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Canadian Recommendations for the Prevention and Treatment of Malaria Among International Travellers 2009

Preface

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

CATMAT gratefully acknowledges the work of Dr. J.D. MacLean for his contributions to the development of the *Canadian Recommendations for the Prevention and Treatment of Malaria Among International Travellers 2009*.

Preamble

The Committee to Advise on Tropical Medicine and Travel (CATMAT) provides the Public Health Agency of Canada with ongoing and timely medical, scientific, and public health advice relating to tropical infectious disease and health risks associated with international travel.

The Agency acknowledges that the advice and recommendations set out in this statement are based upon the best current available scientific knowledge and medical practices, and is disseminating this document for information purposes to both travellers and the medical community caring for travellers.

Persons administering or using drugs, vaccines, insect repellents or other products should also be aware of the contents of the product monograph(s) or other similarly approved standards or instructions for use. Recommendations for use and other information set out herein may differ from that set out in the product monograph(s) or other similarly approved standards or instructions for use by the licensed manufacturer(s). Manufacturers have sought approval and provided evidence as to the safety and efficacy of their products only when used in accordance with the product monographs or other similarly approved standards or instructions for use.

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1. Introduction

Malaria is a common and serious infection caused by five species of the genus *Plasmodium: falciparum, vivax, ovale, malariae* and *knowlesi*. Infections with *P. falciparum* have the highest fatality rates, and infections caused by *P. vivax* and *P. ovale* can relapse from latent liver stages. *P. knowlesi* is a malaria species increasingly described in Southeast Asia and is noteworthy in having a primate reservoir[1, 2]. All species of malaria are transmitted by the bites of infected female anopheline mosquitoes. Rarely, transmission may occur by blood[3], by shared needle use or congenitally from mother to fetus[4].

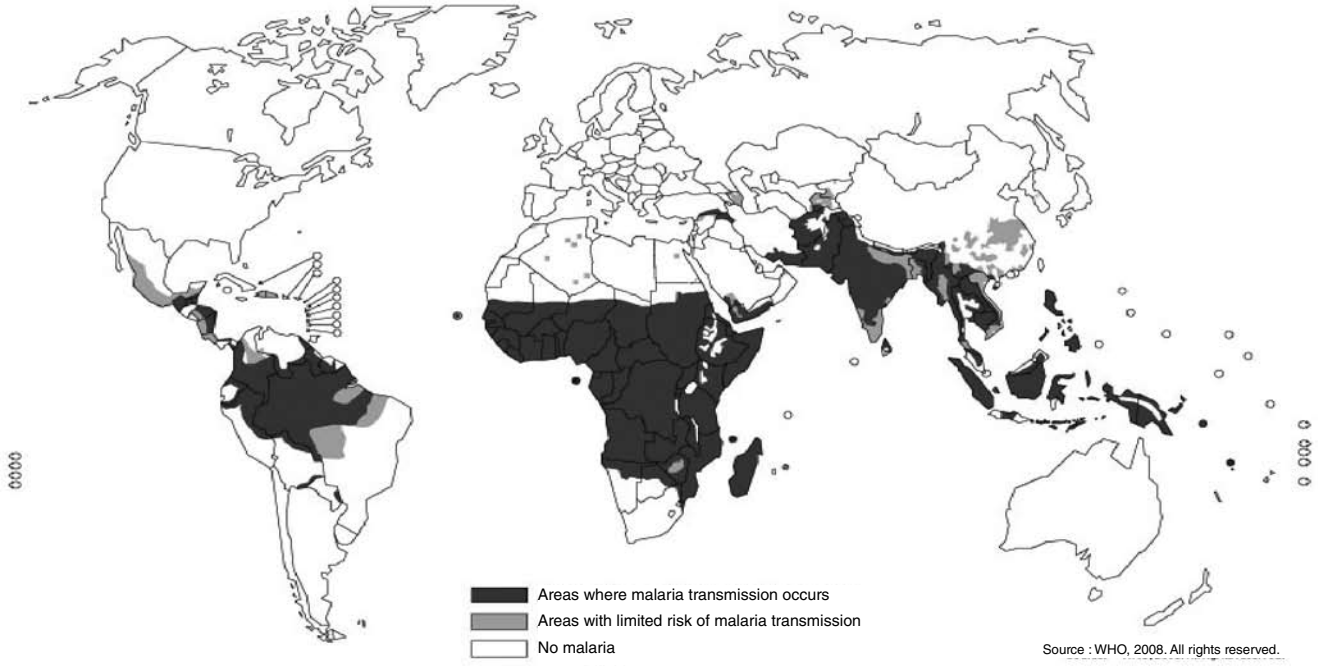
The disease is characterized by fever and "flu-like" symptoms such as myalgia, headache, abdominal pain and malaise. Rigors and chills often occur. The classically described alternate-day fevers or other periodic fevers are often not present. Malaria deaths are frequently the result of delays in the diagnosis and treatment of the infection[5, 6].

Widespread resistance of *P. falciparum* to chloroquine has complicated the prevention and treatment of malaria. Drug-resistant strains of malaria are now common in much of the world.

The symptoms of malaria are non-specific, and diagnosis is not possible without microscopy of a blood film or an antigen detection test (rapid diagnostic test).

According to the World Health Organization (WHO), in 2005 3.2 billion people living in 107 countries and territories were at risk of malaria, resulting in approximately 500 million cases and 1 to 3 million deaths[7]. About 60% of malaria cases occur in Africa, 40% in Asia and less than 5% in the Americas. For *P. falciparum* malaria specifically, the estimated region of distribution is 74% in Africa, 25% in Asia and 1% in the Americas[5]. It is estimated that each year 1 million Canadians travel to areas where they may be at risk of malaria, resulting in 350 to 1000 malaria cases and 1 to 2 deaths annually[6, 8, 9], although under-reporting is estimated to be 30% to 50%[10]. The majority of *P. falciparum* cases imported into Canada are acquired in sub-Saharan Africa, whereas the majority of *P. vivax* cases are acquired on the Indian subcontinent[11].

Figure 1. Map of malaria-endemic zones*



*This map is intended as a visual aid only; see Appendix I for specific country recommendations.

The Canadian Malaria Network (CMN), in collaboration with the Public Health Agency of Canada (PHAC) and Health Canada's Special Access Program, maintains supplies of intravenous artesunate and quinine at major medical centres across the country to facilitate rapid access to effective treatment for severe malaria. From June 2001 to March 2007, there were 88 cases (33% children) of severe or complicated malaria reported to the CMN, a mean of 14.3 cases per year. Most (56; 64%) had been born in a malaria-endemic country. Data on chemoprophylaxis were documented in 83 individuals, of whom only 23 (28%) reported using any, and in only less than 10% of these was it appropriate. There were delays in malaria management; only 20% presented to medical care within 24 hours of symptoms, and 37% waited more than 3 days before seeking medical care. Diagnosis was delayed more than 24 hours in 26%, and treatment was delayed more than 24 hours in 14 patients (18%)[12].

Almost all malaria deaths in travellers are due to *P. falciparum*. The overall case-fatality rate of imported *P. falciparum* malaria varies from approximately 1% to 5% and increases to 20% for those with severe malaria, even when the disease is managed in intensive care units[13]. Progression from asymptomatic infection to severe and complicated malaria can be extremely rapid, with death occurring within 36 to 48 hours. The most important factors that determine patient survival are early diagnosis and appropriate therapy. The majority of infections and deaths due to malaria are preventable.

2. Prevention – Risk Assessment

The components of malaria prevention are often described as the ABCD of malaria. All travellers to malarial areas need to:

a) be aware of the risk of **A**cquiring malaria infection (described in this chapter),

b) know how to avoid mosquito **B**ites (Chapter 3),

c) take **C**hemoprophylaxis, as appropriate (Chapter 3), and

d) understand the need to urgently seek medical advice for **D**iagnosis and treatment if they have a fever (Chapters 3, 6).

Appendix II provides a checklist for the preparation of travellers to malarial areas.

Risk of Acquiring Malaria

Malaria transmission occurs in most of sub-Saharan Africa and New Guinea; in large areas of Southern Asia; in parts of Southeast Asia, Oceania, Haiti, and Central and South America; and in limited areas of Mexico, the Dominican Republic, North Africa and the Middle East. Appendix I provides country-specific information on malaria risk and recommended chemoprophylaxis. The information is based on assessments developed by the World Health Organization (WHO), the United States of America Centers for Disease Control and Prevention (CDC), and the International Association for Medical Assistance to Travellers (IAMAT) and is considered authoritative for decision-making related to travellers and malaria. It should be noted, however, that many factors, such as variation in reporting and surveillance, may significantly affect the reliability of this information. Further, substantial variability may occur within the geographic areas defined in Appendix I.

Malaria transmission occurs primarily between dusk and dawn, corresponding to the biting habits of anopheline mosquitoes. The risk of transmission is increased in rural areas and varies seasonally in many locations, often being higher around the rainy season. Transmission decreases with altitude and may not occur in highland areas (e.g., generally above 2000 m [6500 ft]) and is virtually non-existent over 2500 m (8,000 feet) (see Appendix I for country-specific information on malaria risk and altitude).

Travel to urban and tourist areas of Southeast Asia, and Central and South America are considered to entail minimal risk, whereas urban travel in other malaria-endemic regions, such as sub-Saharan Africa, the Indian subcontinent, and New Guinea (Papua New Guinea [PNG] and Papua [Irian Jaya]) may be associated with significant risk of infection. Although difficult to measure and monitor, retrospective studies of large numbers of travellers have provided an approximation of malaria risk during a 1-month stay, without chemoprophylaxis, as follows[14, 15, 16]:

- Oceania (PNG, Papua [Irian Jaya], Solomon Islands and Vanuatu) 1:20;

  Sub-Saharan Africa 1:50;

  Indian subcontinent 1:500;

  Southeast Asia 1:500;

  South America 1:2,500; and

  Central America and the Caribbean 1:10,000.

It is noteworthy that the highest risk areas for malaria are Oceania, Africa and, to a lesser extent, the Indian subcontinent, where the relative risks of travellers acquiring malaria vary from 50 to 200 times greater than low-risk areas for malaria[16].

In the last decade, there has been further spread of drug-resistant malaria. As well, the emergence or re-emergence of infection, especially with *P. falciparum*, has occurred in certain geographic areas. For example, large outbreaks of malaria have occurred on the Indian subcontinent, where an increasing proportion of malaria cases are due to drug-resistant *P. falciparum*. In recent years, malaria has occasionally surfaced in tourists as a result of the immigration of malaria-infected people from a malaria-endemic area (Haiti) into tourist resort areas in parts of the eastern Dominican Republic[17], Great Exuma Island of the Bahamas[18] and Jamaica[19], previously considered to be free of malaria transmission. Although these malaria outbreaks were successfully contained, they demonstrate the potential for malaria to rapidly emerge or re-emerge in previously malaria-free regions. Therefore, pre-travel health care providers need to continually monitor malaria travel health advisories and alerts.

Exposure Assessment

The travel itinerary should be reviewed in detail and compared with known areas of malaria transmission within a country to determine the likelihood that the traveller will be at risk of acquiring malaria. Factors to consider in determining risk of exposure include the following:

- level of endemicity in the area(s) covered by the travel itinerary;
- presence of *Plasmodium falciparum*;
- duration of exposure;
- rural, periurban, urban travel;
- seasonality (rainy vs. dry);
- night-time exposure; and
- availability and likelihood of use of other interventions, e.g., personal protective measures.

CATMAT considers there to be minimal risk of malaria in urban centres of Southeast Asia, and Central and South America. Recommendations to the Canadian traveller concerning malaria prevention measures in these regions of low malaria transmission risk should take into consideration the estimated risk of acquiring malaria related to the risk factors listed above and the potential risks of malaria chemoprophylactic measures. Clinical judgment is recommended on a case-by-case basis. It is the responsibility of pre-travel health care providers to monitor travel health advisories and alerts (posted on PHAC and CDC websites) in order to maintain up-to-date information on malaria risks in specific destinations, as malaria risk can rapidly change even in regions normally considered of low risk. Regardless of the malaria chemoprophylaxis regimens used, CATMAT recommends the use of personal protection measures. Please refer to CATMAT's Statement on Personal Protective Measures to Prevent Arthropod Bites (**http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/05vol31/asc-dcc-4/**).

The distribution of drug-resistant malaria (see Appendix I) also forms part of the exposure assessment. Chloroquine-resistant *P. falciparum* is widespread in all malaria-endemic areas of the world, except for Mexico, the Caribbean, Central America (west of the Panama Canal), and parts of the Middle East (including Egypt)[5, 20]. *P. falciparum* malaria resistant to chloroquine AND mefloquine has been confirmed on the Thai-Cambodia and Thai-Myanmar (Burma) border areas, as well as the western provinces of Cambodia, the eastern states of

Burma (Myanmar), on the border between Burma and China, in Laos along the borders of Laos and Burma, and in southern Vietnam[20].

Host Assessment

The health of the individual (e.g., age, pregnancy, current medications and chronic illnesses such as HIV), must be considered in order to assess the risk of severe disease if malaria were to occur and in order to choose an appropriate antimalarial drug for chemoprophylaxis (see Chapter 4)[21].

Travellers should be made aware that reliable malaria diagnostic and treatment options may not be available in many travel destinations[22]. Self-diagnosis of malaria using symptoms only, without laboratory diagnostic testing, is considered suboptimal. However, some travellers going to more remote locations may have few options other than self-diagnosis and self-treatment (see Chapter 7).

The following elements should be addressed in an individual risk assessment:

Exposure Assessment

i. Is the traveller likely to be exposed to malaria?

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

Host Assessment

iii. Is the traveller at increased risk of severe malaria disease (e.g., a young child, asplenic individual, HIV infected, pregnant woman)?

iv. Are there any contraindications to the use of a particular antimalarial drug in that particular traveller?

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

Evidence-based medicine (EBM) recommendation	***EBM rating***
Travellers should receive expert advice concerning malaria risks and avoidance strategies[15].	**B III**
Malaria chemoprophylaxis is very effective and is recommended for travel to malaria-endemic regions[20].	**A I**
An assessment of malaria risk (level of malaria endemicity, duration of exposure, personal protective measures) is essential to educating travellers[15, 16].	**B II**
An assessment of the traveller's health is a priority in determining malaria risk[21].	**B II**
An assessment of the quality of, and distance to, medical and laboratory facilities must inform the counseling of the patient on malaria risk[23].	**B II**

3. Prevention – Malaria Education for Travellers

Enhancing adherence to antimalarial chemoprophylaxis and personal protective measures

Adherence to antimalarial prophylactic drug regimens and use of personal protective measures are essential to the prevention of malaria. Most deaths in Canadian travellers due to malaria occur in those who did not take antimalarial medications or who took ineffective medications not recommended by CATMAT[6, 8, 24].

Unfortunately, the evidence demonstrates that non-adherence to malaria prevention recommendations is common and ranges from 30% to 55% of travellers[25, 26, 27, 28, 29]. Non-adherence has even been reported in travelling physicians: less than half of general practitioners practising in the UK who travelled to South Asia admitted to full compliance with malaria prevention practices[28]. Non-adherence to malaria chemoprophylaxis is prevalent among backpacking travellers; immigrants who return to their country of origin to visit friends and relatives; long-term (greater than 1 month) travellers; those who irregularly use insect personal protection measures; travellers less than 40 years; and those given daily dosing schedules[25, 26, 27, 28, 29, 30, 31, 32].

Reasons given for non-adherence are varied and include false beliefs that the travel destination is malaria-free; fear of or past experience with medication side effects; false beliefs in long-term immunity to malaria acquired from prior infections; cost of medications; confusion arising from alternative recommendations; forgetfulness; or no interest in taking antimalarial medications with no specific reason given[25, 26, 27, 29-32].

There are no published data on approaches to improve adherence to malaria prevention practices. Recognizing the type of traveller who is most likely to be non-adherent, as well as the reasons why travellers may become non-adherent, may assist with pre-travel health counselling[33]. Published reasons for non-adherence should form part of the pre-travel health discussion with all travellers seeking malaria prevention advice. If there are concerns about a traveller's ability to tolerate a particular antimalarial prophylactic regimen, malaria chemoprophylaxis may be initiated in advance of travel to assess drug tolerance.

Well-informed health care providers are essential to providing accurate information for travellers; however, family physicians may not provide correct advice[24, 34, 35, 36]. Travellers using only one information source (such as a family physician) are significantly more compliant than those consulting the differing recommendations available from different sources[35].

Early diagnosis and treatment

All travellers must be informed that malaria should be suspected if unexplained fever occurs during or after travel. Medical attention should be sought as soon as possible, and the traveller should request that a thick and thin blood film be immediately obtained and examined for malaria parasites. If the initial blood film is negative and the traveller remains symptomatic, then the blood film should be repeated in 12 to 24 hours. The most important factors that determine the survival of patients with *P. falciparum* malaria are early diagnosis and prompt initiation of appropriate treatment[8].

Evidence-based medicine recommendations	*EBM rating*
Increased education of travellers who traditionally are the least compliant with malaria chemoprophylaxis is recommended (backpacking travellers, immigrants who return to their country of origin to visit friends and relatives, long-term travellers [greater than one month], travellers less than 40 years of age)[25, 26, 28, 30, 31, 32, 33].	**B II**
If there are concerns about a traveller's ability to tolerate a particular antimalarial prophylactic regimen, malaria chemoprophylaxis can be initiated in advance of travel to assess drug tolerance.	**C III**
A traveller must be informed that survival of patients with *P. falciparum* malaria is determined by early diagnosis and prompt initiation of appropriate treatment[8].	**A II**

Insect Repellants and Clothing

All travellers to areas with malaria risk are advised to use personal protective measures to prevent bites from *Anopheles* mosquitoes. This subject has been covered in a previous CATMAT Statement[37], and much of the following is taken directly from this source (available at **http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/05vol31/asc-dcc-4**).

Protection from mosquito bites can reasonably include alteration of the travel itinerary to limit time spent in malarial regions as well as to avoid outdoor activities during and after dusk and before dawn. All travellers to areas with malaria risk are advised to use personal protective measures to prevent bites from *Anopheles* mosquitoes. Use of effective repellents and insecticide-treated clothing, covering up exposed skin and avoidance of areas or times where/when vectors are active are also considered to be important for prevention of malaria[38, 39].

DEET (N,N-diethyl-3-methyl- benzamide, also known as N,N-diethyl-*m*-toluamide) remains the first choice among repellants. Canadian recommendations for domestic use of 10% DEET or less for children < 12 years emphasize the need for frequent re-applications because of the relatively short duration of protection[40]. For protection from malaria-bearing *Anopheles*, CATMAT recommends up to 30% DEET-containing products for all age groups. Extended-duration DEET formulations have useful advantages over other formulations and are preferred[41, 42]. Where extended-duration formulations are unavailable, products that contain up to 35% DEET are preferred. DEET and sunscreen combination products are not recommended[43]; however, if DEET and sunscreen application are both required, apply the sunscreen first, allowing skin penetration for 20 minutes, followed by DEET application (Canadian Dermatology Association). Consider *P-menthane-3,8-diol* (lemon eucalyptus oil) as a second-line alternative repellent if DEET use is not possible (e.g., for persons allergic to DEET)[44]. Consider soybean oil 2% "blocker" repellents as a third-line repellent where arthropod-borne infections present a significant risk[38, 45]. Picaridin (Bayrepel, KBR 3023, Autan), which is available in Europe and the United States and recommended by the WHO, may be as effective as 15% to 50% DEET[46, 47]. Repellents containing citronella oil are not effective[38].

There are several other ineffective insect personal protection measures, which are **not** recommended[37]:

- electronic (ultrasonic) devices
- wristbands, neckbands and ankle bands impregnated with repellents
- electrocuting devices ("bug zappers")
- odour-baited mosquito traps
- citrosa plant (geranium houseplant)
- orally administered vitamin B1
- skin moisturizers that do not contain an approved active repellent.

Insecticide-Treated Bednets

Given the behaviour of malaria vectors (usually night-active), the proper use of insecticide-treated bednets (ITNs) is a critical personal protective measure for malaria[48, 49], and insecticide (permethrin)-impregnated clothing should be considered[50]. Insecticide-impregnated mosquito netting substantially increases the protection afforded by the net[48,50], since arthropods may still bite through the mesh when the traveller's skin is against it or even pass through the net if they are small enough. The mosquito net should be intact (without tears or large holes), and tucked in under a mattress. The period of effectiveness of pyrethroid-impregnated nets varies from 6 to 12 months, depending on the product used and on the number of launderings[37].

