Canada Diseases Weekly Report

ISSN 0382-232X

Date of publication: February 1991 Vol. 17S2

Supplement

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

Health and Welfare Canada

Santé et Bien-être social Canada

Canada

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

prepared by the

COMMITTEE TO ADVISE ON TROPICAL MEDICINE AND TRAVEL (CATMAT)

PREFACE

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

The members of CATMAT include R. Saginur*, MD, Ottawa Civic Hospital (Chairman of CATMAT, and representing the Canadian Infectious Disease Society); D. W. MacPherson*, MD, St. Joseph's Hospital, Hamilton (Chairman of the Malaria Subcommittee and Vice-Chairman of CATMAT); S. Dumas, MD, DSC St-Sacrement, Quebec; M. Fast, MD, Communicable Disease Control of Manitoba, Winnipeg (representing the Advisory Committee on Epidemiology); D. Lawee, MD, and J. Keystone*, MD, Toronto General Hospital; J.D. MacLean*, MD, Montreal General Hospital; R. Pennie*, MD, Children's Hospital of Eastern Ontario, Ottawa; R. Pritchard, PhD, McGill University Institute of Parasitology, Montreal (representing the Canadian Society for International Health); J. Robert*, MD, DSC St-Luc, Montreal; S. Tamblyn, MD, Perth District Health Unit, Stratford, (representing the National Advisory Committee on Immunization); and R. Wilson, CUSO Health Support Services, Ottawa.

The liaison members to CATMAT include the following: H. Lobel, MD, Malaria Branch, Center for Infectious Diseases, and A. Hinman, MD, Center for Prevention Services, Centers for Disease Control, Atlanta; P. Constantinidis, MD, Public Service Health, Medical Services Branch, M. Davis, PhD, Bureau of Biologics, and E. Gadd, PhD*, Bureau of Human Prescription Drugs, HPB, HWC, Ottawa; O. Skjenna, MD, Air Canada, Montreal (representing the Air Transport Association of Canada); and M. Tepper, MD, Directorate of Preventive Medicine, Department of National Defence, Ottawa.

R. Wittes, MD, Chief, Division of Tropical Health and Quarantine, Bureau of Communicable Disease Epidemiology, LCDC, is secretary for CATMAT and its subcommittees.

*denotes member of the Malaria Subcommittee of CATMAT

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

Malaria is caused by the genus *Plasmodium*, of which 4 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. Malaria may be associated with clinical anemia and jaundice, but cannot be diagnosed with certainty without a blood film. Severe malaria due to *P. falciparum* may cause seizures, coma, renal failure, and respiratory failure, which may lead to death.

The widespread resistance of *P. falciparum* to chloroquine has complicated the prevention and treatment of malaria. The alternative agents to chloroquine generally have a higher incidence of severe adverse reactions, or are themselves also relatively ineffective at protecting against disease due to this parasite. Multiple drug-resistant strains of malaria are now common in several regions of the world. Zones of the world considered to have various levels of risk of exposure to chloroquine-resistant strains of *P. falciparum* have been established (Figure 1). These zones need frequent updating as the malaria situation changes.

The following recommendations are to serve as guidelines to health care providers to assist travellers in reducing their risk of acquiring symptomatic malaria, and to reduce the risk of severe illness or death from this disease.

Risk of Acquiring Malaria

Malaria transmission occurs in most of sub-saharan Africa and Haiti; in large areas of the Middle East, Southern Asia, Southeast Asia, Oceania, and Central and South America; and in certain parts of Mexico 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 areas of Southeast Asia and South America is considered to entail minimal risk, although urban travel in the other malaria-endemic zones may be associated with significant risk of infection.

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

General Advice For the International Traveller to a Malaria Endemic Zone

All travellers to malaria endemic zones are advised to use personal insect protective measures to reduce the risk of insect bites.

Medications to reduce the risk of acquiring malaria are recommended for visitors to the following areas: urban and rural areas of sub-Saharan Africa, Haiti, India, and Papua New Guinea; and rural, non-resort areas of Southeast Asia, Asia, Central and South America, and certain parts of Mexico and the Dominican Republic.

Travellers should be informed that there are no currently available antimalarials that guarantee complete protection against malaria. Symptoms due to malaria may occur as early as a week after first exposure in a malaria zone, and as late as several years after leaving a malaria zone or after malaria chemosuppressive medications have been stopped.

Malaria can be effectively treated early in its course, but delay in therapy may result in serious and even fatal outcome. Immediate medical attention (including blood film for malaria parasites) must be sought by individuals who have symptoms suggestive of malaria.

