivory Coast)	All	Mefloquine
Dijbouti	All	Mefloquine

† Adapted from *CDC Health Information for International Travel 1994* [HHS Publ. No. (CDC) 94-8280] and WHO Malaria Recommendations, 1995. 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 Regimen(s)
Dominican Republic	All rural areas. Highest risk is areas bordering Haiti. No risk in tourist areas.	Chloroquine
Ecuador	All areas in provinces of Esmeraldas, Guayas, Manabi, El Oro. Rural areas in provinces of Los Rios, Morona, Santiago, Napo, Pastaza, Zamora, Chinchipe and Pinchincha. (No risk in Quito and vicinity, the central highland tourist areas or the Galapalgos Islands). Chloroquine resistance in Guaquil	Mefloquine
Egypt	Rural areas of Nile Delta, El Faiyum, the oases and part of Southern (upper) Egypt. (No risk in main tourist areas including cruises.)	Choroquine
El Salvador	Rural areas only	Chloroquine
Equatorial Guinea	All	Mefloquine
Eritrea	All, except above 2,000 metres	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 no risk in central highlands	Chloroquine
Guinea	All	Mefloquine
Guinea-Bissau	All	Mefloquine
Guyana	Rural areas in Rupununi and North West Regions	Mefloquine
Haiti	All	Chloroquine
Honduras	Rural areas only	Chloroquine
India	All areas, including Delhi and Bombay, except no risk in Himechel, Pradesh, Jammu, Kashmir and Sikkim	Mefloquine
Indonesia	In general, rural areas only, except high risk in all areas of Irian Jaya. No risk in Jakarta or resort areas of Java or Bali.	Mefloquine
Iran, Islamic Republic of	Rural areas only in the provinces of Sistan-Baluchestan and Hormozgan, the southern parts of Fars, Kohgiluych-Boyar, Lorestan and Chahar Mahal-Bakhtiani and the north of Khuzestan	Mefloquine
Iraq	All areas in northern region; Duhok, Erbil, Kirkuk, Ninawa and Sulaimanya province	Chloroquine
Ivory Coast: see Cote d'Ivoire		
Kenya	All except city of Nairobi and above 2,500 metres	Mefloquine
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	None
Madagascar	All, highest in coastal areas	Mefloquine

† Adapted from *CDC Health Information for International Travel 1994* [HHS Publ. No. (CDC) 94-8280] and WHO Malaria Recommendations, 1995. 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 Regimen(s)
Malawi	All	Mefloquine
Malaysia	In general, rural areas only, 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, Inchiri, Adrar and Tiris-Zemour	Mefloquine
Mauritius	Rural areas only, except no risk on Rodgrigues	Chloroquine
Mayotte	All	Mefloquine
Mexico	Rural areas only No risk in resort areas	Chloroquine
Morocco	Very limited risk in rural areas of coastal provinces	None
Mozambique	All	Mefloquine
Myanmar (formerly Burma)	Rural areas, doxycycline for Thai borders	Mefloquine
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
Panama	Rural areas, west of Canal Rural areas, east of Canal	Chloroquine Mefloquine
Papua New Guinea	All	Mefloquine
New Hebrides: see Vanuatu		
Nicaragua	In general, rural areas only; however, risk exists in outskirts of towns of Chinandega, Leon, Granada, Managua, Nandiame and Tipitapa	Chloroquine
Niger	All	Mefloquine
Nigeria	All	Mefloquine
Oman	All	Mefloquine
Pakistan	All, areas below 2,000 metres.	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 area of Southern Lima	Chloroquine Mefloquine for borders with Brazil
Philippines	Rural areas only, except no risk in Manila and province of Bohol, Catanduanes, Cebu and Leyte Rural areas of Luzon, Basilan, Mindoro, Palawan, Mindanao and Sulu-Archipelago	Chloroquine 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

† Adapted from *CDC Health Information for International Travel 1994* [HHS Publ. No. (CDC) 94-8280] and WHO Malaria Recommendations, 1995. 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 Regimen(s)**
Senegal	All	Mefloquine
Sierra Leone	All	Mefloquine
Solomon Islands	All	Mefloquine
Somalia	All areas	Mefloquine
South Africa	Rural areas (including game parks) in the north, east, and western low altitude areas of Transvaal and in Natal coast	Mefloquine
Sri Lanka (formerly Ceylon)	All areas except Colombo	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 except no risk in districts of Damascus, Deir-es-zor and Sweida	Chloroquine
Tajikistan	In southern border areas	Chloroquine
Tanzania, United Republic of	All	Mefloquine
Thailand	Rural border areas only, no risk in Bangkok or beach resort areas. Mefloquine resistance. Doxycycline recommended on borders with Myanmar and Cambodia for overnight exposure	Doxycycline
Togo	All	Mefloquine
Turkey	Cukorova/Amikova areas and southeast Anatolia	Chloroquine
Uganda	All	Mefloquine
United Arab Emirates	All, except no risk in cities of Dubai, Sharjahg Ajmain, Umm at Qaiwan, and Emirate of Abu Dhabi	Chloroquine
Vanuatu (formerly New Hebrides)	All, except no risk on Fortuna Island	Mefloquine
Venezuela	Rural areas of all border states; Apure, Bolivar, Barinas Merida, Tachira and Zulia states	Mefloquine
Viet Nam	Rural areas only, no risk in Red & Mekong Deltas	Mefloquine
Yemen	All, except no risk in Aden & airport areas	Mefloquine
Yemen, Democratic	All	Mefloquine
Zaire	All	Mefloquine
Zambia	All	Mefloquine
Zimbabwe	All, except no risk in cities of Harare and Bulawayo	Mefloquine

† Adapted from *CDC Health Information for International Travel 1994* [HHS Publ. No. (CDC) 94-8280] and WHO Malaria Recommendations, 1995. 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.