Pyrethroid treatments for bednets are not currently available in Canada but can be obtained from the United States or in several malaria-endemic destinations (such as sub-Saharan African countries). In recent years, long lasting insecticide-treated bednets with durations of efficacy of up to 5 years have become available in sub-Saharan Africa[51].

Pyrethroid-treated netting may be used for more than just beds (e.g., over strollers, playpens and cradles) to protect the very young from mosquito bites. For all children travelling to malarial regions, particular attention should be paid to other personal protective measures, such as protective and permethrin-treated clothing as well as effective insect repellents[37].

Evidence-based medicine recommendations	*EBM rating*
Measures for **all** travellers who are at risk of exposure to arthropod-borne infections • Minimize entry of mosquitoes into work and accommodation areas: place screens on windows, check to ensure that doors are in good repair and closed properly and tightly, and that the walls and the roof are "without holes". • Stay in a mosquito-protected area during the time(s) of day when local mosquitoes are actively biting. • Avoid travelling to a locale during the season that is most strongly (or only) associated with transmission of malaria. • Sleep under insecticide (pyrethroid)-impregnated mosquito nets (in areas where insects cannot be excluded from sleeping area)[48, 50]. • Consider wearing insecticide (permethrin)-impregnated clothing[52].	**B II**
Insecticide (e.g., permethrin)-impregnated mosquito netting substantially increases the protection afforded by the net[48].	**A I**
Physical barriers for **all** travellers who are at risk of exposure to arthropod-borne infections. • Wear long-sleeved shirts (sleeves down, buttoned or zipped, tucked into pants) and long pants (tucked into socks or footwear) to inhibit or prevent mosquito bites. • Dress in light-coloured clothing, which may ward off mosquitoes[53]. • Sleep under a mosquito net that is intact (without tears or large holes), tucked in under a mattress.	**B II**
All travellers at risk of exposure to serious arthropod-borne infections should appropriately use insect repellent containing DEET[38], the preferred insect repellent, unless contraindicated (e.g., allergic reaction).	**A I**

Alternative personal protective measures for **children**: • Use insecticide-impregnated mosquito nets as the first line of defence, especially for infants aged < 6 months. • Use portable mosquito nets, including the self-standing type, placed over a car seat, a crib, playpen or stroller, providing an insect-protected environment for infants. • Consider the judicious use of DEET for children of any age as a complement to the other methods of protection[54].	**A II**
Extended duration DEET formulations have useful advantages over other formulations and, overall, are preferred[41]. If these formulations are unavailable, products that contain up to 35% DEET are preferred.	**B I**
DEET and sunscreen combination products are not recommended[43]; however, if DEET and sunscreen application are both required, apply the sunscreen first, allowing skin penetration for 20 minutes, followed by DEET application[55].	**A II**
Avoid using repellents containing citronella oil[38].	**E II**
Consider *P-menthane-3,8-diol* (lemon eucalyptus oil) as a second-line alternative repellent, if DEET use is not possible (e.g., persons allergic to DEET)[44].	**A II**
Consider soybean oil 2% "blocker" repellents as a third-line repellent where arthropod-borne infections present a significant risk[38].	**A II**
Picaridin (Bayrepel, KBR 3023, Autan), may be as effective as 15% to 50% DEET[46, 47]; however, it is not registered for use in Canada but is available in Europe and the United States.	**A II**
Ineffective insect personal protection measures that are **not** recommended[37]: • electronic (ultrasonic) devices • wristbands, neckbands and ankle bands impregnated with repellents • electrocuting devices ("bug zappers") • odour-baited mosquito traps • citrosa plant (geranium houseplant) • orally administered vitamin B1 • skin moisturizers that do not contain an approved active repellent.	**E II**

4. Prevention – Chemoprophylactic Regimens

Selection of Antimalarial Drugs for Individual Travellers

Malaria causes severe illness, which may be life-threatening. Case-fatality rates associated with *P. falciparum* malaria increase to 20% in severe or complicated cases; therefore, it is preferable to prevent the disease rather than treat someone after symptoms develop. Given the variety of choices in medication, a traveller at risk of malaria should be encouraged to use chemoprophylaxis along with personal protective measures against insect bites[37] (see Chapter 3).

Antimalarial drugs have the potential to cause side effects and should be prescribed only after completion of an individual risk assessment (as outlined in Chapter 2) to ensure that only travellers truly at risk of malaria infection receive antimalarial chemoprophylaxis. In deciding between the various chemoprophylactic options, the health care provider must weigh the traveller's underlying health status; other medications being taken; malaria drug effectiveness; risks for and character of adverse drug reactions; as well as the individual's level of risk avoidance for malaria.

Most users of antimalarial chemoprophylaxis will have no or only minor adverse reactions[56, 57, 58, 59, 60, 61] However, preconceived ideas about side effects may influence the traveller's confidence in a particular medication option and should be considered in the selection process. If adverse events do occur, they can have a significant impact not only on the traveller's health but also on his or her adherence to the medication regimen. One option available is a trial of medication in advance of travel to assess tolerability. To keep adverse effects to a minimum, it is essential that all travellers be well informed about the dosing schedule, including time of day and association with food, as well as precautions regarding sun exposure or other advice, depending on the drug used. While several antimalarial drugs may be equally efficacious when studied in clinical trials, their effectiveness is a measure of protection offered in real life. The more knowledgeable and compliant the patient, the closer the effectiveness will be to the efficacy of a given chemoprophylactic agent.

Fatal malaria has occurred in travellers who have discontinued an effective antimalarial drug in favour of one that is less protective[6, 8, 62, 63]. Therefore, travellers who are tolerating their chemoprophylactic regimen should be advised to continue it regardless of what they are told by other travellers. Medications used in other areas of the world may be less effective or associated with serious adverse effects and are not recommended. Examples include proguanil alone (Paludrine®), pyrimethamine (Daraprim®), dapsone/pyrimethamine (Maloprim®), Chloroquine/proguanil and mefloquine/sulfadoxine-pyrimethamine (Fansimef®).

Selection of Antimalarial Drugs for Specific Regions

Medication should be considered to reduce the risk of travellers acquiring clinical malaria during evening, overnight and/or early morning exposure in the following areas:

Urban and rural areas

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

Low to moderate risk: Haiti, India, Bangladesh, Pakistan, Nepal (Terai region), Bhutan and the Middle East.

Rural areas

Low risk: Southeast Asia; Central and South America; and certain parts of Mexico, North Africa and the Dominican Republic.

Travellers should be informed that antimalarial medication can markedly decrease the risk of acquiring symptomatic malaria[56, 57, 58, 59, 60, 61, 64], but none of these agents can guarantee complete protection. Personal protective measures complement chemoprophylactic drugs[37]. Symptoms due to malaria may occur as early as 1 week after first exposure and as late as several years after travellers leave a malarial region, whether or not chemoprophylaxis has been used. Most travellers who acquire *P. falciparum* infection will experience symptoms within 2 months of exposure[65]. *Falciparum* malaria can be effectively treated early in its course, but delay in therapy may result in a serious and even fatal outcome.

Fever occurring in a traveller within 3 months of departure from a malaria- endemic area is a medical emergency and should be investigated urgently by means of thick and thin blood films. If symptoms persist, these films should be repeated at 12- to 24-hour intervals at least twice.

Although minor differences in expert opinion exist between various jurisdictions (i.e., United States, Europe, Canada), there is universal acceptance that malaria chemoprophylaxis is an essential component of malaria prevention. During travel, many individuals will encounter other travellers or health care providers who will counsel them to change or stop their antimalarial medication (especially mefloquine), leaving them without an acceptable alternative chemoprophylactic and at high risk of acquiring potentially life-threatening malaria. Travellers should be warned of this possibility; as well, the antimalarial guidelines and the risks and benefits of effective chemoprophylaxis should be reinforced. Appendix III, Frequently Asked Questions About Malaria, may aid the practitioner in answering travellers' questions. If desired, this text can be copied and provided to the traveller.

Table 1 summarizes the different chemoprophylactic options according to the presence of drug resistance. Chapter 8 provides details regarding individual chemoprophylactic agents.

Table 1: Malaria chemoprophylaxis regimens for at-risk individuals[a] according to presence of drug resistance

Region	*Drug(s) of choice[b]*	*Alternatives*
Chloroquine sensitive	Chloroquine or hydroxychloroquine	Atovaquone/proguanil,[c] doxycycline[d] mefloquine
Chloroquine resistant	Atovaquone/proguanil,[c] doxycycline[d] or mefloquine	Primaquine[e]
Chloroquine and mefloquine resistant	Doxycycline[d] or atovaquone/proguanil[c]	

a **Important note:** Protection from mosquito bites (e.g., use of bednets, insect repellents) is the first line of defence against malaria for **ALL** travellers.
b See Chapter 8 (Table 6) for adult and pediatric dosing information.
c Contraindicated in pregnancy and insufficient data exist for use in children < 5 kg.
d Contraindicated in pregnancy, during breast-feeding and in children < 8 years.
e Contraindicated in G6PD (glucose-6-phosphate dehydrogenase) deficiency and in pregnancy.

Chloroquine-sensitive regions

Chloroquine-sensitive regions are malarial areas where chloroquine resistance has not been documented or is not widely present. These include Haiti, the Dominican Republic, Central America west of the Panama Canal, North Africa, parts of the Middle East, and west/central China. See individual countries in Appendix I for more specific recommendations.

Drugs of choice: Chloroquine (Aralen®) is the drug of choice for travellers to areas with chloroquine-sensitive malaria. Hydroxychloroquine (Plaquenil®) is an acceptable equivalent alternative[62]. Chloroquine or hydroxychloroquine is taken once weekly, beginning 1 week before entering a chloroquine-sensitive malarial region, during the period of exposure, and for 4 weeks after leaving the malarial region.

Alternatives: For individuals unable to tolerate chloroquine or hydroxychloroquine, atovaquone/proguanil, doxycycline or mefloquine should be used (see next section and Chapter 8).

Chloroquine-resistant regions

The chloroquine-resistant regions refer to most of sub-Saharan Africa, South America, Oceania and Asia. See individual countries in Appendix I for specific recommendations. Note that some border areas of Thailand, Myanmar (Burma), Laos and Cambodia, as well as southern Vietnam, are also mefloquine-resistant regions[20, 66, 67] (see next section).

There are sufficient data in semi-immune and non-immune hosts in various geographic locations to conclude that atovaquone/proguanil, doxycycline and mefloquine are equally efficacious in the prevention of chloroquine-resistant malaria[56, 57, 58, 59, 60, 61].

Drugs of choice: Atovaquone/proguanil, doxycycline or mefloquine[56, 57, 58, 59, 60, 61, 64] (see Table 1 and Chapter 8 for details on each medication).

Atovaquone/proguanil is taken daily, beginning 1 day before entering the malarial region, during the period of exposure, and for 1 week after leaving the malarial region[68].

Doxycycline is taken daily, beginning 1 day before entering the malarial region, during the period of exposure, and for 4 weeks after leaving the malarial region[57].

Mefloquine is taken weekly, beginning 1 week before entering the malarial region (or 3 weeks before, to assess tolerability), during the period of exposure, and for 4 weeks after leaving the malarial region[57].

Alternatives: Although atovaquone/proguanil, doxycycline and mefloquine are well tolerated prophylactic antimalarial drugs[69], for individuals unable to tolerate these drugs primaquine is an acceptable alternative[58]. Primaquine is taken daily, beginning 1 day before entry into the malarial region, during the period of exposure, and for 7 days after leaving the malarial region.

NOTE: Primaquine is CONTRAINDICATED in G6PD (glucose-6-phosphate dehydrogenase) deficiency and CONTRAINDICATED in pregnancy (see Chapters 5 and 8 for details on medication).

Chloroquine- and mefloquine-resistant regions

Resistance to both chloroquine and mefloquine has been reported sporadically from various countries in Asia, Africa and in the Amazon basin. However, it has not been found to be a significant problem except in rural, wooded regions where Thailand borders with Myanmar (Burma), Cambodia[66, 67] and Laos, as well as in southern Vietnam[20, 70]. While these areas are infrequently visited by tourists, use of personal protective measures should be optimized for those travelling there[37].

Drugs of choice: Doxycycline or atovaquone/proguanil (see Table 1 and Chapter 8). Doxycycline is taken daily, beginning 1 day before entering the malarial region, during the period of exposure, and for 4 weeks after leaving the malarial region.

Atovaquone/proguanil (Malarone) has been a successful treatment for multidrug-resistant malaria in Thailand[71], and this medication may be considered for travellers at risk in whom doxycycline is contraindicated or not tolerated. Atovaquone/proguanil is taken daily, beginning 1 day before entering the malarial region, during the period of exposure, and for 1 week after leaving the malarial region.

Alternatives: There are no trials of alternative prophylactic agents for travellers to these areas; therefore, unnecessary travel, especially by pregnant women and preschool children, should be avoided.

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

P. vivax and *P. ovale* parasites can persist in the liver and cause relapses for as long as 5 years after routine chemoprophylaxis has been discontinued[65, 72]. Although considered less virulent than falciparum malaria, *P. vivax* still carries the potential for significant morbidity requiring intensive care[73]. Since most malarial areas of the world (except Haiti and the Dominican Republic) have at least one species causing relapsing malaria, travellers to these areas have some risk of acquiring either *P. vivax* or *P. ovale*. Primaquine decreases the risk of relapses by acting against the persistent liver stages (hypnozoites) of *P. vivax* and *P. ovale*. Primaquine terminal prophylaxis is administered after the traveller has left a malaria-endemic area, usually during or after the post-travel period of chemoprophylaxis. The data pertaining to the risk of relapse are limited. A total of 38 (5.2%) of a 725 US Army Ranger task force of soldiers in Afghanistan were found to have *P. vivax* malaria after leaving Afghanistan, yielding an attack rate of 52.4 cases per 1,000 soldiers. Diagnosis was confirmed at a median of 233 days after return from the malaria-endemic region[73]. Military personnel, long-term travellers and expatriates are groups that warrant consideration for terminal prophylaxis if they have resided in regions with high *P. vivax* endemicity. Any traveller who returns to Canada with a history of a *P. vivax* or *P. ovale* diagnosis while abroad should also be considered for terminal prophylaxis[74]. Primaquine is contraindicated in pregnant women and individuals deficient in G6PD (see Chapter 8 for contraindications and precautions).

Differences in Approaches to Malaria Chemoprophylaxis in Other Jurisdictions

There are more similarities than significant differences between the major expert groups. CATMAT consults all major sources of malaria prevention information, including the WHO[75], the US CDC[20] and the UK Health Protection Agency Advisory Committee on Malaria Prevention (ACMP)[76]. In keeping with the guidelines, CATMAT recommends chloroquine for the prevention of malaria in chloroquine-sensitive regions and atovaquone/proguanil, doxycycline or mefloquine as three equivalent options for the prevention of malaria in chloroquine-resistant regions. The detailed recommendations regarding when to start and stop malaria chemoprophylaxis are also consistent among major guidelines, and they provide the option of emergency standby therapy for travellers who are going to remote areas where they may be unable to access medical assistance within 24 hours.

The differences in guidelines come in some of the details. While guidelines provide detailed country-specific information on malaria risk and malaria chemoprophylaxis recommendations, some recommended regimens may differ from CATMAT guidelines, particularly in countries where malaria risk is lower and chemoprophylactic decisions need to consider drug intolerances as well. For the most part, CATMAT guidelines are consistent with the CDC's *Yellow Book: Health Information for International Travel*[20].

CATMAT guidelines are different from the WHO and ACMP guidelines with respect to drug availability and differences in interpretation of available evidence. In chloroquine-sensitive regions, ACMP recommends proguanil as an alternative to chloroquine; however, proguanil alone is not available in Canada, and CATMAT, CDC and WHO do not recommend its use alone. In areas of low to moderate levels of malaria transmission combined with low to moderate levels of chloroquine-resistance (e.g., parts of South Asia, Southeast Asia, sub-Saharan Africa and South America), WHO and ACMP recommend a combination of chloroquine and proguanil as a first-line chemoprophylaxis. As chloroquine/proguanil chemoprophylaxis has inferior efficacy compared with atovaquone/proguanil, doxycycline or mefloquine[77, 78], CATMAT generally does not recommend this regimen.

Emergency standby therapy for short-term travellers is an option recommended by all guidelines, although CATMAT and CDC have more restrictive criteria as to when it should be used. CDC guidelines only recommend atovaquone/proguanil for this use, whereas WHO, ACMP and CATMAT provide more options for emergency standby therapy. However, CATMAT does not recommend the use of mefloquine for therapy under any circumstances because of the high likelihood of severe adverse reactions when using higher therapeutic doses. While CATMAT recommends standby self-treatment, particularly for travellers taking suboptimal malaria chemoprophylaxis, it is only to be used in the event of suspected malaria in travellers who are unable to access medical assistance within 24 hours. For more information about self-treatment, see Chapter 7.

Coadministration of Antimalarial Drugs with Vaccines

Travellers requiring antimalarial medications may also require vaccination against agents for which live, oral, bacterial vaccines exist. Because such vaccines require bacterial replication to induce a protective immune response, simultaneous administration of antibiotics may interfere with vaccine effectiveness. Doxycycline is an antibiotic and should never be coadministered with any live attenuated oral vaccines. Mefloquine and chloroquine have *in vitro* inhibitory activity against an oral typhoid vaccine[79]. Proguanil has some antibacterial activity, but coadministration of atovaquone/proguanil with live oral typhoid and cholera vaccines to children has demonstrated no decrease in typhoid and cholera antibody response to the vaccine[80]. However, coadministration of proguanil and chloroquine with live oral typhoid and cholera vaccines decreased vaccine immunogenicity[81]. Vaccine efficacy studies measuring the impact on clinical typhoid and cholera of the coadministration of antimalarials other than atovaquone/proguanil with live oral typhoid and cholera vaccines have not yet been performed in children or adults. For chloroquine, mefloquine, atovaquone/proguanil or primaquine, live attenuated oral vaccines should be taken at least 8 hours after taking these antimalarials[79, 81]. Formalin- and/or heat-inactivated oral vaccines (such as Dukoral™) do not contain live bacteria and may be coadministered with antimalarials.

Concurrent use of chloroquine also interferes with the antibody response to intradermal administration of human diploid cell rabies vaccine[82]. If this vaccine is administered to someone taking chloroquine, it is recommended that post-vaccine rabies antibodies be used to verify an adequate immunologic response.

Summary points to keep in mind during the discussion of chemoprophylaxis include the following:

1. *Inform patients that malaria can be fatal, but medications rarely cause serious adverse events if selected and used with care.*
2. *Select a medication that is least likely to exacerbate any past or present medical problems.*
3. *Indicate that medication should be taken in the recommended fashion to minimize significant side effects.*
4. *Discuss the option of a drug trial before travel to check for medication-associated adverse reactions, if this is a concern.*
5. *Discuss strategies to change medication if serious adverse effects should arise during travel.*
6. *Travellers should be presented with all options and given a choice on which chemoprophylaxis they prefer (unless there is a contraindication); all recommended first-line malaria chemoprophylactic regimens are considered to be equally efficacious.*
7. *Travellers should be advised that if a malaria medication is tolerated well they should continue taking it regardless of anecdotal negative rumours about the drug. There is no evidence to suggest that long-term use of currently recommended therapies for short-stay travellers will result in additional risks for severe adverse events.*

Evidence-based medicine recommendations	***EBM rating***
Chloroquine (Aralen®) or hydroxychloroquine (Plaquenil®) is the drug of choice for travellers to areas with chloroquine-sensitive malaria[62]	**A I**
Atovaquone/proguanil, doxycycline or mefloquine are drugs of choice for travellers to areas with chloroquine-resistant/mefloquine-sensitive malaria[56, 57, 58, 59, 60, 61, 64].	**A I**
Atovaquone/proguanil and doxycycline are drugs of choice for travellers to areas with mefloquine resistant malaria[57, 68, 71].	**A I**
Primaquine is recommended for malaria chemoprophylaxis for travellers who are not willing or able to use atovaquone/proguanil, doxycycline or mefloquine in mefloquine-resistance regions[58].	**A I**
Primaquine is recommended as post-travel terminal prophylaxis for travellers who have suffered from vivax or ovale malaria while abroad[74].	**B III**
Better information for travellers about malaria chemoprophylaxis may increase compliance with malaria prevention recommendations and decrease the morbidity and mortality caused by malaria.	**C III**
Stand-by malaria treatment with atovaquone/proguanil or quinine and doxycycline is recommended for travellers who will be more than a day away from malaria diagnostic help.	**C III**
Doxycycline is an antibiotic and should never be coadministered with any live vaccines. Vaccines should be taken at least 8 hours after taking chloroquine, mefloquine, atovaquone/proguanil or primaquine[79, 80, 81].	**B III**
Concurrent use of chloroquine interferes with antibody response to intradermal administration of human diploid cell rabies vaccine[82]. If intradermal rabies vaccine is administered to someone taking chloroquine, it is recommended that post-vaccine rabies antibodies be obtained to verify an adequate immunologic response.	**B III**

5. Prevention in Special Hosts

Malaria Prevention in Children

Travellers should be clearly advised of the risks in taking young children to areas with *P. falciparum* malaria. Many other infectious conditions occur in children that may mimic malaria and delay the diagnosis, but malaria remains an important cause of fever in returning child and adolescent travellers[83, 84]. Among Canadians reported to have malaria since 1999, 20% to 25% are ≤ 19 years old[85], whereas only 9.9% of international travellers are aged ≤ 19 years[86]. As well, severe or complicated malaria, such as cerebral malaria, severe anemia, shock or even death, may develop more quickly in children[87]. According to Canadian Malaria Network data from June 2001 to June 2006, 34% of complicated malaria cases requiring treatment with intravenous quinine were in children; the majority were foreign-born[12].