Personal Insect Protection Measures

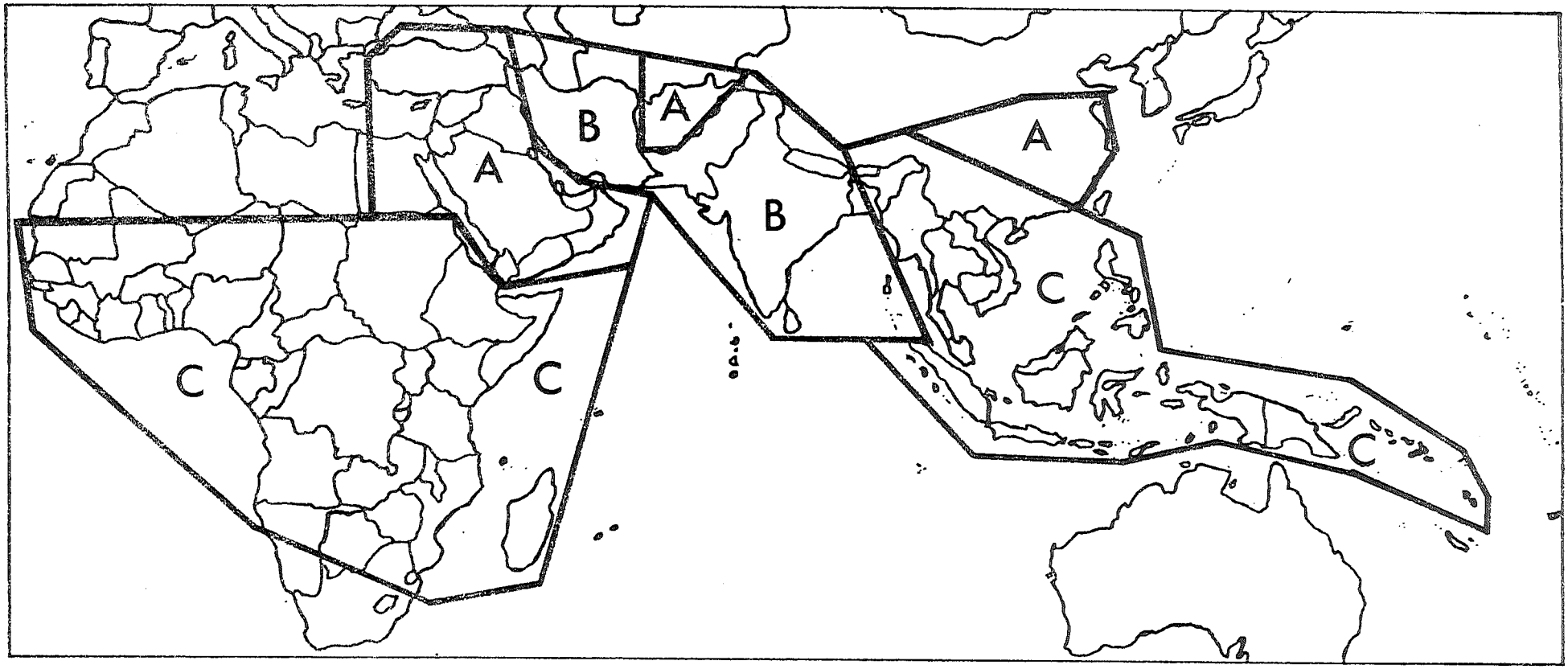
Any measure that reduces exposure to the night-time feeding female *Anopheles* mosquito will also reduce the risk of acquiring malaria. The risk of being bitten by insects between dusk to dawn can be reduced by remaining in well-screened areas, using air conditioning, sleeping under mosquito netting, and wearing clothing that reduces the amount of exposed skin.

In addition, the use of a personal insect repellant for use on exposed skin is also recommended. Insect repellents containing N,N diethylmetatoluamide (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 a few instances, application of insect repellents with high concentrations (>35%) of DEET have been associated with seizures in young children; therefore, DEET should be applied sparingly to exposed surfaces only.

Household insect sprays and mosquito netting treated with insect repellent may be used in conjunction with the above measures.

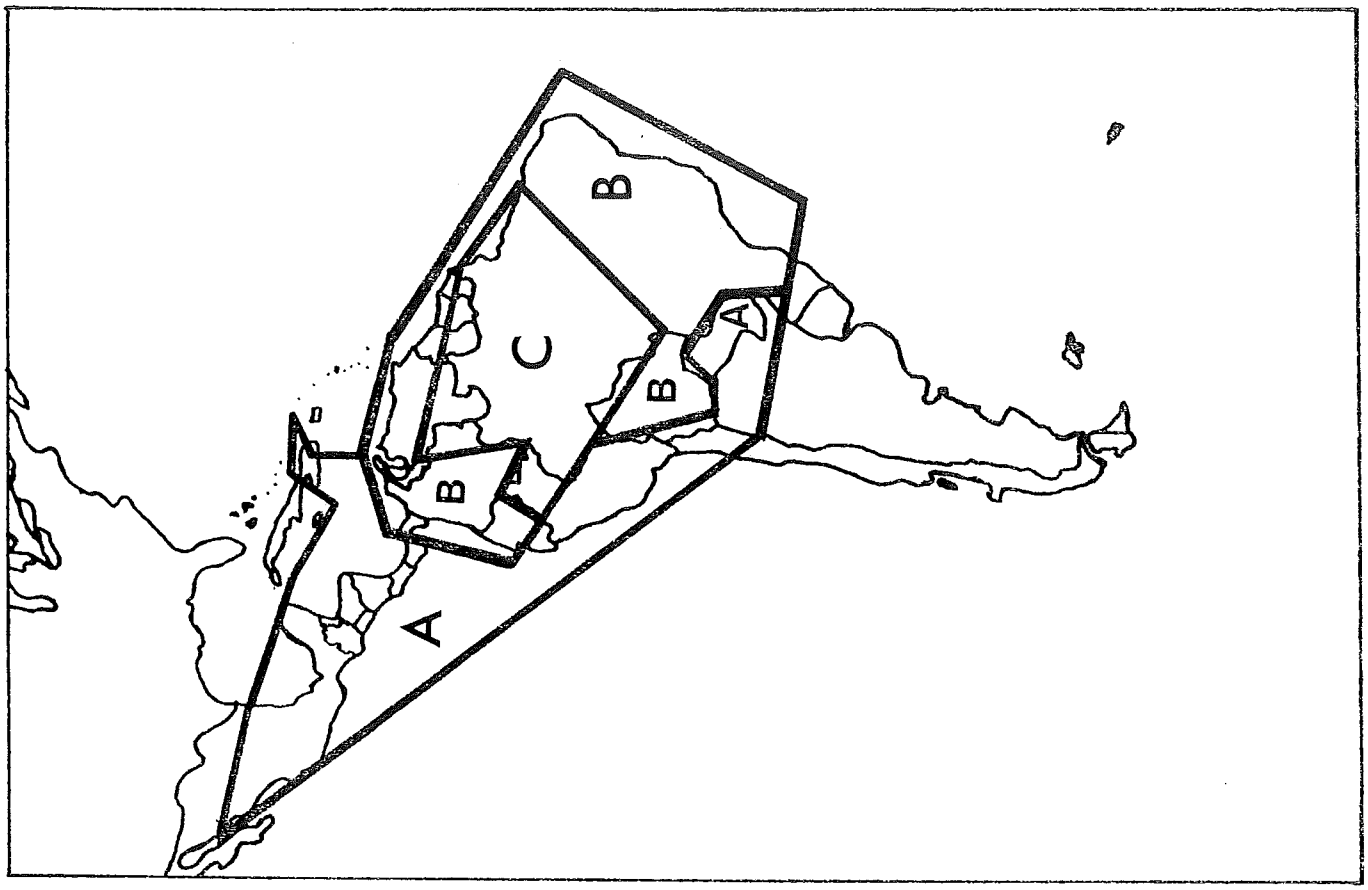
Figure 1

Map of Malaria-Endemic Areas



Definition of zones:

A: Malaria is present; no chloroquine (CQ) resistance.
B: Risk of travellers acquiring CQ-resistant malaria is low.
C: Risk of travellers acquiring CQ-resistant malaria is higher than in zone B.


B
C
B
A
B
A

Chemosuppressive Therapy

For the purposes of making recommendations about the chemosuppression of malaria, CATMAT has divided the world into three zones where malaria is present (Figure 1, Appendix I).

Zone A is made up of areas where malaria is present, but there is no chloroquine-resistant malaria.

Zone B is made up of areas where there is a risk to travellers of acquiring chloroquine-resistant malaria, but the risk is low.

Zone C is made up of areas where the risk to travellers of acquiring chloroquine-resistant malaria is significantly higher than in Zone B.

Within these zones, CATMAT considers there to be no risk of malaria in urban centres of Southeast Asia and South America. Malaria is not transmitted above certain altitudes. While such altitudes vary from place to place, malaria is virtually never transmitted at altitudes exceeding 2500 metres.

Several factors need to be assessed when selecting a chemosuppressive regime 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, accommodations) of the individual in the malaria zone should be considered in estimating the intensity of risk for malaria. The **personal health factors** of the individual (age, possible pregnancy, previous splenectomy, and chronic illness) also need to be known in order to determine the risk of particularly severe disease if malaria infection were to occur.

The following factors must also be assessed:

1. Will the traveller be in a drug-resistant *P. falciparum* zone (zones B-C)?
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?

In prescribing antimalarials, physicians must be aware of the equivalence between **base** and **salt**. The relevant and standard dose of antimalarial drugs is the base. The equivalence between base and salt of various drugs is provided in Table 1; where appropriate, both doses are provided in Tables 2, 3, and 4.

Chemosuppressive Regimes
(See Tables 2 and 3)

Zone A: Chloroquine-Sensitive Strains Only

For travel to areas where chloroquine resistance has **not** been described, it is recommended that **CHLOROQUINE** (Aralen®) be taken alone, once weekly. It is suitable for people of all ages and for pregnant women. Insufficient chloroquine is excreted in the breast milk to protect a nursing infant.

Except for its bitter taste, chloroquine is usually very well tolerated. Other mild side effects may occur (nausea, headache), which 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. 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.

Chloroquine is taken once weekly, beginning one week prior to entering a malaria zone, continuing every week during the period of exposure, and then once weekly 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

TABLE 1

Salt/Base Equivalents of Some Antimalarial Drugs

Drug	Base	Salt
Chloroquine phosphate	150 mg	250 mg
Chloroquine sulfate[1]	100 mg	136 mg
Mefloquine	250 mg	274 mg
Clindamycin hydrochloride	150 mg	225 mg
Quinine sulfate	250 mg	300 mg
Quinine dihydrochloride	5 mg 7.5 mg 15 mg	7 mg 10 mg 20 mg
Quinidine sulfate	7.5 mg 10 mg 15 mg	9 mg 12 mg 18 mg
Quinidine gluconate	7.5 mg 10 mg 15 mg	11 mg 14 mg 22 mg

[1] not available in Canada

TABLE 2

Malaria Chemosuppressive Regimes

Zone	Drug(s) of choice	Alternatives
Zone A: no chloroquine resistance	Chloroquine	Proguanil **or** Pyrimethamine
Zone B: risk to travellers of acquiring CQ-resistant malaria is low	Mefloquine **or** Chloroquine plus back-up Fansidar® for presumptive self-treatment	Chloroquine plus Proguanil
Zone C: risk to travellers of acquiring CQ-resistant malaria is higher than in Zone B	Mefloquine	Doxycycline **or** Chloroquine plus Dapsone plus Pyrimethamine (=Chloroquine + Maloprim®)

All drugs are to be taken starting one week before entering malarial areas, 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, not one week, before entering malarial areas.

Adult doses

Chloroquine phosphate:	Two 250-mg tablets weekly.
Proguanil:	100 mg daily in Zone A, 200 mg daily in Zone B.
Pyrimethamine:	25 mg weekly in Zone A, 12.5 mg weekly in Zone C.
Doxycycline:	100 mg daily.
Dapsone:	100 mg weekly.
Mefloquine:	One 250 mg tablet weekly.
Fansidar® (Sulfadoxine-pyrimethamine):	3 tablets at one time.

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

Zone B: Chloroquine-Resistant Strains Are Present (but Risk of Acquiring Resistant Malaria is Low)

For travel to areas where chloroquine-resistant strains of *P. falciparum* have been described, it is recommended that **either** (1) **MEFLOQUINE** (Lariam®) be taken alone, **or** (2) **CHLOROQUINE** be taken, with the provision of **FANSIDAR®** for presumptive self-treatment when appropriate (see below).

1. **MEFLOQUINE** is suitable for people of all ages, but is teratogenic at high doses in rodents and may be associated with human congenital malformations; therefore, it is contraindicated during pregnancy. Insufficient mefloquine is excreted in the breast milk to protect a nursing infant. There are no pharmocokinetic data upon which to recommend a correct dose for children weighing less than 15 kg.