To reduce the risk of infection when travel to malarial areas is unavoidable, all children, including those who are breast-fed, should be well protected against mosquito bites and, when appropriate, receive appropriate malaria chemoprophylaxis[37] if they are at sufficient risk of infection. Infants do not receive sufficient medication through breast milk to protect them and should be prescribed antimalarial drugs even though their mother is receiving them[88, 89]. Ensuring that young children take antimalarial drugs may be difficult because of the lack of pediatric formulations and the unpleasant taste. Malaria tablets may be crushed and mixed with chocolate syrup, jam, cereal, bananas or formula to mask the taste. Sufficient tablets should be prescribed to allow for a few doses to be vomited or spat out, with clear instructions as to when doses should be repeated. Pre-cut tablets at the pharmacy and/or crushing and insertion into capsules may help increase the accuracy and ease of dosing. Deaths due to inadvertent overdose have been reported with these medications; therefore, they should be kept out of reach of infants and children and stored in child-proof containers[90]. Long-term travelling families should be provided with information to help them adjust the dose of medications, allowing for an increase in weight over time.

Chloroquine remains the preferred agent for chemoprophylaxis in areas with chloroquine-sensitive malaria. Although it is not available in Canada, chloroquine sulfate (e.g., Nivaquine) is widely available as a syrup in malaria-endemic areas. The syrup is often more easily administered than tablets. If parents plan to use this syrup they should be informed that the dose must be carefully determined according to the child's weight and that there is a risk of overdosing.

Mefloquine is one of the drugs of choice in chloroquine-resistant regions; however, there are no studies that specifically analyze its bioavailability and rate of metabolism in children. Although the manufacturer recommends that mefloquine not be given to children weighing < 5 kg, it should be considered for prophylaxis of all children at high risk of acquiring chloroquine-resistant *P. falciparum*, at a dose of 5 mg base/kg once weekly[91]. Young children are less likely to suffer major neuropsychiatric side effects from mefloquine[92] but may be more likely to have emesis[93]. While seizure disorders may be exacerbated by chloroquine and mefloquine, and alternative agents should be used, there is no evidence that febrile seizures in children are a contraindication to these drugs.

Atovaquone/proguanil (Malarone®) is licensed for the prophylaxis and treatment of malaria in children ≥ 11 kg (25 lb) or aged > 3 years[68]. Clinical trials using atovaquone/proguanil to treat malaria in children down to 5 kg suggest it may be safe for infants of this size when the option is required[94]. Daily doses for small infants have been extrapolated from those used in treatment trials

(one-quarter of the treatment dose, or 5 and 2 mg/kg/dose of atovaquone and proguanil components respectively). Based on a pediatric tablet of 62.5 mg atovaquone/25 mg proguanil, the daily doses are ½ pediatric tablet for 5 to 8 kg and ¾ pediatric tablet for > 8 to 10 kg[94].

Doxycycline has been studied as a prophylactic medication in children[95] and can be used at a daily dose of 2 mg/kg (max 100 mg/d) in children ≥ 8 years of age (≥ 25 kg)[88, 96] Primaquine is a consideration for children 9 years of age and older who are unable to take any of the first-line prophylactic agents[58], although it is not licensed in Canada for this indication. As there is no age limitation for primaquine when used for radical cure of *P. vivax* or *P. ovale* maybe it is an option for children of any age as long as they have been screened for adequate G6PD levels. Consultation with a travel medicine or infectious disease expert is advisable unless the prescriber has experience with this medication in the pediatric population.

Evidence-based medicine recommendations	***EBM rating***
Young children should avoid travel to areas with significant transmission particularly of chloroquine-resistant malaria[88].	**C III**
Effective personal protective measures should be strongly encouraged for all children who travel to malaria-endemic areas[38].	**A I**
For children travelling to or residing in chloroquine-resistant areas, mefloquine, doxycycline (≥ 8 yrs) and atovaquone/proguanil (≥ 5 kg) are the drugs of choice for chemoprophylaxis[68, 91, 95, 97].	**A I**
Primaquine chemoprophylaxis is a consideration for children who are unable to take any of the first-line prophylactic agents[58].	**B II**

Malaria Prevention in Pregnancy

Malaria increases the risk of maternal and neonatal death, miscarriage and stillbirth. In addition, low birth weight infants are more frequent among women who are taking ineffective prophylaxis[98]. Pregnant women should defer travel to malaria-endemic areas, particularly to areas with risk of acquisition of drug-resistant falciparum malaria. Pregnant women are twice as likely to be bitten by mosquitoes, thought to be the result of increased body surface temperature, increased CO_2 production and increased likelihood of leaving the protection of the bednet at night[99]. If travel cannot be avoided, special care should be taken, including the use of DEET, which has been shown to be safe in pregnancy, to avoid mosquito bites[100]. In addition, effective chemoprophylaxis should be selected as outlined below.

Doxycycline is contraindicated for malaria prophylaxis during pregnancy because of adverse effects on the fetus, including discoloration and dysplasia of the teeth, and inhibition of bone growth. Attempts to become pregnant should be avoided for a week after completing prophylaxis using doxycycline to allow for complete excretion. Primaquine is also contraindicated during pregnancy (category C - **http://www.perinatology.com/exposures/Drugs/FDACategories.htm**) since the G6PD status of the fetus cannot be established and the drug can be passed transplacentally[96]. Whenever radical cure or terminal prophylaxis with primaquine is indicated in a pregnant woman, chloroquine can be given once a week until delivery, at which time primaquine may be given (see next section on breast-feeding).

Proguanil has long been known to be safe in pregnancy; however, data are lacking on atovaquone. Small malaria treatment trials using atovaquone/proguanil (Malarone®) alone or with artesunate have included women in the second and/or third trimesters of pregnancy. Drug tolerability was good, as were the birth outcomes[93, 101]. Until these data are supported with further trials or experience, atovaquone/proguanil is not routinely recommended during pregnancy. However, when other options cannot be used and the potential benefit outweighs the potential risk to the fetus, it may be considered after the first trimester.

Mefloquine can be used safely for chemoprophylaxis through most of pregnancy. While treatment doses (≥ 5-fold greater than doses for prophylaxis) may be associated with an increased risk of stillbirth[102], the majority of observational and clinical trial data have concluded that the drug does not lead to an increased risk of either stillbirth or congenital malformations at prophylactic doses used during the second and third trimesters[102, 103, 104]. Surveillance data of >1,500 pregnant women found no evidence of increased risk of either teratogenicity or spontaneous abortion when the drug was used at any time from before conception up to and including the third trimester[105]. Although there does not appear to be a concern early in pregnancy, the data are limited before the second trimester. While the use of mefloquine at the time of conception or during the first trimester is not an indication for therapeutic abortion[103, 106], highly risk-averse travellers may choose to avoid pregnancy for up to 3 months after discontinuing mefloquine because of the long half-life of the drug (~3 wks). For expatriates or other long-term travellers in malaria-risk areas, it is safer for both fetus and mother to use effective chemoprophylaxis, given the ongoing risk of disease and the increased risk of severe disease and death during pregnancy[98].

While chloroquine and proguanil are both safe in pregnancy, the combination is ineffective in preventing chloroquine-resistant *P. falciparum* and is not recommended.

Evidence-based medicine recommendations	***EBM rating***
If possible, pregnant women should avoid travel to areas with significant transmission of malaria[98].	**C III**
Personal protective measures, including the appropriate use of DEET and pyrethroid-impregnated bednets, are safe and should be strongly encouraged for all pregnant women who travel to malaria-endemic areas[100].	**A I**
Pregnant women travelling to or residing in chloroquine-sensitive areas should use chloroquine as chemoprophylaxis.	**A I**
Mefloquine is recommended where exposure to chloroquine-resistant falciparum malaria is unavoidable from conception through the first trimester **(A II)**, as well as the second and third trimesters **(A I)**[102, 103, 104].	**A II, A I**
There are no currently approved drugs to prevent malaria in pregnant women travelling to mefloquine-resistant regions. Atovaquone/proguanil (Malarone®) after the first trimester in women who cannot avoid travel to mefloquine-resistant areas (e.g., border areas between Thailand and Cambodia/Myanmar) may be considered after careful discussion of the benefits and risks[93, 101].	**B II**
Although safe in pregnancy, chloroquine and proguanil are inadequate and cannot be recommended in chloroquine-resistant areas[107].	**E I**

Prophylaxis While Breast-Feeding

The availability of antimalarial medication in breast milk is insufficient to provide protection against malaria; therefore, infants requiring chemoprophylaxis should receive a recommended dose of appropriate antimalarial drug. Breast-feeding is not a contraindication for the use of medications that are safe in infancy (chloroquine, mefloquine, atovaquone/proguanil in infants ≥ 5 kg). There is no information on the amount of primaquine that enters human breast milk; therefore, the infant should be tested for G6PD deficiency before primaquine is given to a woman who is breast-feeding. Because of the lack of data on the safety and efficacy of atovaquone in infants weighing < 5 kg, atovaquone/proguanil should not be given to a woman who is breast-feeding an infant of this size unless the potential benefit to the woman outweighs the potential risk to the infant. Limited data are available on the safety of doxycycline use during breastfeeding, but the American Academy of Pediatrics states that no observable effect has been noted in infants of lactating women using tetracyclines, and absorption by the infant is negligible[108].

Evidence-based medicine	*EBM rating*
Infants who are at risk of malaria and who are being breast-fed should receive their own appropriate chemoprophylaxis[94].	**A III**
Atovaquone/proguanil should be avoided if possible in a woman who is breast-feeding a child < 5 kg[94].	**C II**
Limited data suggest that doxycycline absorption through breast milk is negligible and that breast-feeding is not an absolute contraindication to maternal use[108].	**C III**

Malaria Prevention in the Long-Term Traveller or Expatriate

Modern prevention strategies have had a significant, positive impact on the risk of mortality in long-term expatriates, reported to be as high as 60% among missionaries in West Africa during the 19th century[109]. However, the effort to develop unique, evidenced-based guidelines for the long-term (> 6 months) traveller or expatriate has been limited by a lack of medical literature in this area.

Concerns encountered when addressing malaria prevention in long-term travellers and expatriates include safety of the drugs used for chemoprophylaxis, fear of toxic effects with prolonged use of medication, conflicting counsel regarding appropriate chemoprophylaxis and self-treatment, and lack of adherence to chemoprophylaxis, as well as the use of personal protective measures.

The advice of health consultants competes with the opinions of those who assume that their personal experience with adverse events is representative of the general population[110]. Some researchers have observed that the incidence of malaria may be greater among veteran expatriates when compared with their less experienced counterparts. The veterans may have an unreasonable confidence in their clinical self-diagnosis[111] compounded by the impact of false-positive laboratory errors[112]. Counterfeit drugs can also lead to the impression that failure of response is attributed to drug resistance.

Adverse events

At present, there is no evidence to suggest that long-term use of therapies currently recommended for short-stay travellers will result in additional risk of severe adverse events. Chloroquine may

be an exception; however, this drug is seldom indicated currently because of extensive drug resistance. Chloroquine retinopathy is an adverse event experienced by up to 16% of persons using chloroquine treatment for rheumatoid arthritis at a dose far exceeding that used for malaria prophylaxis[113]. However, the cumulative dose may still predispose one to the risk of retinopathy[114, 115]. Lange et al. explored the correlation between the total body burden of chloroquine and the development of retinopathy among 53 missionaries who had taken a median cumulative dose of 300 g[116]. This study failed to demonstrate any association between a weekly chloroquine dosing regimen and retinopathy; however there is a single case report of an expatriate with retinopathy after a cumulative dose of 125 g over 8 years[117]. Although the data supporting long-term use of doxycycline for chemoprophylaxis are limited, the drug is in use for extended periods of time for other indications.

It has been observed that mefloquine tolerance has improved over time, perhaps associated with the relatively early onset of adverse events experienced by those who use mefloquine for prophylaxis [112].

Current malaria prevention practice among expatriates

Malaria chemoprophylaxis use in expatriates is suboptimal. A self-reported summary of malaria prevention strategies of 1,192 long-term expatriates, representing a broad range of government and non-government organizations in sub-Saharan Africa, indicated that their compliance rate was approximately 60% (unpublished data, K. Gamble). Of those receiving chemoprophylaxis, 54% reported changing their prophylactic regimen, 22% because of adverse effects. The severity of side effects was not associated with any specific drug, but the reported incidence of neuropsychiatric side effects was 10% among persons taking chloroquine and proguanil compared with 17% in the mefloquine group. Mefloquine was the only regimen for which participants reported a change in practice based on media influence. Only a small number indicated that availability and cost were factors in their choice of prophylactic regimens. Participants who did not use prophylaxis cited concerns about adverse reactions and long-term effects as the primary reasons for their choice. Personal protective measures were suboptimal: only 38% had screened doors and windows, and 53% used mosquito netting (20% of which were insecticide-treated nets).

Of 336 Canadian expatriates at risk of malaria in tropical countries, only 56% were in compliance with Canadian guidelines, 6.7% did not take any prophylaxis, and 3% asserted that they were not able to tolerate available options (unpublished data, K. Gamble). This is comparable to the outcome of an anonymous, post-deployment survey of US Army Rangers in Afghanistan, where the self-reported compliance rate was 52% for weekly chemoprophylaxis, 41% for terminal (post-deployment) chemoprophylaxis, 31% for both weekly and terminal chemoprophylaxis, 82% for treating uniforms with permethrin and 29% for the application of insect repellent[73].

Support for established guidelines

In general, guidelines for the prevention of malaria in long-term travellers or expatriates should not deviate significantly from standard recommendations for the short-term traveller, though cost will likely limit the use of atovaquone/proguanil.

Data on the incidence of malaria and the effectiveness and tolerance of currently recommended regimens for long-term travellers are limited. Studies of Peace Corps volunteers and studies conducted in chloroquine-resistant regions consistently demonstrate that long-term use of mefloquine is well tolerated and is more effective than chloroquine and proguanil[57, 77, 112, 118].

There is some evidence that better education of travellers has compliance benefits. The incidence of malaria in a cohort of expatriates in Ghana ranged from 1/50 to 1/25 per month between 1993 and 1999 (2%-4%). A malaria prevention program was instituted that included instruction on Canadian guidelines, personal protective measures and self-treatment with self-administered positive rapid diagnostic tests. Surveillance data indicated that the monthly incidence of malaria decreased from 4/1000 in 2000 to 1.7/1000 in 2002 (0.4-0.17%) (unpublished data, K. Gamble).

Insecticide-treated bednets

Long term travellers face challenges in personal protection that differ from those ofshort-term travellers, and these are addressed in Chapter 3. Education about seasonal changes in weather and malaria risk need attention. Rainy seasons require the renewal of the insecticide in bednets, because most long-term travellers are using nets whose insecticide loses its effect after 6 months of use. Liquid permethrin is not available in Canada and must be acquired abroad. The availability of long-lasting insecticide-treated nets in some European countries is an option that can be explored [119].

Rapid diagnostic tests (RDTs)

Without training, there is no reason to believe that the usefulness of these will be any better than that demonstrated in the general travel population[120, 121] (see Chapter 7 for information on malaria diagnosis and RDTs). However, expatriates are often part of a reasonably stable community, which allows for the training of key members on the use of RDTs and the administration of appropriate self-treatment. Caution is warranted as there are no data available from controlled studies on the use of RDTs in the long-term traveller or expatriate populations.

Counterfeit drugs

The production, distribution and sale of counterfeit antimalarial, antiretroviral and other medications are widespread throughout many parts of the Orient, Asia and Africa[122, 123, 124] One-third to one-half of artesunate tablets in Southeast Asia were found to have no active ingredient. Many expatriates purchase their antimalarial drugs over the counter, and they do not have the capacity to evaluate the authenticity of these drugs. Encouragement to purchase brand names may not be adequate[122, 123, 124].

All travellers, and especially long-term travellers, expatriates and missionaries, should be warned about counterfeit drugs. If Coartem®, which is not yet licensed for distribution in Canada but is recommended by the WHO as first-line treatment for falciparum malaria in Africa, is to be recommended, it should be purchased in countries where counterfeiting is unlikely (e.g. Europe). Although atovaquone/proguanil prophylaxis is too expensive for most long-term travellers and expatriates, most could afford one or two courses to ensure that self-treatment is readily accessible.

The counterfeit drug problem is especially important for long-term travellers because they will be dependent for renewal of their antimalarial chemoprophylaxis prescriptions and for stand-by malaria self-treatment drugs from pharmacies in countries where counterfeiting is a problem[122, 123, 124].

Many expatriates purchase their antimalarial drugs over the counter, and they do not have the capacity to evaluate the authenticity of the drugs that they acquire. Counsel to purchase brand names may not be adequate. All expatriates and long-term travellers should be warned about counterfeit drugs and should be encouraged to purchase a supply of medication in countries where strict quality control measures are in place.

Terminal Prophylaxis

Terminal prophylaxis is more of a concern in long-term than in short-term travellers. Expatriates and the military deserve careful consideration. See Chapter 4 Prevention – Chemoprophylactic Regimens for details.

Evidence-based medicine recommendations	*EBM rating*
Guidelines for the prevention of malaria in long-term travellers or expatriates should not deviate significantly from recommendations for short-term travellers[125].	**B III**
Training in the use of rapid diagnostic tests is reasonable for long-term travellers[120, 125].	**C III**
Education about counterfeit antimalarial medications is important for long-term travellers who are more likely to purchase drugs in countries without controls[122, 123, 124].	**C II**
Primaquine should be considered for terminal prophylaxis (see Chapter 8) for military personnel, long-term travellers or expatriates who return from regions with P. vivax transmission[73, 125, 126].	**A I**

Malaria Prevention in Travellers with Co-morbidities

Travellers with underlying medical conditions present a special challenge for a wide variety of reasons. These include the potential for increased susceptibility to and severity of malaria, the deleterious impact of malaria on the underlying condition and the complexity of potential interactions between antimalarials and other medications.

Immunocompromised hosts

i. HIV/AIDS: Recent data suggest a two-way relationship between human immunodeficiency virus (HIV) and *P. falciparum*; each has a deleterious effect on the other. Malaria infection stimulates HIV-1 replication, resulting in increased viral loads that persist for weeks after the infection, although the impact on disease progression is not yet clear[127, 128]. Conversely, it has been shown that those infected with HIV have an increased risk of parasitemia and clinical malaria infection compared with HIV-negative individuals Mathematical modeling suggests large numbers of excess HIV and malaria infections, possibly a result of these interactions. Malaria infection risk and parasite density increase as the immune status deteriorates[128] and appear to be worse in non-immune, non-pregnant individuals than in those with partial immunity[21]. Although the greatest risk of adverse birth outcomes in partially immune women is usually in the first pregnancy, in those with HIV co-infection this risk is spread to all pregnancies[129].