Mefloquine is taken once weekly, beginning one week prior to entering a malaria zone, continuing every week during the period of exposure, and then once weekly for 4 weeks after leaving the malarial area. Although mefloquine is considered to be the drug of choice for the suppression of chloroquine-resistant *P. falciparum*, it is not marketed in Canada. However, it is available in Canada from certain physicians who are participating in an adverse drug reaction monitoring protocol (Appendix II).

Mild non-specific reactions (nausea, heartburn, and mild dizziness) have been described in up to 20% of users. Rarely, severe vertigo, seizures, and psychosis have been reported with weekly mefloquine prophylaxis, but these problems appear to be more frequently observed with higher doses as used for treatment.

Presumptive self-treatment for malaria is **not** recommended for travellers taking mefloquine.

Contraindications to the use of mefloquine include the following:

TABLE 3

Antimalarial Drugs, Doses[1], and Adverse Effects

Generic Name	Trade Name	Tablet Size	Adult Dose	Pediatric Dose	Adverse Effects
1. chloroquine[2] phosphate	Aralen®	250 mg (150 mg base)	500 mg (300 mg base) once weekly **Treatment:** 1.5 g base (2.5 g salt) over 3 days[3]	<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, retinopathy (>100 g base), reversible corneal opacity, partial alopecia **Rare:** nail & mucous membrane discoloration, nerve deafness, photophobia, myopathy, blood dyscrasias
2. proguanil	Paludrine®	100 mg	100 mg once daily; 200 mg daily in chloroquine-resistant areas	≤ 2 yr: 25 mg 3-6 yr: 50-75 mg 7-10 yr: 100mg once daily; double dose in chloroquine-resistant areas	**Occasional:** anorexia, nausea, diarrhea, mouth ulcers **Rare:** hematuria
3. pyrimethamine	Daraprim®	25 mg	25 mg once weekly	≤ 2 yr: 6.25 mg 3-10 yr: 12.5 mg >10yr: 25 mg once weekly	**Occasional:** folic acid deficiency **Rare:** rash, vomiting, shock, convulsions, blood dyscrasias
4. mefloquine	Lariam®	250 mg base (274 mg salt)	250 mg base once weekly	<15 kg: unknown 15-19 kg: 1/4 tab 20-30 kg: 1/2 tab 31-45 kg: 3/4 tab	**Common:** dizziness, nausea, diarrhea, headache **Occasional:** skin rash, sinus bradycardia, vertigo **Rare:** seizures, psychosis
5. pyrimethamine-sulfadoxine	Fansidar®	25 mg 500 mg	**Treatment:** 3 tabs, (75 mg pyrimethamine & 1500 mg sulfadoxine) in a single dose	**Treatment:** 2-11 mos: 1/4 tab 1-3 yr: 1/2 tab 4-8 yr: 1 tab 9-14 yr: 2 tabs >14 yr: 3 tabs as a single dose	**Occasional:** headache, nausea, vomiting, folate deficiency **Rare:** Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis

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 3 (continued)

Antimalarial Drugs, Doses[1], and Adverse Effects

Generic Name	Trade Name	Tablet Size	Adult Dose	Pediatric Dose	Adverse Effects
6. pyrimethamine and dapsone	Maloprim® (Maloprim® is not available in Canada, but the 2 individual drugs are)	12.5 mg 100 mg	one tablet of Maloprim® weekly, equivalent to 1/2 tablet of pyrimethamine and 1 tablet of dapsone weekly	of Maloprim®: ≤ 2 yrs: 1/4 tab 3-10 yrs: 1/2 tab >10 yrs: 1 tab once weekly	**Frequent:** hemolysis in G6PD deficiency **Occasional:** folate deficiency **Rare:** blood dyscrasias, rash, vomiting
7. doxycycline	Vibramycin®, Vibra-Tabs®	100 mg	one tablet once daily **Treatment:** one tablet twice daily for 7 days	< 8 yr: contra-indicated ≥ 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:** G.I. upset, vaginal candidiasis, photo-sensitivity **Occasional:** azotemia in renal disease **Rare:** allergic reactions, blood dyscrasias
8. quinine sulfate	Novoquinine®	300 mg salt (250 mg base)	**Treatment[4], oral:** two tablets three times daily for 3-7 days **Treatment, IV:** See Table 4	**Treatment[4], oral:** 10 mg salt/kg (max. 600 mg) three times daily for 3-7 days **Treatment, IV:** See Table 4	**Frequent:** Cinchonism (tinnitis, nausea, headache, blurred vision) **Occasional:** Cardiac conduction disturbances, hypersensitivity **Rare:** hemolysis
9. clindamycin hydrochloride	Dalacin®	225 mg salt (150 mg base)	**Treatment, oral:** 775 mg salt (450 mg base) every 6 hrs for 3 days **Treatment, IV:** See Table 4	**Treatment, oral:** 20-40 mg salt/kg/day (12-23 mg base/kg/day) divided into 4 equal doses for 3 days **Treatment, IV:** See Table 4	**Frequent:** Diarrhea, rash **Occasional:** Pseudomembranous colitis **Rare:** Hepatotoxicity, blood dyscrasias

[4] Generally, treatment of chloroquine-resistant strains of *P. falciparum* acquired in Southeast Asia should include a longer course (7-10 days) of quinine, as well as the addition of a second drug, as per Table 4.

- Pregnancy: women should not become pregnant while taking mefloquine or for 3 months following their last dose of mefloquine.
- Occupations or activities in which vertigo may be life-threatening, such as airline pilots.
- Seizure disorder or history of severe depression or psychosis.

Precautions for the use of mefloquine include the following:
- Concurrent use of beta blockers or calcium channel blockers.
- Concurrent use of chloroquine or quinine-like drugs.

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.

2. **CHLOROQUINE** may be taken weekly, as described above for Zone A; 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 people allergic to sulpha drugs. If self-treatment with Fansidar® is administered, this 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 self-administered Fansidar® has been taken.

In deciding between (1) mefloquine versus (2) chloroquine plus back-up Fansidar®, the physician must weigh the risks of adverse drug reactions to mefloquine versus the likelihood that the traveller will be exposed to chloroquine-resistant malaria. As discussed above, such a decision should take into account personal health factors, geographic destination, and activities during travel.

Zone C: Chloroquine-Resistant Strains Are Present (and Risk of Acquiring Resistant Malaria Is High)

It is recommended that **MEFLOQUINE** (Lariam®) be taken alone, as described above for Zone B.

Alternative Chemosuppressive Regimes

Zone A: Chloroquine-Sensitive Strains Only

In chloroquine-sensitive malaria areas, when chloroquine can not be taken, **PROGUANIL** (Paludrine®) in a single daily dose may be taken, beginning one week prior to exposure, once every day 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.

Alternatively, **PYRIMETHAMINE** (Daraprim®) in a single weekly dose may be taken, beginning one week prior to exposure, once every week during the period of exposure, and once weekly for 4 weeks after leaving the malarial area.

Pyrimethamine is a folic acid antagonist which, in large doses, may produce teratogenic effects in laboratory animals. The dose used for malaria chemoprophylaxis has not been associated with congenital anomalies. It is safe for children and is very well tolerated.

Zone B: Chloroquine-Resistant Strains Are Present (but Risk of Acquiring Resistant Malaria Is Low)

An alternative for travellers in zone B, who are unable to take mefloquine or sulphonamides, is to take **CHLOROQUINE** (once weekly as above) plus **PROGUANIL** (2 tablets daily).

Zone C: Chloroquine-Resistant Strains Are Present (and Risk of Acquiring Resistant Malaria Is High)

For travellers unable to take mefloquine the following alternatives are available:

1. **DOXYCYCLINE** (Vibramycin ®) alone is taken once daily, beginning 2 days prior to entering a malarial 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 under the age of 8 years.

Doxycycline may cause gastrointestinal upset, which is less likely to occur if the drug is taken with food. It should not be taken simultaneously with Pepto-Bismol®. Because doxycycline is photosensitizing, it may make 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.

OR

2. **CHLOROQUINE** (weekly as above) plus the combination of **DAPSONE** (Avlosulfon®), 100 mg and **PYRIMETHAMINE**, 12.5 mg taken once weekly, beginning one week prior to entering the malarial area, weekly throughout the period of exposure, and weekly for 4 weeks after leaving the malarial area. This combination of dapsone and pyrimethamine is equivalent to Maloprim®, a drug not available in Canada. This regime is suitable for children. Furthermore, empirical data have suggested that this combination is safe during pregnancy. Dapsone is a

sulfone, related to, but distinct from, sulphonamides; a history of an allergic reaction to a sulphonamide is not a contraindication to the administration of dapsone.

Chemosuppressive Regimes For Children

Of the drugs described, doxycycline is contraindicated among children < 8 years of age. There are no data on the safety or appropriate dose of mefloquine for infants <15 kg weight. Of note, chloroquine sulfate (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 admixed with cereal, jam, etc.

Chemosuppressive Regimes For Women Who Are or May Become Pregnant While In Malaria Zones B and/or C

Both mefloquine and doxycycline are contraindicated during pregnancy. This creates a dilemma for women who are, plan to be, or become pregnant while in Zones B and/or C. Malaria causes greater morbidity during pregnancy to both the mother and the fetus. The malaria chemo-prophylactic drugs which are safe to take during pregnancy may not be as efficacious as mefloquine or doxycycline in preventing drug-resistant *P. falciparum* infection. In certain situations, the combination of chloroquine plus back-up Fansidar® may provide appropriate chemosuppression for a woman visiting or residing in zone B. Otherwise, it may be prudent for non-immune women who are pregnant or who plan a pregnancy to avoid lengthy trips or periods of residence in Zones B and/or C during that time.

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. In order to reduce the risk of relapse following the treatment of symptomatic *P. vivax* or *P. ovale*, primaquine is indicated to provide "radical cure". Primaquine should be reserved for those cases of malaria that are documented or strongly suspected to be due to *P. vivax* or *P. ovale*.

Most people tolerate this treatment very well, but individuals with glucose phosphate dehydrogenase deficiency (G6PD deficiency) may experience brisk hemolysis when using primaquine. A G6PD level should be determined prior to administering primaquine.

There is currently an acute shortage of primaquine in Canada. The means for obtaining it during this shortage were described in the *Canada Diseases Weekly Report*, 4 August 1990;16:154-5.

Management of Malaria

The changing character of malaria world-wide has been reflected in the type and severity of malaria cases seen in Canada; an increasing proportion of the Canadian cases seem to be due to *P. falciparum* and to be severe. This has been documented at the two largest Canadian tropical disease clinics; in addition, 5 Canadians died of falciparum malaria acquired in Africa during a 5-month period during 1989. Travellers and health-care providers alike must promptly consider the diagnosis of malaria for any febrile illness which occurs following travel to a malarial area. A travel history must be sought, and clearly-defined geographic exposure obtained, to assist in the diagnosis and management of malaria. Although falciparum malaria usually presents clinically within 2 months of last exposure if infection was acquired, malaria may occur months to several years after travel in endemic areas in the tropics.

The examination of thick and thin blood films is essential for the diagnosis of malaria. The clinical presentation (history and physical examination) of malaria are insufficient to make a diagnosis of this infection, but can only be suggestive of its possibility. When malaria is considered a clinical possibility, 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 performed as soon as possible. If this facility is not available at the point of presentation of the patient, then a referral should be made immediately to a facility in a position 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 management of malaria is very dependent on the exact species of parasite, it is now essential that every effort be made to speciate malaria from the blood film on an urgent basis. In addition, *P. falciparum* malaria acquired in zones B or C must be considered to be possibly or likely chloroquine-resistant, and therefore should be treated as such. A detailed geographic history is essential to the management of malaria infections. Malaria is a reportable disease in all provinces; physicians are required to report all cases to their local public health authorities. 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 suggesting to the examining physician that the patient did have a positive blood smear abroad. Excluded are patients with a history of fever that responded to anti-malarials but for whom a blood smear was never prepared."