Women who are co-infected with HIV may have a higher risk of mother-to-child HIV transmission as a result of disruption of placental architecture[130]. Unfortunately, malaria treatment failure is greater among HIV-infected adults than HIV-negative adults[131]. Treatment of HIV often includes multiple antiretroviral drugs, several of which (particularly non-nucleoside reverse transcriptase inhibitors and protease inhibitors) may interact with antimalarial drugs, resulting in toxicity from or reduced effec-tiveness of either drug[132]. Overlapping adverse effect profiles may also be problematic[133]. Various antiretroviral drugs may have direct or indirect antimalarial activity, although the clinical utility has yet to be determined[134]. Consultation with a travel or tropical medicine expert in conjunction with the traveller's HIV-specialist is advised.

ii. Asplenia: The spleen facilitates phagocytosis and promotes removal of parasitized red blood cells. Delayed clearance of parasites has been demonstrated in asplenic patients despite the use of effective malaria therapy[135]. Splenectomy increases the risk and magnitude of parasitemia, even among partially immune individuals in malaria-endemic countries[136], and severe malaria has been reported in travellers with asplenia[137]. Standby self-treatment should be considered *in addition* to prophylactic measures if remote regions are being visited and/or access to care is limited (see Chapter 6). Fever in an asplenic individual may represent malaria *or* infection with an encapsulated bacterial organism, so antibacterial standby treatment should also be discussed[132].

iii. Other immunosuppressive conditions: There is limited information about the natural history of malaria in individuals with other immunocompromising conditions. The clinical course of malaria in these individuals is presumably similar to or worse than in other individuals. However, the practitioner must also consider any immunosuppressive medications that are being used, many of which are metabolized in the liver by the microsomal enzymes and thus may interact with certain antimalarial medications. A travel or tropical medicine expert should work closely with the specialist caring for such travellers to advise appropriately.

Other conditions

i. Cardiovascular: Although mefloquine has been reported to cause arrhythmias when used for prophylaxis[138], this has not been confirmed with small studies of the drug in volunteers[139]. There are reports of mefloquine, doxycycline and proguanil potentiating warfarin, resulting in abnormal coagulation and sometimes bleeding[139, 140, 141, 142, 143]. If these medications are used (including proguanil as a component of Malarone®), a medication trial should be done several weeks in advance in order that serial testing of the International Normalized Ratio (INR) can be done to allow adjustment of the anticoagulant dose.

ii. Neuropsychiatric: Seizure disorders may be exacerbated by chloroquine and mefloquine, so alternative agents should be used. There is no evidence that febrile seizures in children are a contraindication for these drugs. Concurrent use of anticonvulsant drugs that induce hepatic microsomal enzymes (e.g., barbiturates, phenytoin, carbamazepine) may decrease serum levels and half-life of doxycycline, and may require a dosage adjustment[143] (see Chapter 8). Mefloquine may be associated with an increased risk of psychiatric conditions, including depression and anxiety disorders, and therefore careful history-taking is needed to rule out such conditions before mefloquine is used[144]. There are no data demonstrating that attention deficit disorder increases the risk of neuro-psychiatric side effects; however, it is prudent to ensure that psychiatric conditions such as those noted above do not co-exist[93].

iii. Hepatic or renal dysfunction: Moderate to severe hepatic or renal dysfunction may result in significant alteration in antimalarial medication levels. If either the liver or kidneys are compromised, there must be careful consideration given to the selection and dose of medications for the prophylaxis and treatment of malaria. If the course of action is unclear after review of a standard reference, consultation with a travel medicine expert is recommended.

Evidence-based medicine recommendations	*EBM rating*
Individuals who are immunosuppressed or have other co-morbidities should consult with a travel medicine or infectious disease expert in conjunction with the principal physician for their underlying condition[20].	**B III**
Potential drug interactions warrant careful review before antimalarial drugs are prescribed for an HIV-infected individual[133].	**A I**
An advance trial with INR testing should be done if mefloquine, doxycycline or proguanil (including atovaquone/proguanil) are to be used in individuals taking warfarin[140, 141, 142, 143].	**A II**
Mental health conditions should be carefully elicited to ensure that psychotic, depressive or anxiety disorders are absent before mefloquine use is considered[144].	**A I**

6. Malaria Diagnosis

Falciparum malaria can be rapidly fatal, particularly in the non-immune host, and is the most urgent diagnosis to confirm or exclude in the febrile traveller who has been in a malarial zone. Although other signs and symptoms may be present in patients with malaria, they are neither sensitive nor specific. For example, fever is frequently not cyclic, and splenomegaly is rarely present early in the course of *P. falciparum* malaria[145]. Clinical assessment, even by experts, cannot reliably confirm or exclude a diagnosis of malaria[146]. Most cases of *P. falciparum* present within 2 to 3 months of exposure, although clinical presentation may be delayed in travellers who have taken chemoprophylaxis. Other malaria species may present as late as several years after exposure.

It is critical that any traveller who has been in a malaria-endemic area, particularly within the previous 3 months, and who develops an unexplained fever should be strongly advised to present for medical and laboratory assessment within 24 hours and should inform his or her health care provider of the relevant travel history. Travellers should be informed of this as part of their pre-travel assessment. Physicians should include a travel history in the assessment of febrile patients.

Confirmation or exclusion of a diagnosis of malaria depends upon laboratory examination of a blood sample. The standard test involves microscopic examination of thick and thin blood smears. Accurate blood smear examination requires considerable training and experience, particularly in the interpretation of the thick smear and in the speciation of identified parasites. Lack of experienced personnel may limit the accuracy of malaria diagnosis in laboratories in Canada[147], while diagnosis in low-income countries is often unreliable because of problems with the quality of the microscope or the stains, and supervision and quality control of the laboratory[148]. For example, among Peace Corps volunteers whose malaria was diagnosed by blood smear in local clinics in Africa, the diagnosis could be confirmed in only 25% of cases[112].

When malaria is suspected in Canada, a result indicating the presence or absence of malaria and, in most cases, the species should be available within 1-2 hours of the receipt of a blood specimen by the laboratory[148]. In a minority of cases, when the level of parasitemia is low, an initial smear may be falsely negative, requiring one or two additional smears at 12- to 24-hour intervals to confirm or exclude the diagnosis. It is important to obtain repeat smears at regular intervals rather than potentially delay the diagnosis by attempting to time sample taking with the fever cycle[149].

An essential element of malaria smear interpretation is the speciation of the parasite. Correct speciation may be critical to the correct choice of life-saving treatment and other decisions, such as hospitalization. Quantitation of parasitemia is also important for initial determination of the need for parenteral treatment or, exceptionally, the use of exchange transfusion and the need for admission to an intensive care unit. Finally it is important for monitoring treatment of *P. falciparum* infections.

Rapid Diagnostic Tests

RDTs do not require microscopy or specialized laboratory skills and can play a valuable adjunctive role in the diagnosis of malaria[150]. A variety of rapid diagnostic tests are licensed by Health Canada for use in Canada[151]. RDTs are immunochromatographic assays that use monoclonal antibodies to capture malaria antigens in a patient sample, producing a visible colour change. All tests include a positive control band that becomes visible as the sample migrates along the strip. The absence of a control band is indicative of an invalid test, but the presence of a visible control band does not assure reliability[152].

These tests require small volumes of blood (2-50 µL) and can be done on fingerstick specimens or on anticoagulated blood or plasma. The current targets for RDTs are histidine-rich protein-2 of *P. falciparum* (PfHRP-2) or enzymes from the parasite glycolytic pathway (e.g., parasite-specific lactate dehydrogenase [pLDH] or *Plasmodium* aldolase, also called pan malarial antigen). Lactate dehydrogenase-based tests may detect all species of malaria or may be specific for *P. falciparum* or *P. vivax*. Combinations of target antigens can be used to detect infection due to *P. falciparum*, *P. vivax*, mixed *P. falciparum/P. vivax* or mixed *P. falciparum* with non-falciparum species. To date, tests specific for *P. malariae* and *P. ovale* are not available[153].

Although some of these tests were originally developed for use by travellers who would not have access to effective malaria diagnosis during travel, their reliability in this setting has proved suboptimal. Significant proportions of travellers are unable to complete the test procedure or interpret the results correctly[154, 155], and rates of false-negative results are unacceptable[156]. However, when used by trained laboratory staff, these tests can contribute to the rapid diagnosis of malaria pending confirmatory testing with microscopy and/or polymerase chain reaction (PCR)[150].

Operating characteristics of RDTs reported in the literature show significant variability. In general, RDTs perform best in the detection of *P. falciparum* with sensitivities in the range of 88%-100% and specificities of 92%-95%[157]. At parasite densities below 100/µL, sensitivity is decreased, with sensitivities of < 70% at parasite densities less than 50/µL[138]. The sensitivity for the detection of *P. vivax* is inferior to that of *P. falciparum*. For *P. vivax*, the data are limited, but the threshold for satisfactory detection of parasitemia may be higher (> 1,000 parasites/µL)[154].

RDTs cannot be recommended as a means of assessing the response to antimalarial therapy. PfHRP-2 persists for prolonged periods after clearance of asexual stage parasites from blood with 68% positivity at 7 days and 27% positivity at 28 days after initiation of therapy[158]. Parasite aldolase-based tests also remain positive after clearance of asexual stage parasites and may remain positive even longer than PfHRP-2 based tests.

The advantage of RDTs is that they are simple to use, can be performed by laboratory staff who are untrained in malaria microscopy and require no equipment. However, inaccurate results can occur if instructions are not followed carefully. Results must be read according to the time frame specified by the manufacturer, as test lines may become positive several hours after the test is performed in the absence of true parasitemia. Heat and humidity can damage the test system; therefore, test packages must be opened immediately before use.

The presence of autoantibodies such as rheumatoid factor, heterophile antibodies and anti-mouse antibodies have been shown to give false-positive results in some test kits. The likelihood of a false-positive result in the presence of rheumatoid factor varies with the test antibody. Occasional reports of negative RDTs in patients with high grade parasitemias are likely due to prozone phenomenon in which an excess of antigen masks the test antibody[150, 159]. Occasionally there may be cross-reaction between species, for example, the aldolase- or pLDH-based tests with falciparum and non-falciparum bands may give a positive reaction on both bands when only *P. falciparum* infection is present, making accurate diagnosis of mixed infections difficult[157]. Geographic variation between *P. falciparum* stains could also affect test sensitivity[160].

Polymerase Chain Reaction (PCR)

Although not practical for immediate patient care because of limited availability, PCR is emerging as the gold standard for both high sensitivity and specificity, as well as speciation (Table 2). It is increasingly used for "quality control". PCR techniques (e.g., real-time PCR) providing more rapid results are likely to become more available in the near future[131, 162, 163].

Table 2: Comparison of diagnostic tests for malaria

	Approximate parasite density threshold	*Speciation*	*Accessibility*	*Resistance detection*
Microscopy – thick films	50/µL (0.001%)	Fair	Limited	No
Microscopy – thin films	> 100/µL (0.002%)	Good	Limited	No
RDTs	> 100/µL (0.002%)	+/- (limited)	Good	No
PCR	5/µL (0.0001%)	Good	Poor	Yes

Evidence-based medicine recommendations	*EBM rating*
Suspected malaria should be considered a medical emergency, particularly if there is evidence of organ dysfunction, such as altered mental status[147, 164, 165, 166].	A II
Travellers to malaria-endemic areas should be advised to present themselves for medical attention, including laboratory assessment, as soon as possible but always within 24 hours of onset of an unexplained fever, particularly within the first 2 to 3 months after return, and to inform their health care provider of their travel history[147].	A III
Malaria should be suspected in any patient with a history of travel to a malaria-endemic area and a history or finding of fever[146].	A III
Blood should be sent immediately for malaria examination if malaria is suspected. If expertise in reading malaria smears is not available at the site where the patient presents, diagnosis should involve the local use of an RDT and then the rapid transfer of a blood sample to a reference centre. The result of the RDT or initial blood smear should be available within 2 hours of bloodtaking[150].	A III
If the initial smears are negative, an additional two smears should be taken and examination repeated at 12- to 24-hour intervals[167].	B III
A thin smear should be examined under oil emersion for 15-20 minutes (200-300 oil immersion fields at 100 times magnification) and a thick smear for 5-10 minutes (200-300 oil immersion fields at 100 times magnification) by someone experienced in analysis of thick smears, before the smears are declared negative for malaria[168, 169].	A III
A laboratory should provide the blood smear interpretation as positive or negative with parasite quantification within 1-2 hours of the blood reception and should provide speciation within 12 hours, if this is not possible immediately[167, 168].	B III
RDTs are essential diagnostic tools in regions of Canada where malaria microscopy results are not available within 2 hours[147].	B III
RDT results (both positive and negative) must be verified by expert microscopy or PCR to determine the level of parasitemia and species identification. Parasitemia levels are essential for patient management of falciparum malaria[170, 171].	A II
RDTs should not be used to assess response to therapy[172, 173].	E II
RDTs should not be routinely recommended to travellers[120, 147, 154].	D II

7. Treatment of Malaria

Uncomplicated malaria refers to symptomatic malaria without evidence of severe disease or evidence of vital organ dysfunction. The objective of treating uncomplicated malaria is to cure the infection. This is important since treatment will, in cases of *P. falciparum*, help prevent progression to severe disease. When choosing treatment regimens, drug tolerability, the adverse effect profile and the speed of therapeutic response are important considerations.

Severe or complicated malaria refers to symptomatic malaria with hyperparasitemia (≥ 5%) or evidence of end organ damage/complications, as listed in Table 3. The primary objective of treatment is to prevent death. For cerebral malaria, prevention of neurological deficits is also an important objective.

In the treatment of severe malaria in pregnancy, saving the life of the mother is the primary objective. The prevention of recrudescence and avoidance of minor adverse effects are secondary.

In Canada, all patients (especially children) with malaria due to *P. falciparum* should be considered for admission to hospital or should receive initial treatment in an observation unit to ensure that treatment can be tolerated and to confirm decreasing parasitemia with treatment. Severe or complicated disease (Table 3) or the inability to tolerate oral therapy requires parenteral therapy and close clinical monitoring, preferably in an intensive care unit. If required, assistance in the management of malaria cases can be obtained through access to the Canadian Malaria Network (CMN) in the appropriate area (see contact information in Appendix V).

Table 3: Criteria for severe falciparum malaria*

Clinical manifestation	*Laboratory test*
Prostration/impaired consciousness	Severe anaemia (haematocrit < 15%; Hb ≤ 50 g/dL)
Respiratory distress	Hypoglycaemia (blood glucose < 2.2 mmol/L)
Multiple convulsions	Acidosis (arterial pH < 7.25 or bicarbonate < 15 mmol/L)
Circulatory collapse	Renal impairment (creatinine > 265 umol/L)[180]
Pulmonary oedema (radiological)	Hyperlactataemia
Abnormal bleeding	Hyperparasitaemia (> 5%)
Jaundice	
Haemoglobinuria	

* In a patient with *P. falciparum* asexual parasitemia and no other obvious cause of symptoms, the presence of one or more of the clinical or laboratory features in the Table classifies the patient as suffering from severe malaria.

Adapted from: *Guidelines for the treatment of malaria*, World Health Organization. 2006, Geneva[126].

General Principles of Management

The initial management of the patient depends on many factors, including the infecting species of malaria, the severity of infection, the patient's age, the pattern of drug resistance in the area of acquisition, as well as the safety, availability and cost of antimalarial drugs. At times, management decisions may be necessary before parasitology laboratory results become available. When managing malaria, there are three questions that need to be addressed in order to initiate effective treatment:

1. **Is this infection caused by *P. falciparum*?**
   Treatment varies according to the species of malaria (see below).
2. **Is this a severe or complicated infection? (see Table 3)**
   Severe or complicated malaria usually requires parenteral therapy and sometimes an exchange transfusion. Parenteral artesunate and/or quinine are available through the CMN (see Appendix V).
3. **Has the infection been acquired in an area of known drug-resistant malaria? (see Appendix I)**
   Treatment should be adjusted accordingly.

Management of Falciparum Malaria

The following guidelines have been derived, in part, from the WHO Guidelines for the Treatment of Malaria[126] and Management of Severe Malaria [175]. The interested reader is referred to these documents for a more detailed discussion of these issues.

As a rule, all non-immune patients and all children with *P. falciparum* malaria, whether severe or not, should be considered for admission to hospital in order to ensure that antimalarial drugs are tolerated and to detect complications or early treatment failure. If hospital admission is not planned, then all cases must be observed during their first dose of therapy to ensure that the drug has been tolerated before discharge from the emergency department. To prevent adverse outcomes, prior to discharge further treatment doses should be provided, or the patient should be directed to a pharmacy that can fill the prescription appropriately. An algorithm for the management of malaria is presented in Figure 1. This algorithm is based on two essential requirements, a timely (within 2 hours) parasitology laboratory result, and the timely (within 1-2 hours) availability of an appropriate antimalarial drug. Malaria management when these important prerequisites are not available is discussed below. Treatment of malaria does not stop with the selection of appropriate antimalarial medications. For all malaria cases clinical assessment should be carried out daily until fever ends, and at any time there is a recurrence of symptoms; for *P. falciparum* cases, repeat malaria smears should be carried out daily until negative.

Severe malaria

Severe malaria is usually due to falciparum infection. Although *P. vivax* is considered to be a benign infection, it very occasionally leads to severe disease, including severe anemia, severe thrombocytopenia, pancytopenia, jaundice, splenic rupture, acute renal failure and acute respiratory distress syndrome[176, 177, 178, 179]. Prompt and effective treatment and case management should be the same as for severe and complicated falciparum malaria (see next).

Severe *P. falciparum* infections may have a mortality rate of 20% or higher. Patients with these infections require immediate hospitalization and urgent, intensive medical management, ideally, in an intensive care unit[180]. Clinical observations should be made as frequently as possible and should include vital sign monitoring, with accurate assessment of respiratory rate and pattern, coma score and urine output. Blood glucose should be monitored every 4 hours using rapid stick tests, especially in unconscious patients. Seizures should be treated promptly with benzodiazepines; however, there is no role for prophylactic antiseizure medication[126]. Individuals with severe falciparum malaria are at risk of all the adverse outcomes defined in Table 3, as well as other adverse outcomes, including permanent neurologic deficits, chronic renal insufficiency and death.

Two classes of drugs are effective for the parenteral treatment of severe malaria, cinchona alkaloids (quinine and quinidine) and the artemesinin derivatives (artesunate, artemether and artemotil). A recent report of an open-labeled, randomized controlled trial in 1,461 patients with severe falciparum malaria in Asia demonstrated a 35% reduction in mortality (15% vs 22%). The authors, along with the WHO, advocate that artesunate should become the treatment of choice for severe falciparum malaria in adults[126,133, 181].

All patients with **severe** *P. falciparum* infections and all those who are unable to tolerate drugs orally should receive parenteral therapy. Intravenous artesunate and/or quinine (see Table 4) are available 24 hours per day through the CMN (see Appendix V for more information). When available, the use of parenteral artesunate is preferable to parenteral quinine for 1) the treatment of severe malaria, 2) when the patient is unable to take or tolerate oral medications or 3) when there is a quinine intolerance, contraindication or failure. If neither parenteral artesunate nor parenteral quinine or quinidine is available within an hour of the diagnosis of severe malaria, oral quinine can be started, if necessary after a dose of an anti-emetic to decrease the risk of vomiting or by nasogastric tube, while awaiting parenteral therapy. Parenteral quinine is preferred over quinidine because the cardiotoxicity of quinidine requires electrocardiographic monitoring and dose reduction with cardiac toxic effects (infusion rates should be decreased if the corrected QT interval is prolonged by more than 25% of baseline). When quinine or quinidine is administered to a patient who has taken mefloquine or halofantrine in the previous 2 weeks, there is a risk of drug-induced cardiac arrhythmia; such patients should not receive a loading dose of therapy and should be monitored electrocardiographically.

Many ancillary treatments have been suggested for the management of severe malaria, but few have been shown to improve outcome[126]. Fluid resuscitation should be individualized on the basis of estimated deficit. The optimal rate of resuscitation, the role of colloids versus crystalloids, and the optimal electrolyte composition of the resuscitation solution have not been established. Hypoglycemia (potentially exacerbated by quinine therapy, which stimulates insulin release) should be suspected in any patient who deteriorates suddenly and should be treated immediately. The use of steroids to treat severe or cerebral malaria has been associated with worse outcomes and should be avoided[182]. In cases of complicated *P. falciparum* infection with high parasitemia (> 10%), exchange transfusion has been used on an experimental basis as a potentially life-saving procedure. The rational for the use of exchange blood transfusion includes the following: 1) the removal of infected red blood cells (RBCs) from the circulation and thereby reduction of the parasite load; 2) rapid reduction of the antigen load and burden of parasite-derived toxins and metabolites; 3) removal of host-derived toxic mediators; and 4) replacement of rigid unparasitized RBCs with normal functioning cells, which thereby reduces microcirculatory obstruction. Exchange blood transfusion requires a safe blood supply, intensive nursing and multiple units of packed red blood cells (PRBC). There is no consensus on the indications or on the volume of blood to be exchanged; however, a volume of 5-10 PRBC units should be anticipated[183, 184]. When managing a patient with severe or complicated falciparum malaria, consultation with an infectious or tropical disease expert is strongly recommended (see Appendix V for contact information for the CMN).