Management of Non-Falciparum Malaria

Although there have been a few case reports of chloroquine-resistant *P. vivax* malaria in Oceania, at this time all non-falciparum malaria should be treated with chloroquine, as per Table 3. The use of primaquine for *P. vivax* and *P. ovale* malaria has been discussed above.

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). The interested reader is referred to this document for a more detailed discussion of this subject.

Severe *P. falciparum* infections are defined by the criteria in Table 5. This diagnosis may have a risk of mortality of 30% or higher. These patients require immediate hospitalization, and urgent and intensive medical management. Consideration to admit all *P. falciparum* infection cases, whether severe or not, should be given to allow for monitoring of the patient during initiation of therapy.

Non-severe *P. falciparum* infections unequivocally acquired in a chloroquine-sensitive zone (zone A), may be treated with chloroquine alone, as per Table 3. Non-severe *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 quinine and the second drug should be administered as per Table 3.

All severe *P. falciparum* infections, and those non-severe cases unable to tolerate oral quinine, should be administered intravenous quinine or quinidine. At this time, parenteral quinine is an emergency release drug, and has a limited hospital distribution in Canada. It is available at those hospitals and through Health and Welfare 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 after quinine, either orally (as per Table 3), or if not possible, then parenterally (as per Table 4).

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 electrocardiographically-monitored.

In cases of complicated *P. falciparum*, or hyperparasitemia (>5% in non-immune individuals), exchange transfusion has been used on an experimental

TABLE 4

Chemotherapy of Severe Falciparum Malaria[a]

1. Quinine[b]: 7 mg dihydrochloride salt/kg (=5 mg base/kg) (loading dose)[c] intravenously by infusion pump over 30 minutes followed immediately by 10 mg salt/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, 10 mg salt/kg 8 hourly to complete 7 days' treatment.

   OR

2. Quinine[b]: 20 mg dihydrochloride salt/kg (=15 mg base/kg) (loading dose)[c] by intravenous infusion over 4 hours, then 10 mg salt/kg over 4 hours, 8 hourly until patient can swallow, then quinine tablets to complete 7 days' treatment.

   OR

3. Quinidine[d]: 10 mg base/kg (=12mg quinidine sulfate salt /kg = 14 mg quinidine gluconate salt/kg) (loading dose)[c] by intravenous infusion over 1-2 hours, followed by 0.02 mg base/kg/min by infusion pump for 72 hours or until the patient can swallow, then quinine tablets to complete 7 days' treatment.

   OR

4. Quinidine[d]: 15 mg base/kg (=18 mg quinidine sulfate salt/kg = 22 mg quinidine gluconate salt/kg) (loading dose)[c] by intravenous infusion over 4 hours, then 7.5 mg base/kg over 4 hours, 8 hourly until 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/kg (to a maximum of 100 mg) twice daily; contraindicated if age <8 years.

   OR

2. Fansidar®, 3 tablets at one time; pediatric dose = 3 tabs/60 x weight in kg.

   OR

3. Clindamycin, 10 mg base/kg (loading dose) intravenously, followed by 5 mg/kg every 8 hours until blood is clear of asexual parasites.

---

[a] In patients requiring more than 48 hours of parenteral therapy, reduce the quinine or quinidine maintenance dose by one-third to one-half (i.e., 5-7 mg/kg 8 hourly).

[b] Parenteral quinine dihydrochloride is stocked by Health and Welfare Canada and may be obtained on a patient-by-patient basis with authorization from the Bureau of Human Prescription Drugs, Health Protection Branch, Health and Welfare Canada, Tower B, Place Vanier, 355 River Road, Ottawa, Ontario, K1A 1B8; (613) 993-3105.

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

[d] Parenteral quinidine sulfate and gluconate are marketed in Canada.

TABLE 5

Defining Criteria of 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 of the following eleven features:

1) Impaired consciousness or coma
2) Severe normocytic anaemia
3) Renal failure
4) Pulmonary oedema
5) Hypoglycemia
6) Circulatory collapse, shock
7) Spontaneous bleeding/disseminated intravascular coagulation
8) Repeated generalized convulsions
9) Acidemia/acidosis
10) Haemoglobinuria
11) Parasitemia of > 5% in non-immune individuals

basis, as a potentially life-saving procedure. Consultation with a haematologist and an expert in Tropical Diseases is strongly recommended if this situation arises.

Protocol for Mefloquine in Canada

Mefloquine (MFQ) is not licensed in Canada. Hoffman-La Roche (HLR), the pharmaceutical manufacturer of MFQ, has developed a "treatment investigational new drug (IND)" protocol for the use of MFQ in Canada, which has been approved by the Bureau of Human Prescription Drugs (BHPD). The terms of the protocol require surveillance of serious adverse drug reactions (ADRs) to MFQ. Serious ADRs are reportable immediately to both BHPD and HLR. Periodic reporting of drug usage and of minor ADRs are required to both BHPD and HLR. In addition to the passive surveillance of ADRs associated with the IND protocol, an active surveillance project for serious, rare ADRs is currently under consideration.

Under the terms of the protocol, a limited number of principal investigators (PIs) were chosen from among the heads of selected Canadian travel and tropical disease clinics or public health agencies (see Appendix II). Co-investigators will be qualified Canadian physicians whose patients require MFQ and who are designated by the PIs. HLR will sell an initial 6-month supply of MFQ to a pharmacy designated by each PI; continued supply of MFQ from HLR will thereafter be conditional upon the compliance of the PI with reporting requirements. Similarly, the designated pharmacy of each PI may in turn sell a supply of MFQ to a pharmacy designated by each co-investigator; continued supply to the co-investigator will be conditional upon the compliance of the co-investigator with reporting requirements, as determined by the PI who designated the co-investigator. Patients will pay for their MFQ as they would for a licensed drug. Physicians who wish to be co-investigators should apply to the nearest PI.

APPENDIX I

Malaria Risk by Geographic Area in Countries with Endemic Malaria

Country	Areas of risk within country	Recommended Regimen(s)
Afghanistan	All	A
Algeria	Sahara region.	C
Angola	All	C
Argentina	Rural areas near Bolivian border.	A
Bangladesh	All, except no risk in city of Dhaka.	B,C
Belize	Rural areas, except no risk in Belize District.	A
Benin	All	C
Bhutan	Rural areas in districts bordering India.	C
Bolivia	Rural areas only, except no risk in Oruro Department and province of Ingavi, Los Andes, Omasuyos, Pacajes, Southern and Central Potosi Department.	B,C
Botswana	Northern part of country (North of 21 degree South).	C
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.	B,C
Burkina Faso	All	C
Burma: see Myanmar		
Burundi	All	C
Cambodia: See Kampuchea		
Cameroon	All	C
Central African Republic	All	C
Ceylon: see Sri Lanka		
Chad	All	C
China	Rural areas only in Anui, Fujian, Guangdong, Guangxi, Guizhou, Hebei, Henan, Hubei, Hunan, Jiangsu, Jiangxi, Liaoning, Shanxi, Shenxi, Shandong, Sichuan, Yunnan, Xingjiang and Zhejiang Provinces/autonomous regions.	A,C
Colombia	In general, rural areas only, except no risk in Bogota and vicinity.	B,C
Comoros	All	C
Congo	All	C
Costa Rica	None in central highlands. Limited risk in rural areas of Alajuela, Guanacaste, Limon, and Puntarenas Provinces.	A
Cote d'Ivoire (formerly Ivory Coast)	All	C
Djibouti	All	C
Dominican Republic	Highest risk in areas bordering Haiti. Possible transmission has been reported in resort areas of north coast.	A
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 Galapagos Islands).	B,C

APPENDIX I (continued)

Malaria Risk by Geographic Area in Countries with Endemic Malaria

Country	Areas of risk within country	Recommended Regimen(s)
Egypt	Rural areas of Nile Delta, El Faiyum area, the oases, and part of southern Egypt.	A
El Salvador	Rural areas only.	A
Equatorial Guinea	All	C
Ethiopia	All; no risk in Addis Ababa and above 2000 metres.	C
French Guiana	All	B,C
Gabon	All	C
Gambia	All	C
Ghana	All	C
Guatemala	Rural areas only, except no risk in central highlands.	A
Guinea	All	C
Guineau-Bissau	All	C
Guyana	Rural areas in Rupununi and North West Regions.	B,C
Haiti	All	A
Honduras	Rural areas only.	A
India	All	B,C
Indonesia	In general, rural areas only, except high risk in all areas of Irian Jaya. No risk in resort areas of Bali.	C
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 Mahai-Bakhtiani and the north of Khuzestan.	B
Iraq	All areas in northern region: Duhok, Erbil, Kirkuk, Ninawa, Sulaimaniya province.	A
Ivory Coast: See Cote d'Ivoire		
Kampuchea (formerly Cambodia)	All	C
Kenya	All except city of Nairobi and above 2500 metres.	C
Lao People's Democratic Republic	All areas, except no risk in city of Vientiane.	C
Liberia	All	C
Libyan Arab Janahiriya	Very limited risk in two small foci in southwest of country.	C
Madagascar	In general, coastal areas. Limited risk in Antananarivo, Andramasina, Antsirabe, and Manjakandriana.	C
Malawi	All	C
Malaysia	In general, rural areas only, but throughout Sabah. Otherwise, none in urban and coastal areas.	C
Maldives	Rural areas only, except no risk in Male Island, Kaafu Atoll, and resort areas.	A
Mali	All	C
Mauritania	All areas, except no risk in the northern areas of Dakhet-Nouadhibou, Inchiri, Adrar, and Tris-Zemour.	C
Mauritius	Rural areas only, except no risk on Rodrigues Island.	A
Mexico	Rural areas only.	A

APPENDIX I (continued)

Malaria Risk by Geographic Area in Countries with Endemic Malaria

Country	Areas of risk within country	Recommended Regimen(s)
Morocco	Very limited risk in rural areas of coastal provinces.	A
Mozambique	All	C
Myanmar (formerly Burma)	All	C
Namibia	All areas of Ovamboland, and Caprivi Strip.	C
Nepal	Rural areas in Terai District and hill districts below 1200 meters. No risk in Katmandu.	B
New Hebrides: see Vanuatu		
Nicaragua	In general, rural areas only; however, risk exists in outskirts of towns of Chinandega, Leon, Granada, Managua, Nandaime, and Tipitapa.	A
Niger	All	C
Nigeria	All	C
Oman	All	A
Pakistan	All	B
Panama	Rural areas of province of Darien and territories of Chiman and Puerto de Obaldia.	A,B
Papua New Guinea	All	C
Paraguay	In general, only rural areas bordering Brazil.	A
Peru	In general, all rural areas, except no risk in Lima and vicinity and coastal area south of Lima.	A,C
Philippines	Rural areas only, except no risk in Manila and province of Bohoi, Catanduanes, Cebu, Leyte.	C
Rwanda	All	C
Sao Tome and Principe	All	C
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, Medini and Taif.	A
Senegal	All	C
Sierra Leone	All	C
Solomon Islands	All	C
Somalia	All areas, except very low risk in Mogadishu.	C
South Africa	Rural areas (including game parks) in the north, east, and western low altitude areas of Transvaal, and in Natal coast.	C
Sri Lanka (formerly Ceylon)	All areas except Colombo.	B
Sudan	All	C
Surinam	Rural areas only, except no risk in Paramaribo district and coastal areas north of 5 degree North.	B,C
Swaziland	All lowland areas.	C
Syrian Arab Republic	Rural areas only except no risk in districts of Damascus, Deir-es-zor, and Sweida.	A
Tanzania, United Republic of	All	C
Thailand	Rural border areas, and no risk in Bangkok or beach resort areas.	C