Table 4: Chemotherapy of severe or complicated *P falciparum* malaria

Parenteral artesunate therapy andlor quinine is available 24 hours per day through the Canadian Malaria Network. For contact information see Appendix V or http:llwww.phac-aspc.travelhealth.gc.ca Note: A switch to oral therapy should be made as soon as possible.

PARENTERAL ARTESUNATE

Artesunate is given, over 1-2 minutes, as a 2.4 mg/kg intravenous bolus at 0, 12, 24 and 48 hours, and then therapy is continued with oral medications (e.g., doxycycline, atovaquone/proguanil or clindamycin). If oral medications are not possible, daily artesunate doses can continue for a total of 7 days

PLUS (start 4 hours after final dose of artesunak)

1. Atovaquone/proguanil: adults, 4 tablets daily for 3 days; pediatric, 20 mg/kg atovaquone and 8 mg/kg proguanil once daily x 3 days

OR

2. Doxycycline: adults, 100 mg orally twice daily for 7 days; pediatric dose, 2 mg/kg (to a maximum of 100 mg) twice daily (contraindications: pregnancy, breast-feeding or if age < 8 years).

OR

3. Clindamycin: 10 mg/kg (loading dose) intravenously, followed by 5 mg/kg every 8 hours for a total of 7 days (should be used only if patient is unable to take doxycycline or atovaquone/proguanil).

PARENTERAL QUININE*

1. **If an infusion pump is available:** quinine (base) 5.8 mg/kg loading dose (quinine dihydrochloride [salt] 7 mg/kg) intravenously by infusion pump over 30 minutes followed immediately by 8.3 mg base/kg (quinine dihydrochloride [salt] 10 mg/kg) diluted in 10 mL/kg isotonic fluid by intravenous infusion over 4 hours (maintenance dose), repeated 8 hourly until the patient can swallow, then quinine tablets to complete 3 to 7 days of treatment (7 days for SE Asia).
2. **Without an infusion pump:** quinine (base) 16.7 mg/kg loading dose, (quinine dihydrochloride [salt] 20 mg/kg) by intravenous infusion over 4 hours, then 8.3 mg base/kg (quinine dihydrochloride [salt] 10 mg/kg) diluted in 10 mL/kg isotonic fluid by intravenous infusion over 4 hours (maintenance dose), repeated 8 hourly until the patient can swallow, then quinine tablets to complete 5 to 7 days of treatment (7 days for SE Asia).

PLUS (either concurrently or immediately after quinine)

3. Atovaquone/proguanil: 4 tablets once daily for three days (see Table 6, Chapter 8, for pediatric dosage).

OR

4. Doxycycline: 100 mg orally twice daily for 7 days; pediatric dose, 2 mg/kg (to a maximum of 100 mg) twice daily (contraindications: pregnancy, breast-feeding or if age < 8 years).

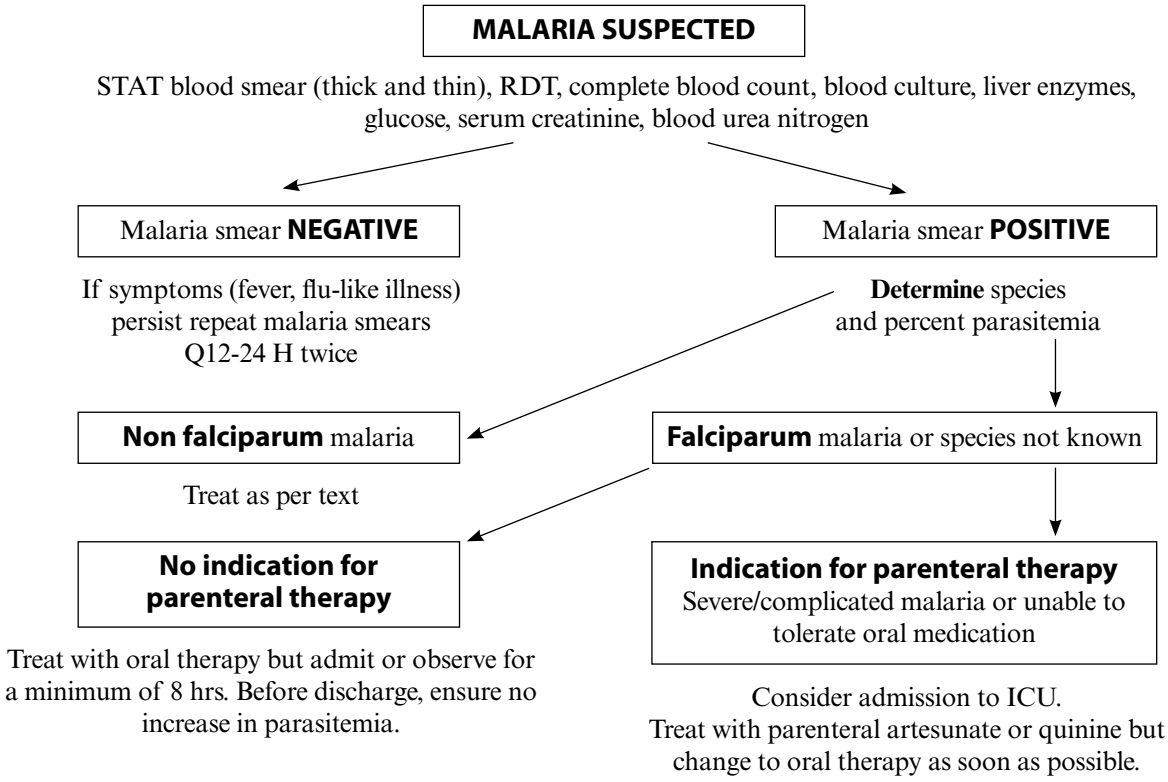
OR

5. Clindamycin: 10 mg/kg (loading dose) intravenously, followed by 5 mg/kg every 8 hours until blood is clear of sexual parasites (should be used only if patient is unable to take doxycycline or atovaquone/proguanil).

*Loading dose should not be used if patient received quinine or quinidine within the preceding 24 hours or mefloquine within the preceding 2 weeks. Parenteral quinine dihydrochloride may be obtained through the Canadian Malaria Network (see Appendix V for contact information). Switch to oral therapy as soon as possible. In patients requiring > 48 hours of parenteral therapy, reduce the quinine maintenance dose by one-third to one-half.

Note: Parenteral quinidine should be used only if parenteral quinine is unavailable. Because of increased risk of cardiac toxic effects with quinidine, cardiac monitoring is required. Parenteral quinidine gluconate may be obtained on a patient-by-patient basis with authorization from the Special Access Programme, Therapeutic Products Directorate, 2nd Floor, Holland Cross, Tower A 11 Holland Ave., A.L. 3002C Ottawa, ON, K1A 0K9. **TEL:** (613) 941-2108 **FAX:** (613) 941-3194; **'-MAIL:** SAPdrugs@hc-sc.gc.ca (613) 941-3061 (after hours).

Figure 1: Algorithm for the management of malaria



Uncomplicated P. falciparum

Uncomplicated cases of *P. falciparum* can progress to severe malaria if not treated and monitored properly. Infections acquired in a chloroquine-sensitive zone may be treated with chloroquine alone (as per Table 6, Chapter 8). The WHO advocates the use of oral combination therapy containing artemesinin derivatives as the first choice for oral therapy[126]. Until these agents are available in Canada, infections possibly or definitely acquired in drug-resistant regions (most cases of *P. falciparum* malaria seen in Canada) should be treated with atovaquone/proguanil or quinine and a second drug (preferably doxycycline). If the patient can tolerate quinine orally, quinine and doxycycline (or clindamycin for those in whom doxycycline is contraindicated) should be administered simultaneously or sequentially (start quinine first). If oral medication cannot be tolerated, parenteral artesunate or quinine should be administered as per Table 6, Chapter 8.

Management of Non-Falciparum Malaria (*P. vivax, P. ovale, P. malariae, P. knowlesi*)

Chloroquine remains the treatment of choice for non-falciparum malaria outside of New Guinea (Papua New Guinea and Papua [Irian Jaya]) as per Table 6, Chapter 8. A clinical assessment should be carried out daily until fever ends and any time there is a recurrence of symptoms. A recurrence of asexual parasitemia < 30 days after treatment suggests chloroquine-resistant *P. vivax*; recurrence after 30 days suggests primaquine-resistant *P. vivax*.

Recent reports have confirmed the presence and high prevalence (80%) of chloroquine-resistant *P. vivax* in Irian Jaya. Sporadic cases of chloroquine-resistant *P. vivax* malaria have been reported elsewhere (e.g., in Indonesia, Papua New Guinea, the Solomon Islands, Myanmar and Guyana[72]). At present, chloroquine can no longer be relied upon either for chemoprophylaxis or treatment of *P. vivax* acquired in New Guinea, and the optimal treatment

is unknown. A 7-day course of quinine is often required to cure *P. vivax* infection from New Guinea[126, 175]. Mefloquine and halofantrine have been shown to be efficacious in small clinical trials, but each is limited by safety issues associated with therapeutic doses[126].

Standard chloroquine doses (25 mg base/kg over 72 hours) combined with high-dose primaquine (0.5 mg base/kg daily for 14 days) have been suggested as treatment for chloroquine-resistant *P. vivax* acquired in Irian Jaya but have failed in cases from Guyana. Limited data also suggest that a combination of standard dose atovaquone/proguanil (4 tablets daily x 3 days) in combination with primaquine (0.5 mg base/kg daily x 14 days) may be effective[185]. Expert advice from an infectious or tropical disease specialist should be sought for the management of these cases (see CMN contact information, Appendix V).

Management of Malaria When Laboratory Results or Treatment Drugs Are Delayed

When a case is diagnosed as a severe or complicated *P. falciparum* infection and parenteral quinine or artesunate is indicated but will not be available for more than an hour, it is appropriate to start quinine orally (after a dose of gravol or by nasogastric tube if necessary) until the parenteral drug becomes available. If fever, travel history and initial laboratory findings (low white blood count and/or platelets) suggest a diagnosis of malaria and the malaria smear is delayed more than 2 hours, it is appropriate to start an antimalarial.

Primaquine Treatment

P. vivax and *P. ovale* have a persistent liver phase (hypnozoites) that is responsible for relapses and susceptible only to treatment with primaquine. Relapses caused by the persistent liver forms may appear months and, rarely, up to 5 years after exposure. None of the currently recommended chemoprophylaxis regimens will prevent relapses due to these two species of *Plasmodium*. 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". The possibility of G6PD deficiency should be excluded before antirelapse therapy with primaquine is given. A recent retrospective study of 63,302 US army personnel found G6PD deficiency in 2.5% of males and 1.6% females. The highest rates were among African American males (12.2%), followed by Asian males (4.3%), African American females (4.1%), Hispanics (males 2%; females 1.2%), and Asian females (0.9%). The rates among Caucasians were low (0.3% males and 0/4018 females). None had class I deficiency; however, 46 males and one female had class II deficiency, which can be associated with severe, life-threatening hemolysis[186].

In patients with known or suspected G6PD deficiency, expert medical advice should be sought, since primaquine may cause hemolysis in such patients. Primaquine use is contraindicated in pregnancy. *P. vivax* or *P. ovale* infections during pregnancy should be treated with standard doses of chloroquine (Table 6, Chapter 8). Relapses can be prevented by weekly chemoprophylaxis with chloroquine until after delivery, when primaquine can be safely used for mothers with normal G6PD levels.

Primaquine is not routinely recommended to prevent relapsing malaria in asymptomatic returning travellers (terminal prophylaxis). However, it is generally indicated for people with prolonged exposure in malaria-endemic areas where vivax or ovale malaria occurs (e.g., long-term travellers or expatriates, see Chapter 5). For terminal prophylaxis, primaquine is administered after the traveller has departed from a malaria-endemic area, usually during or after the last 2 weeks of chemoprophylaxis (see Chapter 3 and Table 6 for dosage recommendations).

P. vivax isolates with a decreased responsiveness to primaquine are well documented in Southeast Asia, in particular Papua New Guinea and Papua. Recently, primaquine radical treatment failure has

been reported from Thailand and Somalia. As well, there have been reports of primaquine radical treatment failure from other areas[187]. Therefore, the recommended dosage of primaquine to prevent relapse has increased to 30 mg (0.5 mg/kg) base daily for 14 days.

Blood infection with *P. malariae* may persist for many years, but it is not life-threatening and is easily cured by a standard treatment course of chloroquine (see Table 6).

Plasmodium knowlesi has emerged as a threat in Southeast Asia. It can be confused by microscopists as *P. malariae* but has a higher (> 1%) parasitemia than is seen in *P. malariae* infections. Systemic symptoms and complications can mimic *P. falciparum* malaria. It is suggested that patients from Southeast Asia with parasite levels > 1% and a parasite morphology resembling that of *P. malariae* be diagnosed as *P. knowlesi*. Treatment with chloroquine is reportedly effective, but systemic symptoms and complications similar to hyperparasitemic *P. falciparum* infections require very close monitoring and careful management[1, 188].

Evidence-based recommendations	***EBM rating***
The treatments of choice for uncomplicated *P. falciparum* malaria include • Oral atovaquone/proguanil[126] • Oral quinine combined with oral doxycycline or clindamycin[126] • Combination therapy with an artemesinin derivative (not yet available in Canada)[126]	B III
• Primaquine phosphate (30 mg base daily for 2 weeks) should follow a chloroquine treatment of *P. vivax* and *P. ovale* malaria to prevent relapses[189]	B I
• Parenteral artesunate is recommended as first-line treatment for severe/complicated *P. falciparum* malaria, with parenteral quinine combined with doxycycline or clindamycin as an alternative treatment[190].	A I
• Exchange transfusion may have benefits for treating hyperparasitemic cases of *P. falciparum*[184].	C III
• The use of steroids to treat severe or cerebral malaria has been associated with worse outcomes and should be avoided[182].	E I

Self-treatment of Presumptive Malaria

Self-treatment of malaria has received little study, yet it is a frequent occurrence that demands guidelines and good advice for the traveller. Counsel is of particular value for all travellers to regions of high malaria endemicity, remote access or limited medical resources. Ninety percent of global episodes of malaria morbidity and mortality occur in sub-Saharan Africa; therefore, particular focus should be given to persons travelling to that region. Reasons for self-treatment include travel to remote regions where health care is a problem and travel to regions where malaria risk is small and the traveller would rather use self-treatment rather than long-term prophylaxis[125, 191, 192, 193]. If presumptive self-therapy is prescribed, the traveller should be informed of the following points.

- ☐ Travellers to high-risk regions should never rely exclusively on a self-treatment regimen[20, 75, 193, 194].
- ☐ Individuals at risk of malaria and unable to seek medical care within 24 hours or adequate malaria treatment drugs should carry medication for self-treatment of presumptive malaria[193].

- The signs and symptoms of malaria are non-specific; malaria can be mimicked by influenza, dengue, typhoid, meningitis and febrile gastroenteritis.
- Self-treatment should never be undertaken lightly as there are potential adverse reactions to malaria therapy.
- Neither expatriates nor physicians can diagnose malaria without a malaria laboratory test[121, 195, 196].
- A combination drug treatment is better than a single drug[126].
- Although not recommended by the WHO, semi-immune locals may benefit from partial treatment; the non-immune traveller must always take full treatment[126].
- Both false-negative and false-positive malaria smears are reported to varying degree by all malaria diagnostic laboratories.
- Self-treatment is *not* definitive treatment but, rather, a temporary, life-saving measure while medical attention is sought within 24 hours.
- Presumptive treatment with a drug being used by the traveller for suppression is not appropriate[20, 125, 193].

Evidence-based recommendations	***EBM rating***
For individuals in chloroquine-sensitive regions, whether using chloroquine as prophylaxis or not, self-treatment with chloroquine should be taken and then chloroquine prophylaxis resumed or started[193].	**A I**
In chloroquine- and mefloquine-resistant *P. falciparum* regions, self-treatment should consist of an alternative to the drug being used for prophylaxis, choosing from one of the following: a. Malarone or, b. oral quinine and doxycycline or, c. artemether-lumefantrine purchased in a country with rigorous pharmaceutical standards (e.g., Europe or the U.S.). Counterfeit artemether-lumefantrine is an important problem[122, 123].	**A I**
A number of antimalarial drugs are contraindicated for treatment of malaria (self-treatment or otherwise): a. mefloquine[197, 198] b. sulfadoxine/pyrimethamine (Fansidar)[5] e. mefloquine/Fansidar[198] f. halofantrine[126] g. chloroquine/Fansidar[126, 191]	**E II**

8. Drugs for the Prevention and Treatment of Malaria

Travellers should be reminded that antimalarials, like all drugs, have the potential to cause adverse effects. These drugs should be prescribed after an individual risk assessment (as outlined in Chapter 2) to ensure that only those travellers truly at risk of malaria infection receive antimalarial chemoprophylaxis. Any drugs taken for chemoprophylaxis should be used in conjunction with personal protective measures to prevent mosquito bites (see Chapter 2). Most people using antimalarial chemoprophylaxis will have no or only minor adverse reactions, which can be minimized by careful adherence to dosing guidelines, precautions and contraindications. If there are concerns as to the ability of the traveller to tolerate a particular antimalarial regimen and if time permits, malaria prophylaxis may be initiated several weeks before travel in order to assess drug tolerance.

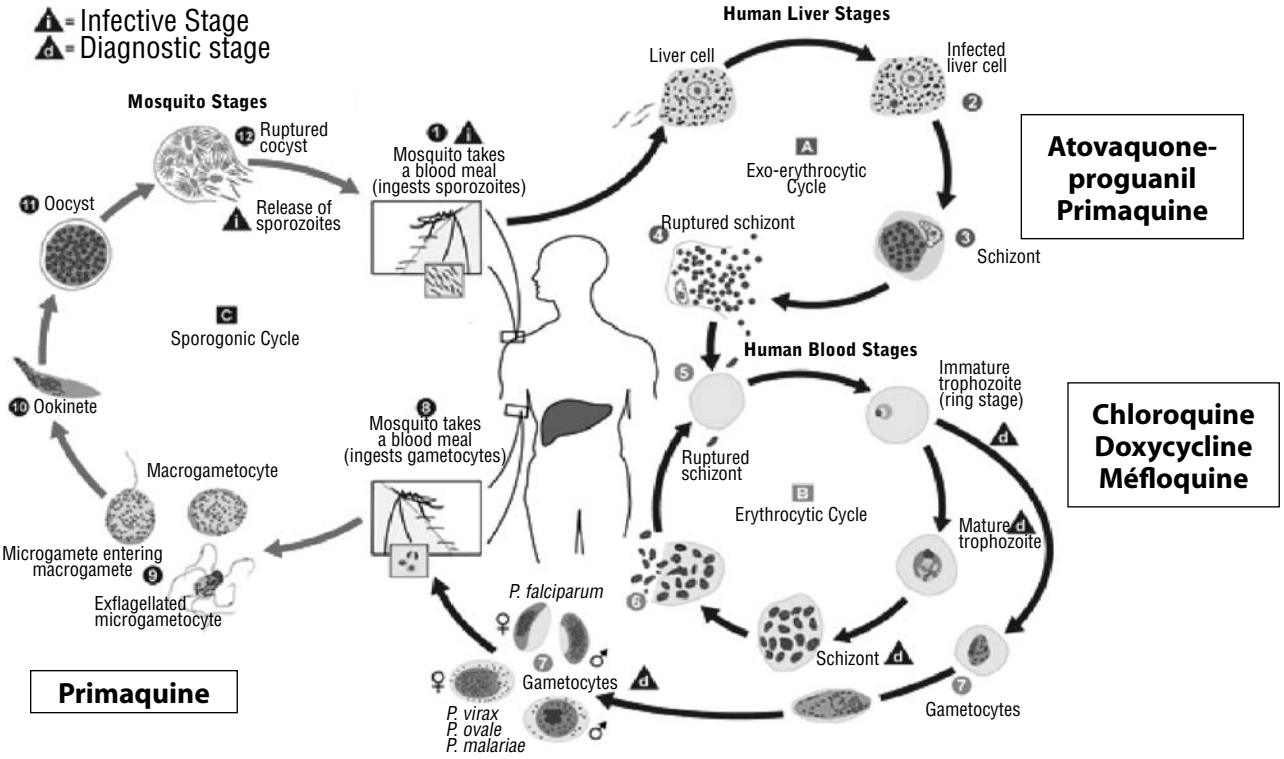
In light of the increasing prevalence of counterfeit medications in some countries and the potentially serious consequences of inadequate antimalarial prophylaxis or treatment, travellers should be advised to purchase their antimalarial medications prior to departure from Canada whenever possible (see Chapter 5, Counterfeit Drugs).