APPENDIX I (continued)

Malaria Risk by Geographic Area in Countries with Endemic Malaria

Country	Areas of risk within country	Recommended Regimen(s)
Togo	All	C
Turkey	Cukorova/Amikova areas and southeast Anatolia.	A
Uganda	All.	C
United Arab Emirates	All, except no risk in cities of Dubai, Sharjah Ajmin, Umm al Qaiwan, and Emirate of Abu Dhabi.	A
Vanuatu (formerly New Hebrides)	All, except no risk on Futuna Island.	C
Venezuela	Rural areas of Apure, Bolivar, Barinas Merida, Tachira and Zulia States.	B,C
Viet Nam	Rural areas only.	C
Yemen	All, except no risk in Sada and Hajja provinces.	A
Yemen, Democratic	All, except no risk in city of Aden or airport perimeter.	A
Zaire	All	C
Zambia	All	C
Zimbabwe (formerly Rhodesia)	All, except no risk in city of Harare.	C

APPENDIX II

Principal Investigators of Mefloquine in Canada

British Columbia

Dr. John Farley
Consultant Epidemiologist
Communicable Disease
B.C. Centre for Disease Control
828 West 10th Avenue
Vancouver, B.C., V5Z 1L8
Tel: (604) 660-6063
Fax: (604) 660-6066

Alberta

Dr. Stan Houston
2E4.11 Walter MacKenzie Centre
University of Alberta Hospital
Edmonton, Alberta, T6G 2B7
Tel: (403) 492-6221
Fax: (403) 492-7137

Dr. Margaret Russell
International Travel Immunization Clinic
Health Sciences Centre
3330 Hospital Drive N.W.
Calgary, Alberta, T2N 4N1
Tel: (403) 220-4271
Fax: (403) 283-4740

Saskatchewan

Dr. Paul Hasselback
Associate Medical Officer of Health
City Health Department
1910 McIntyre Street
Regina, Saskatchewan, S4P 2R3
Tel: (306) 777-6618
Fax: (306) 525-1801

Manitoba

Dr. R.S. Stanwick
Interim Medical Health Officer
City of Winnipeg Health Department
280 William Avenue
Winnipeg, Manitoba, R3B OR1
Tel: (204) 986-2122
Fax: (204) 947-3957

Ontario

Dr. D.W. MacPherson
Director
Infectious Disease & Tropical Medicine Clinic
Chedoke - McMaster Hospital
McMaster University Medical Centre
1200 Main Street West
Hamilton, Ontario, L8N 3Z5
Tel: (416) 521-2100
Fax: (416) 521-6066

Dr. Ross A. Pennie
Paediatric Infectious Diseases
Children's Hospital of Eastern Ontario
401 Smyth Road
Ottawa, Ontario, K1H 8L1
Tel: (613) 737-2765
Fax: (613) 738-3216

Dr. Raphael Saginur
Director
Infectious and Tropical Disease Clinic
Ottawa Civic Hospital
1053 Carling Avenue
Ottawa, Ontario, K1Y 4E9
Tel: (613) 761-4155
Fax: (613) 729-6770

Dr. David Lawee and
Dr. Jay Keystone
Toronto General Hospital
200 Elizabeth Street
Toronto, Ontario, M5G 1L7
Tel: (Dr. Keystone) (416) 340-3675
Fax: (Dr. Keystone) (416) 595-5826
Tel: (Dr. Lawee) (416) 340-3959
Fax: (Dr. Lawee) (416) 340-5110

APPENDIX II

Principal Investigators of Mefloquine in Canada

Québec

Dr. Jean Robert
Chef
Département de santé communautaire
Clinique de vaccination aux voyageurs
Hôpital Saint-Luc
1001, rue St-Denis
2 ième étage
Montréal (Québec), H2X 3H9
Tel: (514) 281-2121
Fax: (514) 281-4099

Dr. J. Dick MacLean
Director
Centre for Tropical Diseases
Montreal General Hospital
McGill University
1650 Cedar Street
Montréal (Québec), H3G 1A4
Tel: (514) 937-6011 Ext. 1254
Fax: (514) 937-2455

Dr. Serge Dumas
Centre Santé-Voyages
DSC St-Sacrement
1000, chemin Ste-Foy, salle 116
Québec (Québec), G1S 2L6
Tel: (418) 688-1385
Fax: (418) 688-3249

Dr. C. Fortin
Département de Santé communuataire
Du Centre Hosp. de L'Université Laval
2050 Boul. St. Cyrille Ouest
Ste-Foy (Québec), G1V 2K8
Tel: (418) 687-1090
Fax: (418) 681-5635

Nova Scotia

Dr. T.J. Marrie
Division of Infectious Diseases
Victoria General Hospital
1278 Tower Road
Halifax, Nova Scotia, B3H 2Y9
Tel: (902) 428-2084
Fax: (902) 428-2023

Newfoundland

Dr. Gordon Noseworthy
Medical Officer of Health
St. John's and District Health Unit
P.O. Box 8700
St. John's, Newfoundland, A1B 4J6
Attention: Forest Road office
Tel: (709) 576-3435
Fax: (709) 576-2165

Prince Edward Island

Dr. Lamont Sweet
Chief Health Officer
Department of Health and Social Services
P.O. Box 2000
Charlottetown, PEI, C1A 7N8
Tel: (902) 368-4996
Fax: (902) 368-5544

Yukon Territory

Dr. Bruce Beaton
Pine Medical Clinic
5110 5th Avenue
Whitehorse, Yukon Territory, Y1A 1L4
Tel: (403) 668-4353
Fax: (403) 668-3087

Northwest Territories

Dr. Richard Nuttall
Medical Health Officer
Government of the Northwest Territories
P.O. Box 520
Yellowknife, NWT, X1A 2N4
Tel: (403) 920-8486
Fax: (403) 920-4015