This chapter reviews the drugs (in alphabetical order) used for the prevention (chemoprophylaxis) and treatment of malaria. This information is not designed to be comprehensive. It is important to note that product recommendations are subject to change, and therefore providers should consult up-to-date information, including recent drug monographs, for any updates, particularly with respect to compatibility, adverse reactions, contraindications and precautions. Further details and discussion on recommendations concerning the use of these drugs for chemoprophylaxis and treatment can be found in Chapter 3 and in this chapter, respectively.

Table 5 provides information on the base/salt equivalents of selected antimalarial drugs, and Table 6 summarizes information, including doses, for the antimalarial drugs routinely used in Canada.

Figure 2 depicts the malaria lifecycle and the sites of action of recommended chemoprophylactic drugs.

Figure 2: Malaria life cycle and primary areas of drug activity (modified from the U.S. Centers for Disease Control and Prevention DPDx site)



The malaria parasite life cycle involves two hosts. During a blood meal, a malaria-infected female anopheline mosquito inoculates sporozoites into the human host **(1)**. Sporozoites infect liver cells **(2)** and mature into schizonts **(3)**, which rupture and release merozoites **(4)**. In *P. vivax* and *P. ovale*, a dormant stage (hypnozoites) can persist in the liver and cause relapses by invading the bloodstream weeks or even years later. After this initial replication in the liver (exo-erythrocytic schizogony **A)**, the parasites undergo asexual multiplication in the erythrocytes (erythrocytic schizogony **B)**. Merozoites infect red blood cells **(5)**. The ring stage trophozoites mature into schizonts, which rupture releasing merozoites **(6)**. Some parasites differentiate into sexual erythrocytic stages (gametocytes) **(7)**. Blood stage parasites are responsible for the clinical manifestations of the disease.

Agents used for **causal chemoprophylaxis** include atovaquone/proguanil and primaquine. These drugs act at the liver stage of the malaria life cycle, prevent blood-stage infection, and need only be taken for 1 week after leaving a malaria-endemic area. Agents used for **suppressive chemoprophylaxis** (including mefloquine, chloroquine, doxycycline) act at the erythrocytic (asexual) stage of the malaria life cycle, and hence need to be taken for 4 weeks after departure from a malaria-endemic area.

Artemisinin and Derivatives

These are endoperoxide-containing natural anti-malarials from sweet wormwood *(Artemisia annua)*. Artemisinin (qinghaosu) derivatives, including artesunate, artemether, arteether and dihydro-artesinin, are available in oral, parenteral and suppository formulations. They are all metabolized

to a biologically active metabolite, dihydroartemisinin, and exert their antiparasitic effects on the younger, ring-forming parasites. They thereby decrease the numbers of late parasite forms that can obstruct the microvasculature of the host. All artemisinin preparations have been studied and used for treatment only. They are **not** recommended for prophylaxis because of their short half-life.

Artemisinin and its derivatives produce rapid clearance of parasitemia and rapid resolution of symptoms. They reduce parasite numbers by a factor of approximately 10,000 in each asexual cycle, which is more than other current antimalarials (which reduce parasite numbers 100- to 1000-fold per cycle)[199]. The artemisinin derivatives act rapidly against drug-resistant *P. falciparum* strains but have high recrudescence rates (about 10% to 50%) when used as monotherapy for fewer than 5 days. Studies have examined longer durations of therapy (7 days) and combinations of artemisinin derivatives with mefloquine, lumefantrine, amodiaquine or tetracycline/doxycycline to prevent recrudescence. In Thailand, treatment with oral artesunate (over 3 to 5 days) combined with mefloquine (15 to 25 mg/kg) was more effective than mefloquine or artesunate alone. Combination therapy results in > 90% cure rates of primary and recrudescent *P. falciparum* infections.

Coartemether (Riamet® in Europe, Coartem® in Africa) is a combination of artemether and lumefantrine that is currently licensed in some European countries and the U.S. and is becoming widely distributed in Africa for the treatment of malaria. A six-dose regimen of artemether-lumefantrine appears more effective than antima-larial regimens not containing artemisinin derivatives[200]. Available data suggest that mefloquine plus artesunate is as effective and possibly superior to artemether-lumefantrine[201]. Combinations of artesunate and mefloquine appear to be the most active drug regimens for treatment of multidrug-resistant falciparum malaria in Southeast Asia[202].

Randomised trials comparing parenteral artesunate and quinine in patients from East Asia with severe malaria show clear evidence of benefit with artesunate. In the largest multi-centre trial, which enrolled 1,461 patients (including 202 children < 15 years), mortality was reduced by 35% compared with the quinine group[126].

Artemisinin-based combination treatments are now accepted as the best current treatment for uncomplicated falciparum malaria[126]. Parenteral artesunate is recommended by the WHO as the treatment of first choice for severe or complicated malaria[126]. Artemisinin and its derivatives are available and increasingly used in Southeast Asia and Africa, and parenteral artesunate is now available in Canada and can be obtained from the CMN (see Appendix V).

Artemisinin and its derivatives have been used in over 1 million patients and are generally well tolerated[203]. Neurological lesions involving the brainstem have been seen in rats, dogs and primates given repeated doses of artemisinin derivatives, in particular the lipid soluble derivatives. Such effects have not been observed with oral administration of any artemisinin derivative or with intravenous artesunate. Treatment of uncomplicated malaria with coartemether may be associated with hearing loss in some patients, possibly from synergy between potentially ototoxic agents in combination[204]. To date, there have been two human cases of complete heart block associated with the use of artemisinins, but most volunteer and clinical studies have found no evidence of cardiac adverse effects. The safety of artemisinin derivatives in pregnancy has not been established. Based on a recent review, the limited data available suggest that artemisinins are effective and unlikely to cause foetal loss or abnormalities when used in late pregnancy[126, 205]. It is important to note that none of these studies had adequate power to rule out rare serious adverse events, even in the second and third trimesters. There is currently not enough evidence

to effectively assess the risk-benefit profile of artemisinin compounds for pregnant women, particularly for first trimester exposure[205]. Although there is good evidence that therapy with artemisinin compounds is generally safe, questions about cumulative neurological toxicity of intramuscular preparations still require resolution. Additional studies to monitor subtle neurological changes and hearing loss are required, especially in patients undergoing repetitive treatment.

Oral artemisinin derivatives are not yet licensed or available in Canada but have been approved recently in the U.S by the Food and Drug Administration. There is concern that the quality of artemisinin derivatives available in developing countries may be questionable, as they may not be produced in accordance with the good manufacturing production standards required in North America, or they may be counterfeit[123]. Orally administered artemisinin drug combinations, such as the combination artemisinin-lumefantrine (CoArtem®), are recommended by the WHO as the treatment of choice for uncomplicated falciparum malaria. Such drugs would increase the treatment choices for oral therapy of falciparum malaria in Canada, where atovaquone/proguanil (Malarone®) is frequently used for chemoprophylaxis (and hence may be disqualified as a therapeutic choice), and the only other treatment choice, quinine in combination with a tetracycline, is often poorly tolerated. Furthermore, Canadians travelling (particularly for longer periods) to malaria-endemic areas where these drugs are available cannot safely rely on local drugs, since counterfeit artemisinins are becoming a serious problem in many countries[123] (see Chapter 5, Counterfeit Drugs).

Artemisinin and derivatives: evidence-based medicine recommendations	***EBM rating***
Artemether in combination with lumefantrine (Riamet® in Europe, Coartem® in Africa and the U.S.) is widely distributed in Africa for the treatment of *P. falciparum* malaria. A six-dose regimen of artemether-lumefantrine appears more effective than antimalarial regimens not containing artemisinin derivatives[200, 201].	**A I**
Parenteral artesunate is recommended as the first-line treatment of severe or complicated *P. falciparum* malaria. Parenteral administration of artesunate should be followed by a full course of oral combination therapy (artemisinin-based combination treatments, or quinine plus doxycycline or clindamycin)[126].	**A II**
On the basis of their short half-life, artemisinin compounds should not be used for chemoprophylaxis.	**C III**

Atovaquone/Proguanil (ATQ/PG)

Trade Name: Malarone®, Malarone® Pediatric: licensed in Canada for malaria chemoprophylaxis in adults and in children weighing 11 kg and above, and for treatment of uncomplicated malaria in adults and in children weighing 11 kg and above[206] (see Chapter 5 for dosage in children weighing between 5 and 11 kg). There are two formulations of Malarone® available: Malarone® tablets containing 250 mg of atovaquone and 100 mg proguanil hydrochloride, and Malarone® pediatric tablets, containing 62.5 mg atovaquone and 25 mg proguanil hydrochloride.

Mechanism of action

Atovaquone/proguanil is a fixed drug combination of atovaquone and proguanil in a single tablet. The two components are synergistic, inhibiting electron transport and collapsing mitochondrial membrane potential. Atovaquone/proguanil is effective as a

causal (acting at the liver stage) as well as a suppressive (acting at the blood stage) prophylactic agent. Atovaquone/proguanil must be taken daily. Because of the causal effects, atovaquone/proguanil can be discontinued 1 week after departure from a malaria-endemic area.

Indications and efficacy

For malaria **chemoprophylaxis**, atovaquone/proguanil has equal efficacy (i.e., ~ 95%) to that of doxycycline and mefloquine against chloroquine-resistant falciparum malaria[207]. It is also effective along the borders of Thailand, where chloroquine and mefloquine resistance is documented[75, 97]. Daily atovaquone/proguanil can now be considered as first-line chemoprophylaxis for travellers to areas with multidrug-resistant falciparum malaria (with attention to contraindi-cations and precautions)[75, 199, 207].

In clinical trials of **treatment** of acute, uncomplicated *P. falciparum* malaria conducted in Southeast Asia, South America, and Africa, the efficacy of the combination of atovaquone/proguanil (dosed once daily for 3 days) has exceeded 95%[71]. As well, published case reports have documented that it successfully treated multidrug-resistant malaria that had failed to respond to other therapies[208]. Therefore, atovaquone/proguanil, an effective and well-tolerated therapy, is considered first-line treatment of non-complicated *P. falciparum* infection, including multidrug-resistant *P. falciparum*[209]. However, there have been sporadic documented cases of atovaquone/proguanil-resistant *P. falciparum* malaria acquired in sub-Saharan Africa[210, 211, 212].

There is insufficient evidence at this time to recommend atovaquone/proguanil for the routine treatment of non-falciparum malaria, although limited data suggest efficacy for the treatment of *P. vivax* malaria when atovaquone/proguanil is combined with primaquine (beginning immediately after the 3 days of treatment with atovaquone/proguanil)[213].

Adverse effects, contraindications and precautions

Compared with other standard antimalarial regimens, the atovaquone/proguanil combination for chemoprophylaxis has demonstrated excellent safety and tolerance[203]. During treatment, the most frequent adverse events are those associated with the gastrointestinal tract: approximately 8% to 15% of adults and children experience nausea, vomiting, abdominal pain or diarrhea, and 5% to 10% develop transient, asymptomatic elevations in transaminase and amylase levels. Serious adverse events associated with atovaquone/proguanil, such as seizure, hepatitis and rash, are rare. Atovaquone has been associated with fever and rash in HIV-infected patients, requiring discontinuation of therapy, and has been shown to be teratogenic in rabbits but not in rat models (US Food and Drug Administration category C drug). Proguanil is well tolerated, and although oral aphthous ulcerations are not uncommon they are rarely severe enough to warrant discontinuing this medication. Proguanil may potentiate the anticoagulant effect of warfarin and similar anticoagulants (those metabolized by CYP 2C9) through possible interference with metabolic pathways[199].

Pregnancy, severe renal insufficiency (creatinine clearance < 30 mL/min) and hypersensitivity to either component is a contraindication to atovaquone/proguanil use.

Malarone: evidence-based medicine recommendations	*EBM rating*
Atovaquone/proguanil **prophylaxis** has equal efficacy (i.e., ~ 95%) to that of doxycycline and mefloquine against chloroquine-resistant falciparum malaria[207, 208].	**A I**
Daily atovaquone/proguanil can now be considered as first-line chemoprophylaxis for travellers to areas with multidrug-resistant falciparum malaria[75, 207].	**A I**
Atovaquone/proguanil is considered a first-line **treatment** for acute, uncomplicated *P. falciparum* malaria from Southeast Asia, South America, and Africa with an efficacy of ~ 95%[208].	**A I**
There is insufficient evidence at this time to recommend atovaquone/proguanil for the routine treatment of non-falciparum malaria[208, 213].	**C III**

Chloroquine (or Hydroxychloroquine)

Trade Name: Novo-Chloroquine (or Plaquenil®, Apo-Hydroxyquine, Gen-Hydroxychloroquine)

Mechanism of action

Chloroquine is a synthetic 4-aminoquinoline, which acts against the intra-erythrocytic stage of parasite development. It interferes with the digestion of hemoglobin within the red cell and leads to toxic metabolite formation within the food vacuole of the parasite.

Indications and efficacy

Chloroquine/hydroxychloroquine, taken once weekly, is effective for malaria **prevention** in travellers to areas with chloroquine-sensitive malaria[75]. It remains the drug of choice for malaria **chemoprophylaxis** of travellers to areas with chloroquine-sensitive malaria and the drug of choice for the **treatment** of chloroquine-sensitive falciparum malaria, chloroquine sensitive *P. vivax*, as well as *P. ovale* and *P. malariae* infections[126, 213].

Chloroquine is suitable for people of all ages and for pregnant women. There is insufficient drug excreted in breast milk to protect a breast-feeding infant, and therefore nursing infants should be given chloroquine (adjusted for changing weight, see Table 6). Since overdoses are frequently fatal, instructions for childhood doses should be carefully followed, and the medication should be kept out of the reach of children.

Weekly chloroquine plus daily proguanil (Saverine®) is less efficacious than atovaquone/proguanil, doxycycline or mefloquine and is **not** routinely recommended for **prevention** of malaria in Canadian travellers to sub-Saharan Africa[77, 207].

Adverse effects, contraindications and precautions

Except for its bitter taste, chloroquine is usually well tolerated. Taking the drug with food may reduce other mild side effects, such as nausea and headache. Black-skinned people may experience generalized pruritus, which is not indicative of drug allergy. Transient, minor visual blurring may occur initially but should not be a reason to discontinue chloroquine. Retinal toxic effects, which may occur with long-term daily doses of chloroquine (> 100 g total dose) used in the treatment of other diseases, is extremely unlikely with chloroquine given as a weekly chemoprophylaxis. Chloroquine may worsen psoriasis and, rarely, is associated with seizures and psychosis. Therefore, chloroquine should not be used in individuals with a history of epilepsy or generalized psoriasis[72, 203]. Concurrent use of chloroquine interferes with antibody response to intradermal human diploid cell rabies vaccine.

Chloroquine: evidence-based medicine recommendations	*EBM rating*
Chloroquine/hydroxychloroquine, taken once weekly, is effective for malaria **prevention** in travellers to areas with chloroquine-sensitive malaria[75].	**A I**
Chloroquine is the drug of choice for the **treatment** of malarias caused by chloroquine-sensitive *P. falciparum* and *P. vivax* and all *P. ovale* and *P. malariae* infections[126, 213].	**A I**
Weekly prophylaxis with chloroquine plus daily proguanil (Saverine®) is less efficacious than atovaquone/proguanil, doxycycline or mefloquine and is not recommended for Africa[77, 207].	**E I**
Chloroquine should not be used in individuals with a history of epilepsy or generalized psoriasis[72, 203].	**C III**

Clindamycin

Trade Name: Dalacin C®, Apo-Clindamycin, Novo-Clindamycin

Mechanism of action

Clindamycin is an antimicrobial that inhibits the parasite apicoplast.

Indications and efficacy

Clindamycin is indicated only for the **treatment** of malaria and only in restricted circumstances.

Clindamycin, although less effective than doxycycline or atovaquone/proguanil, is used in combination with quinine for those unable to tolerate, or who have contraindications to, the use of first-line agents (e.g., pregnant women and young children).

Adverse effects, contraindications and precautions

The most frequent adverse events with clindamycin are diarrhea and rash. *Clostridium difficile* associated disease, including pseudomembranous colitis, has been reported.

Clindamycin: evidence-based medicine recommendations	*EBM rating*
Until artemisinin and its derivatives become readily available in North America, clindamycin combined with quinine is recommended as treatment of chloroquine- or mefloquine-resistant *P. falciparum* malaria in pregnant women, children (< 8 years of age) and tetracycline intolerant adults[213].	**A I**

Doxycycline

Trade Name: Vibra-Tabs™, Apo-Doxy, Doxycin, Novo-Doxylin, Nu-Doxycycline, ratio-Doxycycline

Mechanism of action

Doxycycline is an antimicrobial that inhibits parasite protein synthesis.

Indications and efficacy

Doxycycline is effective for the **prevention** and **treatment** of chloroquine-resistant *P. falciparum*. It has been shown to have equivalent efficacy to that of atovaquone/proguanil and mefloquine for the **prevention** of chloroquine-resistant *P. falciparum*[75]. Doxycycline is an efficacious chemoprophylactic agent against mefloquine-sensitive and mefloquine-resistant *P. falciparum* malaria[75] but must be taken daily for it to work. The major reason for doxycycline failures is non-compliance with this daily regimen.

Adverse effects, contraindications and precautions

Doxycycline can cause gastrointestinal upset and, rarely, esophageal ulceration, which is less likely

to occur if the drug is taken with food and large amounts of fluid. It should not be taken in the 30 minutes before lying down nor simultaneously with Pepto-bismol® or antacids. Because doxycycline is photosensitizing, it may make the skin burn more easily; use of a sunscreen that blocks ultraviolet A rays may reduce this problem. Doxycycline may also increase the risk of vaginal candidiasis; therefore, women should carry antifungal therapy for self-treatment of vaginal candidiasis. Although tetracyclines and other antibiotics have been cited as a cause of oral contraceptive failure, a controlled clinical trial failed to demonstrate any significant association[214]. Concurrent use of doxycycline with barbiturates, carbamazapine or phenytoin may result in a 50% decrease in doxycycline serum concentration because of induction of hepatic microsomal enzyme activity and resulting reduction of the half-life of doxycycline.

Doxycycline is **contraindicated** during pregnancy, in breast-feeding women and in children < 8 years of age. Although the long-term safety (> 3 months) of doxycycline has not been established, historically tetracycline derivatives have been used at lower doses over many years for skin disorders.

Doxycycline: evidence-based medicine recommendations	***EBM rating***
Doxycycline is equivalent in efficacy to mefloquine and atovaquone/proguanil for the **prevention** of chloroquine-resistant *P. falciparum* and to atovaquone/proguanil for mefloquine-resistant *P. falciparum*[75].	**A I**
Travellers should be informed about the small doxycycline-associated risks of oesophageal ulceration, vaginal candidiasis and photosensitivity[75, 126].	**A I**
Doxycycline is **contraindicated** during pregnancy, in breast-feeding women and in children < 8 years of age[75, 126].	**A I**
Concurrent use of doxycycline with barbiturates, carbamazapine or phenytoin may result in a 50% decrease in doxycycline serum concentration[75, 126].	**A I**

Mefloquine

Trade Name: Lariam®, Apo-Mefloquine

Mechanism of action

Mefloquine is a quinoline-methanol. It is a lipophylic drug that acts on the intraerythrocytic asexual stages of parasite development, inhibiting heme polymerization within the food vacuole.

Indications and efficacy

Mefloquine is an effective **chemoprophylactic** and therapeutic agent against drug-resistant *P. falciparum*. In Canada, it is routinely recommended only for chemoprophylaxis because of a higher rate of adverse effects with treatment doses. It is one of the drugs of choice, along with atovaquone/proguanil or doxycycline, for the prevention of malaria in travellers to chloroquine-resistant regions[75]. However, treatment failures in excess of 50% with mefloquine are being reported in border areas between Cambodia, Myanmar and Thailand[75, 126, 199].

There is no evidence that toxic metabolites of mefloquine accumulate, and long-term use of mefloquine (> 1 year) by Peace Corps volunteers in Africa was not associated with additional adverse effects[203]. It is recommended, therefore, that the duration of mefloquine use not be arbitrarily restricted in individuals who tolerate this medication and are at risk of acquiring malaria.

For travellers who will be at immediate high risk of drug-resistant falciparum malaria, consideration may be given to the use of a loading dose of mefloquine. If time permits, mefloquine should preferably be initiated up to 3 weeks before travel in order to assess tolerance

and achieve higher blood levels before the traveller enters malaria-endemic areas. This strategy also allows the traveller time to contact the prescribing physician to arrange an alternative antimalarial. Alternatively, data from several trials indicate that mefloquine taken once daily for 3 days before travel followed by a once weekly dose is relatively well-tolerated and an effective way to rapidly achieve therapeutic blood levels (reaching steady state levels in 4 days compared with 7 to 9 weeks with standard weekly dosing of mefloquine)[143]. In controlled studies, only about 2% to 3% of loading dose recipients discontinued mefloquine, and most of these did so during the first week.

Adverse effects

Mefloquine is generally well tolerated when used for **chemoprophylaxis**. Approximately 25% to 50% of travellers will experience side effects from either mefloquine or chloroquine; most of these are mild and self-limiting[215, 216]. The most frequent minor side effects reported with mefloquine use are nausea, strange vivid dreams, dizziness, mood changes, insomnia, headache and diarrhea. Approximately 1% to 6% of mefloquine users may have to discontinue prophylaxis because of adverse effects. Tens of millions of travellers have used mefloquine prophylaxis, and severe reactions (seizure, psychosis) to this drug are rare (reported from 1 in 6,000 to 1 in 13,000 users). The great majority of mefloquine users (about 95%) have either no side effects or only mild and temporary ones. Occasionally, a traveller (in particular, women[69, 203]) will experience a less severe but still troublesome neuropsychological reaction (e.g., anxiety, mood change) to mefloquine (1 in 250 to 500 users), requiring a change to an alternative drug. This can sometimes be prevented by splitting the weekly dose into one half of a tablet twice a week for the same total weekly. Adverse reactions are generally reversible, but on rare occasions neuropsychological complaints have persisted long after mefloquine has been stopped, and rare cases of suicidal ideation and suicide have been reported; no relation to drug administration has been confirmed with any of these rare adverse events.

CATMAT does not routinely recommend mefloquine for the **treatment** of malaria, because in treatment doses (25 mg base/kg) it is less well tolerated. Severe neuropsychiatric reactions are reported to be 10 to 60 times more frequent, occurring in 1/215 to 1/1,700 users of treatment doses of mefloquine[203].

Contraindications

These include known hypersensitivity or past severe reaction to mefloquine; history of serious psychiatric disorder (e.g., psychosis, severe depression, generalized anxiety disorder, schizophrenia or other major psychiatric disorders); and seizure disorder.

Precautions

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

When mefloquine is prescribed for prophylactic use, individuals should be advised that if they experience psychiatric symptoms, such as acute anxiety, depression, restlessness or confusion, these may be prodromal to more serious adverse events. They should report these adverse events immediately, the drug should be discontinued, and an alternative medication should be substituted.

There have been concerns regarding the co-administration of mefloquine and agents known to alter cardiac conduction, including beta-blockers, calcium channel blockers, phenothiazines, non-sedating antihistamines and tricyclic antidepressants. However,

at present these concerns remain theoretical, and the concurrent use of these agents is not contraindicated. A review of available data suggests that mefloquine may be used in people concurrently taking most beta-blockers if they have no underlying conduction delays or cardiac arrhythmia. Co-administration of mefloquine and erythromycin or ketoconizole can lead to toxic levels of mefloquine.

Insufficient mefloquine is excreted in breast milk to protect a nursing infant. Although the package insert recommends that mefloquine not be given to children weighing < 5 kg, it should be considered for children at high risk of acquiring chloroquine-resistant *P. falciparum* malaria (see Chapter 4). There are no pharmacokinetic data upon which to recommend a correct dose for children weighing < 15 kg. The WHO has suggested a chemosuppressive dose of 5 mg base/kg weekly for children weighing > 5 kg.

Mefloquine: evidence-based medicine recommendations	***EBM rating***
It is one of the drugs of choice, along with atovaquone/proguanil or doxycycline, for the **prevention** of malaria in travellers to chloroquine-resistant regions[75].	A I
Treatment failures in excess of 50% with mefloquine are being reported in border areas between Cambodia, Myanmar and Thailand[75].	**B II**
Long-term use of mefloquine (> 1 year) in Africa is not associated with additional adverse effects, and its use should **not** be arbitrarily restricted in individuals who tolerate this medication[203].	B II
The most frequent minor side effects reported with mefloquine use are nausea, strange vivid dreams, dizziness, mood changes, insomnia, headache and diarrhea. Approximately 1% to 6% of mefloquine users may have to discontinue prophylaxis because of adverse effects[215].	**B II**
Mefloquine is not recommended as a **treatment** of malaria. Severe neuropsychiatric reactions are reported to occur in 1/215 to 1/1,700[203].	**E III**
Mefloquine is contraindicated in individuals with known hypersensitivity, past severe reaction to mefloquine, a history of serious psychiatric disorder (e.g., psychosis, severe depression, generalized anxiety disorder, schizophrenia or other major psychiatric disorders), seizure disorder and cardiac conduction delays[75, 203].	**C1-E1**

Primaquine

Trade Name: Primaquine (primaquine phosphate)

Mechanism of action

Primaquine is an 8-aminoquinoline antimalarial that is active against multiple life cycle stages of the *Plasmodia* that infect humans; it has been used for over 50 years. Its mechanism of action is incompletely understood. However, primaquine has activity against the developing liver stages (causal effect), thereby preventing establishment of infection; against liver hypnozoites, preventing relapses in established *P. vivax* and *P. ovale* infections; against blood stages; and against gametocytes, thereby preventing transmission.

Indications and efficacy

Evidence is accumulating that primaquine is an effective chemoprophylactic agent for *P. falciparum* malaria[216]. Recent studies have shown efficacy in semi-immune and non-immune subjects, although data for travellers and for varied geographic regions are limited. Given at a dose of 0.5 mg/kg base per day (adult dose 30 mg base per day) for 11 to 50 weeks, primaquine

had a protective efficacy of 85% to 93% against both *P. falciparum* and *P. vivax* infections[217]. Primaquine was well tolerated in people who were not G6PD deficient. Because of the causal effects of primaquine, it can be discontinued 1 week after departure from a malaria-endemic area. All travellers need to be evaluated for G6PD deficiency before primaquine is initiated. Although not a first-line chemoprophylactic agent, primaquine may be considered an alternative chemoprophylactic agent (with attention to contraindications and precautions) for those without G6PD deficiency when other regimens are either inappropriate or contraindicated.

P. vivax and *P. ovale* parasites can persist in the liver and cause relapses for as long as 5 years after departure from a malaria-endemic area. Since most malarial areas of the world (except Haiti and the Dominican Republic) have at least one species of relapsing malaria, travellers to these areas have some risk of acquiring either *P. vivax* or *P. ovale*, although actual risk for an individual traveller is difficult to define. Primaquine decreases the risk of relapses by acting against the liver stages of *P. vivax* and *P. ovale*. Primaquine terminal prophylaxis is administered after the traveller has left a malaria-endemic area, usually during or after the last 2 weeks of chemoprophylaxis. Terminal prophylaxis with primaquine is generally indicated only for people who have had prolonged exposure in malaria-endemic regions (e.g., long-term travellers or expatriates)[74]. None of the other currently recommended chemoprophylaxis regimens will prevent relapses due to *P. vivax* and *P. ovale*.

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 should be initiated for radical cure after chloroquine therapy has been completed and the acute febrile illness is over (about 1 to 2 weeks). *P. vivax* isolates with a decreased responsiveness to primaquine are well documented in Southeast Asia and, in particular, Papua New Guinea and Papua (Irian Jaya)[126]. On the basis of increasing numbers of reports of resistance to primaquine at the standard dose of 0.25 mg/kg, the recommended dose for radical cure has been increased to 30 mg (0.5 mg/kg) of primaquine base daily for 14 days in Oceania and South-East Asia[126].

Adverse effects, contraindications and precautions

Primaquine is generally well tolerated but may cause nausea and abdominal pain, which can be decreased by taking the drug with food. More importantly, primaquine may cause methemoglobinemia and oxidant-induced hemolytic anemia, particularly among individuals with G6PD deficiency, which is more common in those of Mediterranean, African and Asian ethnic origin. As well, those receiving > 15 mg base/day have a greater risk of hemolysis. Therefore, all individuals should have their G6PD level measured before primaquine therapy is initiated.

Primaquine is contraindicated in patients with severe G6PD deficiencies. In mild variants of G6PD deficiency, primaquine has been used safely at a lower dose for radical cure to prevent *P. vivax* and *P. ovale* relapses (0.8 mg base/kg weekly; adult dose 45 mg base weekly for 8 weeks); however, this reduced dose is insufficient for chemoprophylactic activity. When used at prophylactic doses (0.5 mg base/kg daily) in children and men with normal G6PD activity, mean methemoglobin rates (5.8%) were below those associated with toxicity (> 10%). Patients should be advised to stop their medication and report to a physician immediately if jaundice, gray skin or abnormally dark or brown urine is noted.

Primaquine use is contraindicated in pregnancy. *P. vivax* or *P. ovale* infections occurring during pregnancy should be treated with standard doses of chloroquine (Table 6). Relapses can be prevented by weekly chemoprophylaxis with choloroquine until after delivery, when primaquine can be safely used for mothers with normal G6PD levels. However, primaquine should only be used in nursing mothers if the infant has been tested and found not to be G6PD deficient.

Primaquine: evidence-based medicine recommendations	*EBM rating*
Primaquine (30 mg base daily) is an effective chemoprophylactic agent with a protective efficacy of 85% to 93% against both *P. falciparum* and *P. vivax* infections; it is recommended when the first-line agents mefloquine, doxycycline and atovaquine/proguanil cannot be used or in the prophylaxis of *P. vivax* or *P. ovale* malaria, when there is no G6PD deficiency[216, 218].	**A I**
Primaquine 30 mg base daily for 2 weeks is effective as a radical cure to prevent relapses of *P. vivax* or *P. ovale* acquired in SE Asia[126].	**B I**

Quinine and Quinidine

Mechanism of action

These quinoline-containing antimalarials are alkaloid derivatives of cinchona bark that act on the intra-erythrocytic asexual stage of the parasite.

Indications and efficacy

Quinine and quinidine are indicated only for the treatment of malaria and not for prophylaxis. Quinine (or quinidine) should not be used alone: a second drug such as doxycycline should always be used concurrently.

Oral treatment with quinine is indicated for uncomplicated falciparum malaria and as step-down therapy after parenteral treatment of complicated malaria.

Quinine and artesunate are first-line drugs for the parenteral therapy of severe or complicated malaria, but artesunate has been shown to be the more effective. Because of the significant cardiotoxic effects associated with parenteral quinidine it is to be considered only if the two first-line drugs are unavailable, and in that case cardiac monitoring is required

Adverse effects, contraindications and precautions

Minor adverse events are common with quinine and quinidine use. These include cinchonism (tinnitus, nausea, headache, blurred vision), hypoglycemia (especially in pregnant women and children), nausea and vomiting. Occasionally, hypersensitivity and nerve deafness have been reported. Parenteral quinidine has the potential to increase the QTc interval and therefore requires electrocardiographic monitoring.

Quinine: evidence-based medicine recommendations	*EBM rating*
Oral therapy with quinine (with a second agent) is indicated for the treatment of uncomplicated falciparum malaria and as step-down therapy after parenteral treatment of complicated malaria[213].	**A I**
Parenteral quinine is the alternative drug for the treatment of severe or complicated malaria when parenteral artesunate is not available[126].	**A I**

Other Drugs Not Available Or Not Routinely Recommended in Canada (in alphabetical order)

It is important for travellers and providers to understand that the medical management of malaria in countries where the disease is endemic may differ significantly from management in Canada. In countries where malaria is endemic there may be a limited number of effective medications available for treatment; indeed, some of the drugs used may be ineffective in non-immune travellers or be associated with unacceptable adverse outcomes. As well, the level of health care available in some of these countries

may put travellers at risk of other infectious diseases[145,146].

Amodiaquine is a 4-aminoquinoline that was first introduced as an alternative to chloroquine. Resistance to this drug has followed the path of chloroquine resistance. Bone marrow toxicity and hepatotoxicity have been noted when it is used for malaria prophylaxis. Amodiaquine is not recommended for malaria chemoprophylaxis.

Azithromycin (Zithromax™) is a macrolide antimicrobial that inhibits the parasite apicoplast. Azithromycin has been shown to not be very effective in the prevention of *P. falciparum* malaria. Studies performed to date indicate that azithromycin is less effective than atovaquone/proguanil, doxycycline, mefloquine or primaquine. There is insufficient evidence to recommend azithromycin as an alternative antimalarial except under circumstances in which other, more effective and safer, medications are not available or are contraindicated.

Azithromycin is considered to be safe in pregnancy and for children, and is available in suspension. However, in view of the serious consequences of malaria in pregnancy and in young children, use of this suboptimal antimalarial would not routinely be recommended.

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

Piperaquine is a bisquinoline antimalarial drug that was first synthesised in the 1960s and used extensively in China for malaria prophylaxis and treatment for about 20 years. With the development of piperaquine-resistant strains of *P. falciparum* and the emergence of the artemisinin derivatives, its use declined during the 1980s. However, in the 1990s piperaquine was rediscovered by Chinese scientists as one of a number of compounds suitable for combination with an artemisinin derivative. Recent Indochinese studies have confirmed the excellent clinical efficacy of piperaquine-DHA combinations (28-day cure rates > 95%) and have demonstrated that currently recommended regimens are not associated with significant adverse effects. The pharmacokinetic properties of piperaquine have also been characterized recently, revealing that it is a highly lipid-soluble drug with a large volume of distribution at steady state, long elimination half-life and a clearance that is markedly higher in children than in adults. The tolerability, efficacy, pharmacokinetic profile and low cost of piperaquine make it a promising partner drug for use as part of artemisinin-based combination treatments[150].

Proguanil should **not** be used as a single agent for chemoprophylaxis[219]. Proguanil is well tolerated. Although oral aphthous ulcerations are not uncommon, they are rarely severe enough to warrant discontinuing this medication. Proguanil is considered safe during pregnancy and breast-feeding, but insufficient drug is excreted in the milk to protect a nursing infant.

Pyrimethamine alone (Daraprim®) is not recommended for malaria chemoprophylaxis because of widespread drug resistance in Asia and Africa and evidence of some resistance in Haiti[219, 220].

Pyrimethamine-sulfadoxine (Fansidar®) is a fixed drug combination antimetabolite that inhibits parasite folate synthesis. Historically, this drug has been used for treatment, including self-treatment, of *P. falciparum*, but increasing resistance means it has limited utility for the treatment of *P. falciparum* and is no longer recommended. Resistance has been reported in the Amazon Basin, Southeast Asia, and increasingly throughout Africa.

Pyrimethamine-sulfadoxine is not recommended by CATMAT, CDC or WHO for chemoprophylaxis because of the life-threatening complication of Stevens-Johnson syndrome and toxic epidermal necrolysis.

Pyronaridine is a benzonaphthyridine synthesized in China in 1970, which has been used for the treatment of *P. vivax* and *P. falciparum* for more than 20 years and has been shown to be effective in the treatment of falciparum malaria in children in Cameroon. It has more gastrointestinal side effects than chloroquine. Pyronaridine has been used in combination with the artemisinin derivatives in the treatment of falciparum malaria[221].

Savarine: Weekly chloroquine plus daily proguanil (Saverine®) is less efficacious than atovaquone/proguanil, doxycycline or mefloquine and is **not** routinely recommended for prevention of malaria in Canadian travellers[77, 214, 222, 223].

Tafenoquine is a long-acting, 8-aminoquinoline with a half-life measured in weeks rather than hours. Initial research has shown efficacy with weekly chemoprophylaxis and evidence of causal prophylaxis. Studies are ongoing in semi- and non-immune individuals. In the future, tafenoquine may provide another option for chemoprophylaxis in those without G6PD deficiency[224, 225].

Evidence-based medicine	*EBM rating*
Azithromycin has been shown to not be very effective in the prevention of *P. falciparum* malaria[226].	**E II**
Amodiaquine is not recommended for malaria chemoprophylaxis because if its established risks of fatal hepatic or bone marrow toxicity[203, 216, 227].	**D III**
Halofantrine has been associated with cardiac toxicity and should not be used as an antimalarial[203, 216]. Travellers should be forewarned, as it may still be available in some countries.	**D III**
Piperaquine tolerability, efficacy, pharmacokinetic profile and low cost make it a promising partner drug for use as part of an artemisinin-based combination treatment[228].	**B II**
Pyrimethamine alone (Daraprim®) is not recommended for malaria chemoprophylaxis because of widespread antifolate drug resistance[219].	**D III**
Proguanil should **not** be used as a single agent for chemoprophylaxis because of widespread drug resistance[229].	**D III**
Pyrimethamine-sulfadoxine (Fansidar®) is not recommended for chemoprophylaxis because of the life-threatening complication of Stevens-Johnson syndrome and toxic epidermal necrolysis[203, 229].	**E III**
Pyronaridine has received insufficient study to recommend its use for the treatment of malaria in non-immune travellers.	**D III**
Savarine is less effective than mefloquine, doxycycline and atovaquone/proguanil and is not routinely recommended for malaria prophylaxis[77, 220, 223].	**EII**
Tafenoquine shows promise for future use as a long duration chemoprophylactic in those without G6PD deficiency[224, 225].	**B II**

Table 5: Base/salt equivalents of selected antimalarial drugs

Drug	*Base (mg)*	*Salt (mg)*
Chloroquine phosphate	155.0	250.0
Chloroquine phosphate[a]	100.0	136.0
Clindamycin hydrochloride	150.0	225.0
Mefloquine	250.0	274.0
Primiquine	15.0	26.3
Quinidine gluconate	5.0	8.0
	7.5	12.0
	10.0	16.0
	15.0	24.0
Quinidine sulfate[b]	7.5	9.0
	10.0	12.0
	15.0	18.0
Quinine dihydrochloride	5.0	6.0
	7.5	9.0
	15.0	18.0
	16.7	20.0
Quinine sulfate	250.0	300.0

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

Table 6: Drugs for the treatment and prevention of malaria

Drug, generic (trade) name	*Indication*	*Adult dosage*	*Pediatric dosage*	*Advantage*	*Disadvantage*	*Adverse effects*
ATOVAQUONE/ PROGUANIL (ATQ/PG) (Malarone®) (Malarone® Pediatric)	Prevention and treatment of *P. falciparum*	**Adult tablet:** 250 mg atovaquone plus 100 mg proguanil hydrochloride **Prevention:** 1 tablet daily; start one day before entering malarial area and continue for 7 days after leaving malarial area **Treatment:** 1000 mg atovaquone AND 400 mg proguanil (4 tablets) once daily x 3 days	**Pediatric tablets** 62.5 mg atovaquone plus 25 mg proguanil hydrochloride **Adult tablet:** 250 mg atovaquone plus 100 mg proguanil hydrochloride **Prevention:** start 1 day before entering malarial area and continue for 7 days after leaving area; < 11 kg: see Chapter 4 11-20 kg: 1 pediatric tablet daily > 20-30 kg: 2 pediatric tablets daily (as single dose) > 30-40 kg: 3 pediatric tablets daily (as single dose) > 40 kg: 1 adult tablet daily **Treatment:** 20 mg/kg atovaquone AND 8 mg/kg proguanil once daily x 3 days; < 11 kg: see Chapter 4 (based on a pediatric tablet of 62.5 mg atovaquone/25 mg proguanil, the daily doses are ½ pediatric tablet for 5 to 8 kg, and ¾ pediatric tablet for > 8 to 10 kg) 11-20 kg: 1 adult tablet daily >20-30 kg: 2 adult tablets daily >30-40 kg: 3 adult tablets daily > 40 kg: 4 adult tablets daily	Causal prophylaxis – only have to continue for 7 days after exposure	Daily dosing for prophylaxis	**Frequent:** Nausea, vomiting, abdominal pain, diarrhea, increased transaminases **Rare:** Seizures, rash, mouth ulcers, hepatitis
ARTESUNATE Vial 110 mg powder and vial buffered diluent	Treatment of severe and complicated malaria	**Treatment:** 2.4 mg/kg at hours 0, 12, 24 and 48 with possible doses daily for total of 7 days if concurrent doxycycline, atovaquone/ proguanil of clindamycin are not tolerated	**Treatment:** 2.4 mg/kg at hours 0, 12, 24, 48 and 72 with possible doses daily for total of 7 days if concurrent doxycycline, atovaquone/proguanil of clindamycin are not tolerated	Faster response than parenteral quinine; no cardiovascular or hypoglycemic effects	Requires concurrent therapy with second drug	
CHLOROQUINE (Novo-Chloroquine) Tablet: 155 mg base	Prevention and treatment in chloroquine-sensitive *P. falciparum* areas Treatment of *P. vivax, P. ovale, P. malariae*	**Prevention:** 310 mg base once weekly; start 1 week before entering malarial area and continue for 4 weeks after leaving area **Treatment:** Loading dose of 620 mg base, followed by 310 mg base 6 hours later. This is followed by 310 mg base on each of the next 2 days for a total of 1.55 g base	**Prevention:** once weekly dose, start 1 week before entering malarial area and continue for 4 weeks after leaving area < 15 kg: 5 mg base/kg 15-<20 kg: one half tablet (125mg chloroquine diphosphate) 20-<25 kg: ¾ tablet (187.5mg) 25-<35 kg: 1 tablet (250 mg) 35-50 kg: 1½ tablets (375 mg) > 50 kg: 2 tablets (500 mg) **Treatment:** 25 mg base/kg total over 3 days: 10 mg base/kg on days one and two, 5 mg base/kg on day 3	Long-term safety data for prophylaxis	Most areas now report chloroquine resistance	**Frequent:** Pruritis in black-skinned individuals, nausea, headache **Occasional:** Skin eruptions, reversible corneal opacity **Rare:** Nail and mucous membrane discoloration, partial alopecia, photophobia, nerve deafness, myopathy, retinopathy with daily use, blood dyscrasias, psychosis and seizures

CLINDAMYCIN (Dalacin C®, Apo-Clindamycin, Novo-Clindamycin)	Alternative treatment for *P. falciparum* with a second drug if standard therapy contraindicated	**Prevention:** no indication **Treatment oral:** 300 mg base every 6 hrs for 7 days **Treatment IV:** 10 mg/kg (loading dose) IV followed by 5 mg/kg every 8 hours for 7 days until oral therapy is tolerated. NOTE: Should only use if patient is unable to take doxycycline or ATQ/PG	**Prevention:** no indication **Treatment oral:** 5 mg base/kg every 6 hours for 7 days **Treatment IV:** 10 mg/kg (loading dose) IV followed by 5 mg/kg every 8 hours for 7 days until oral therapy is tolerated. NOTE: Should only use if patient is unable to take doxycycline or ATVPG	Safe in pregnancy and young children	Lower efficacy than atovaquone/ proguanil alone or combination of doxycycline plus quinine	**Frequent:** Diarrhea, rash **Occasional:** Pseudomembranous colitis **Rare:** Hepatotoxicity, blood dyscrasias
DOXYCYCLINE (Vibra-TabsTM, Apo-Doxy, Doxycin, Novo-Doxylin, Nu-Doxycycline, ratio-Doxycycline)	Prevention and treatment of chloroquine-resistant *P. falciparum*	**Prevention:** 1 tablet (100 mg) once daily; start 1 day before entering malarial area and continue for 4 weeks after leaving area **Treatment:** 1 tablet (100 mg) twice daily for 7 days	**Prevention:** < 25 kg or < 8 yr: contraindicated Start 1 day before entering malarial area and continue for 4 weeks after leaving area 2 mg base/kg once daily (max 100 mg daily) 25-35 kg: 50 mg daily > 35 kg-50 kg: 75 mg daily > 50 kg: 100 mg daily **Treatment:** < 25 kg or < 8 yr: contraindicated 2 mg base/kg twice daily (max. 200 mg daily) 25-35 kg: 50 mg twice daily > 35-50 kg: 75 mg twice daily > 50 kg: 100 mg twice daily for 7 days	Protection against leptospirosis	Daily dosing required for chemoprophylaxis	**Frequent:** Gastrointestinal upset, vaginal candidiasis, photosensitivity **Occasional:** Azotemia in renal diseases **Rare:** Allergic reactions, blood dyscrasias, esophageal ulceration
HYDROXY-CHLOROQUINE (Plaquenil, Apo-Hydroxyquine, Gen-Hydroxychloroquine) Tablet: 155 mg base	Prevention and treatment in chloroquine-sensitive *P. falciparum areas Treatment of P. vivax, P. ovale, P. malariae*	**Prevention:** 310 mg base once weekly; start 1 week before entering malarial area and continue for 4 weeks after leaving area **Treatment:** Loading dose of 620 mg base, followed by 310 mg base 6 hours later. This is followed by 310 mg base on each of the next 2 days for a total of 1.55 g base	**Prevention:** 5 mg base/kg once weekly; maximum 310 mg base weekly; start 1 week before entering malarial area and continue for 4 weeks after leaving area **Treatment:** Total dose of 25 mg base/ kg over 3 days: 10 mg base/kg (not to exceed 620 mg base) on days 1 and 2, 5 mg base/kg on day 3	Long-term safety data for prophylaxis	Most areas now report chloroquine resistance	**Frequent:** Pruritis in black-skinned individuals, nausea, headache **Occasional:** Skin eruptions, reversible corneal opacity **Rare:** Nail and mucous membrane discoloration, partial alopecia, photophobia, nerve deafness, myopathy, retinopathy with daily use, blood dyscrasias, psychosis and seizures

MEFLOQUINE (Lariam®, Apo-Mefloquine)	Prevention of *P. falciparum*	**Prevention:** Start at least 1 week (preferably 2-3 weeks) before departure and continue for 4 weeks after leaving malarial area **Loading dose** – see see text 250 mg once weekly **Treatment:** not routinely recommended, see text	**Prevention:** Start at least 1 week (preferably 2-3 weeks) before departure and continue for 4 weeks after leaving malarial area **Loading dose** – see see text 5 mg/kg once weekly < 5 kg: no data. See Chapter 4 5-10 kg: 1/8 tablet > 10-20 kg: ¼ tablet > 20-30 kg: ½ tablet > 30-45 kg: ¾ tablet > 45 kg: 1 tablet **Treatment:** not routinely recommended, see text	Weekly dosing Long-term safety data	There have been occasional publicized cases of severe intolerance to mefloquine, which may result in increased concern. If mefloquine is the best choice but concern is expressed, consider either a loading dose or start 3 weeks before departure to test for tolerability – see Chapter 9	**Frequent:** Dizziness, headache, sleep disorders, nightmares, nausea, vomiting, diarrhea **Occasional:** Sensory and motor neuropathies, seizures, abnormal coordination, confusion, hallucinations, forgetfulness, emotional problems, including anxiety, aggression, agitation, depression, mood changes, panic attacks, psychotic or paranoid reactions, restlessness **Rare:** Suicidal ideation and suicide (relation to drug administration not established)
PRIMAQUINE (Primaquine phosphate)	Prevention of chloroquine-resistant *P. falciparum* Terminal prophylaxis for *P. vivax* and *P. ovale* Radical cure for *P. vivax* and *P. ovale* infections	**Prevention: Primary prophylaxis** 30 mg base daily. Start 1 day before entering malarial area and continue for 7 days after leaving area **Terminal prophylaxis or radical cure:** 30 mg base/day for 14 days	**Prevention:** Primary prophylaxis 0.5 mg base/kg daily. Start 1 day before entering malarial area and continue for 7 days after leaving area **Terminal prophylaxis or radical cure:** 0.5 mg base/kg daily for 14 days	Causal prophylaxis – only have to continue for 7 days after exposure	Daily dosing Require G6PD* testing, see text	**Occasional:** GI upset, hemolysis in G6PD deficiency, methemoglobinemia
QUINIDINE GLUCONATE/ SULFATE		**Prevention:** no indication **Treatment:** see Table 4	**Prevention:** no indication **Treatment:** see Table 4 28 mg base/kg daily, divided q 8 hourly.**		Parenteral therapy requires cardiac monitoring	**Frequent:** Vomiting, cramps, cinchonism (tinnitus, nausea, headache, blurred vision) **Occasional:** Widening of QRS complex, cardiac disturbance, fever, delirium, rashes **Rare:** Acute hemolytic anemia
QUININE DIHYDRO-CHLORIDE		**Prevention:** no indication **Treatment:** See Table 4	**Prevention:** no indication **Treatment:** See Table 4			**Frequent:** Cinchonism (tinnitus, nausea, headache, blurred vision), hypoglycemia **Occasional:** Cardiac conduction disturbances, hypersensitivity **Rare:** Hemolysis

QUININE DIHYDRO-CHLORIDE		**Prevention:** no indication **Treatment oral:** 500 mg base 3 times daily for 3-7 days (7 days for SE Asia) **IV:** See Table 4	**Prevention:** no indication **Treatment oral:** 7.5 mg base/kg (max 500 mg base) 3 times daily for 3-7 days (7 days for SE Asia) **IV:** See Table 4			Similar to above

* Glucose-6-phosphate dehydrogenase
** Suggested mixing instructions: to make 120 mL solution of concentration 8.3 mg base/mL combine 60 mL Orasweet and 60 mL Oraplus with 6 x 200 mg tablets of crushed quinidine sulfate.

Appendix I

Malaria Risk by Geographic Area in Countries with Endemic Malaria (2008)

Note: While relatively accurate in the shorter term, the risk areas, elevations and seasonality data cannot be interpreted as absolute; such data can change from year to year and season to season. For the major malaria-risk countries, where risk occurs in all areas and all year, there is expected to be little variation from year to year that would affect malaria chemoprophylaxis recommendations. However, in other areas, risk may vary; hence, it is recommended that travel health practitioners keep abreast of potential changes, e.g., by regular monitoring of the Public Health Agency of Canada's *Travel Health Program* at **http://www.phac-aspc.gc.ca/travelhealth.gc.ca**, the World Health Organization's International Travel and Health 2009 at **http://www.who.int/ith/en/**, and the US Centers for Disease Control and Prevention, *Health Information for International* Travel, 2008 at **http://wwwn.cdc.gov/travel/contentYellowBook.aspx**

Key:

CQ = chloroquine, MEF = mefloquine, DOXY = doxycyline, A/P = atovaquone/proguanil

Country[1]	Malarious Areas[2]	Seasonality (inclusive)[3]	% *Plasmodium falciparum (Pf)*[(4)]	Chloroquine-resistant *Pf* reported[(2)]	Chemoprophylaxis recommended by CATMAT
Afghanistan	All areas below 2,000 metres elevation	May-Nov	10	yes	MEF, DOXY, A/P
Algeria	One small focus in the Sahara region in Ihrir (Illizi Department)	Not reported; assumed to be Jan-Dec	< 1	no	Risk is very limited; therefore, prophylaxis is not recommended
Angola	*All areas*	Jan-Dec	90	yes	MEF, DOXY, A/P
Argentina	Rural areas of Salta and Jujuy provinces (along the Bolivian border) and Misiones and Corrientes provinces (along the border of Paraguay)	Oct-May[(3)]	0	no	CQ
Armenia	Limited to the Ararat Valley in the Ararat and Artashat region; greatest risk in Masis district	Jun-Oct	0	no	CQ
Azerbaijan	Rural lowlands near Kura and Arax rivers in the provinces of Agcabadi, Barda, Beylaqan, Bilasuvar, Calilabad, Fuzuli, Imisli, Kurdamir, Nakhichivan, Sabirabad, Saatli and Zardab	Jun-Oct	0	no	CQ
Bahamas	Intermittantly rare cases reported in Greater Exuma Island	Jan-Dec [(4)]		no	Risk is very limited; therefore, prophylaxis is not recommended
Bangladesh	All areas, except no risk in city of Dhaka	Jan-Dec	44	yes	MEF, DOXY, A/P
Belize	All areas, except no risk in Belize City	Jan-Dec [(3)]	14	no	CQ
Benin	All areas	Jan-Dec	87	yes	MEF, DOXY, A/P
Bhutan	The 5 southern belt districts of: Chirang, Samchi, Samdrup Jongkhar, Sarpang and Shemgang at elevations less than 1,700 metres[2]	Jan-Dec	41	yes	MEF, DOXY, A/P
Bolivia	The following departments: Beni, Chuquisaca, Cochabamba, La Paz, Pando, Santa Cruz and Tarija. No risk in city of La Paz or at elevations greater than 2,500 metres	Jan-Dec	5	yes	MEF, DOXY, A/P

Botswana	North of 22°S in the northern provinces of Central, Chobe, Ghanzi, Ngamiland and including safaris to the Okavango Delta area. No risk in the city of Gaborone	Nov-Jun	95	yes	MEF, DOXY, A/P
Brazil	States of Acre, Rondônia, Amapá, Amazonas, Roraima and Tocantins. Parts of states of Maranhaõ (western part), Mato Grosso (northern part), and Pará (except Belem City). Transmission also occurs in urban areas, including large cities such as Porto Velho, Boa Vista, Macapa, Manaus, Santarem and Maraba, where transmission occurs on the urban periphery. Risk at elevations up to 900 metres	Jan-Dec [3]	25	yes	MEF, DOXY, A/P
Burkina Faso	All areas	Jan-Dec	> 85	yes	MEF, DOXY, A/P
Burundi	All areas	Jan-Dec	> 85	yes	MEF, DOXY, A/P
Cambodia	Throughout the country, including risk in the temple complex at Angkor Wat. No risk in Phnom Penh and around Lake Tonle Sap	Jan-Dec	90	Yes (also mefloquine resistance reported in western provinces bordering Thailand)	DOXY, A/P in the provinces of Preah Vihear, Siemreap, Oddar, Meanchey, Banteay Meanchey, Battambang, Pailin, Koh Kong, and Pursat bordering Thailand. All other areas MEF, DOXY, A/P
Cameroon	All areas	Jan-Dec	> 85	yes	MEF, DOXY, A/P
Cape Verde	Limited to Saõ Tiago Island	Aug-Nov	Not reported	yes	MEF, DOXY, A/P
Central African Republic	All areas	Jan-Dec	> 85	yes	MEF, DOXY, A/P
Chad	All areas	Jan-Dec	> 85	yes	MEF, DOXY, A/P
China	Rural areas only of the following provinces: (at elevations of 1,500 metres and below) Hainan, Yunnan, Fuijan, Guangdong, Guangxi, Guizhou, Sichuan, Tibet (in the Zangbo River valley only), Anhui, Hubei, Hunan, Jiangsu, Jiangxi, and Shandong	North of 33º N, Jul-Nov; between 25º N and 33º N, May-Dec; south of 25º N, Jan-Dec [2]	9	yes (in Hainan and Yunan)	DOXY, AP along China-Burma border in the western part of Yunnan province and MEF, DOXY, A/P in Hainan and other parts of Yunnan province (NOTE: travellers to cities and popular tourist areas, including Yangtze River cruises, are not at risk and do not need to take chemoprophylaxis)
Colombia	All rural/jungle areas below 1,600m; no risk in Bogotá and vicinity	Jan-Dec	38	yes (in Amazonia, Pacifico, and Uraba-Bujo Cauca)	MEF, DOXY, A/P
Comoros	All areas	Jan-Dec	88	yes	MEF, DOXY, A/P
Congo	All areas	Jan-Dec	90	yes	MEF, DOXY, A/P
Congo, Democratic Republic of the (formerly Zaire)	All areas	Jan-Dec	93	yes	MEF, DOXY, A/P
Costa Rica	In Alajuela, Limón, Guanacaste and Heredia provinces; no risk in Limón city (Puerto Limon)	Jan-Dec	< 1	no	CQ
Côte D'Ivoire (Ivory Coast)	All areas	Jan-Dec	88	yes	MEF, DOXY, A/P
Djibouti	All areas	Jan-Dec	98	yes	MEF, DOXY, A/P

Dominican Republic	Rural, with highest risk in provinces bordering Haiti; in addition, risk in all areas of La Altagracia Province, including resort areas	Jan-Dec	99	no	CQ
Ecuador	All areas 1,500 metres elevation and below; no risk in the cities of Guayaquil and Quito, the central highland tourist areas, and the Galápagos Islands	Jan-Dec	15	yes	MEF, DOXY, A/P
Egypt	Very limited risk in El Faiyûm area only; no risk in tourist areas, including Nile River cruises	Jun-Oct	< 1	no	None (risk is very limited; therefore, prophylaxis is not recommended)
El Salvador	Rural areas of Santa Ana, Ahuachapán and La Unión departments; no risk in the city of San Salvador	Jan-Dec [3]	< 1	no	CQ
Equatorial Guinea	All areas	Jan-Dec	> 85	yes	MEF, DOXY, A/P
Eritrea	All areas 2,200 m elevation and below; no risk in Asmara	Jan-Dec	85	yes	MEF, DOXY, A/P
Ethiopia	All areas 2,000 m elevation and below; no risk in Addis Ababa	Jan-Dec	> 85	yes	MEF, DOXY, A/P
French Guiana	All areas except no risk on Devil's Island (Ile du Diable) and the other coastal islands	Jan-Dec	45	yes	MEF, DOXY, A/P
Gabon	All areas	Jan-Dec	95	yes	MEF, DOXY, A/P
Gambia	All areas	Jan-Dec	> 85	yes	MEF, DOXY, A/P
Georgia	In southeastern part of the country near Azerbaijan border and Kura River and in the districts of Gardabanis, Marneulis and Sighnaghis in the Kakheti and Kveno Kartli regions; no risk in Tbilisi	Jul-Oct	0	no	CQ
Ghana	All areas	Jan-Dec	> 85	yes	MEF, DOXY, A/P
Guatemala	Rural areas at 1,500 metres elevation and below; no risk in Guatemala City, Antigua or Lake Atitlán	Jan-Dec	5	no	CQ
Guinea	All areas	Jan-Dec	92	yes	MEF, DOXY, A/P
Guinea-Bissau	All areas	Jan-Dec	90	yes	MEF, DOXY, A/P
Guyana	All rural areas at 900 metres elevation and below	Jan-Dec	50	yes	MEF, DOXY, A/P
Haiti	All areas	Jan-Dec	100	no	CQ
Honduras	Throughout the country at altitudes below 1,000 m (< 3,281 ft) and in Roatán and other Bay Island; risk exists in the outskirts of Tegucigalpa and San Pedro Sula	Jan-Dec [3]	3	no	CQ
India	All areas throughout country, except no risk in areas above 2,000 meters in Himachal Pradesh, Jammu, kashmir and Sikkim; in urban areas below 2,000 m, including Delhi and Mumbai (Bombay)	Jan-Dec	45	yes	MEF, DOXY, A/P
Indonesia	Rural Sumatra, Sulawesi, Kalimantan and Nusa Tenggara Barat (no risk in urban areas); in all areas of eastern Indonesia (provinces of Papua Indonesia, Irian Jaya Barat, Nusa Tenggara Timur, Maluku, and Maluku Utara); no risk in Jakarta, resort areas of Bali and the island of Java, except for the Menoreh Hills in central Java	Jan-Dec	66	yes	MEF, DOXY, A/P

Iran	Rural areas of Sistan- Baluchestan, the southern tropical part of Kerman, and Hormozgan province; in Ardebil and East Azerbijan provinces north of the Zagros mountains	Mar-Nov in areas of Kerman (tropical part), Hormozgan and southern Sistan-Baluchestan; summer months in Ardebil and East Azerbijan provinces north of the Zagros mountains	41	yes	MEF, DOXY, A/P
Iraq	Basrah province and below 1,500 metres in provinces of Duhok, Erbil, Ninawa, Sulaimaninya and Ta'mim ; no risk in Baghdad, Tikrit and Ramadi	May-Nov	0	no	CQ
Jamaica	Very limited risk, in Kingston	Jan-Dec [4]	unreported	no	CQ
Kenya	All areas (including game parks) below 2,500 metres elevation; no risk in Nairobi	Jan-Dec	> 85	yes	MEF, DOXY, A/P
Korea, Democratic People's Republic of (North Korea)	Limited risk in some southern areas	Not reported; assumed to be Jan-Dec	0	no	CQ
Korea, Republic of (South Korea)	Limited to Demilitarized Zone (DMZ) and to rural areas in the northern parts of Kyonggi and Kangwon Provinces	Not reported; assumed to be Jan-Dec	0	no	CQ
Kyrgyzstan	Some southern and western parts of the country, mainly in the provinces of Batken, Osh, and Jalal-Abad in the areas bordering Tajikistan and Uzbekistan; also in the capital city Bishkek.	Jun-Oct	0	no	CQ
Lao People's Democratic Republic (Laos)	All, except no risk in city of Vientiane	Jan-Dec	97	yes	DOXY, A/P in the provinces of Bokèo and Louang Namtha along the Laos-Burma border and along the Laos-Thailand border in the province of Saravane and Champassack. All other areas MEF, DOXY, A/P
Liberia	All areas	Jan-Dec	90	yes	MEF, DOXY, A/P
Madagascar	All areas	Jan-Dec	> 85	yes	MEF, DOXY, A/P
Malawi	All areas	Jan-Dec	90	yes	MEF, DOXY, A/P
Malaysia	Rural areas, particularly in the forested, hilly and underdeveloped interior areas; no risk in urban and coastal areas. Note: no risk in Republic of Singapore.	Jan-Dec [3]	65	yes	MEF, DOXY, A/P
Mali	All areas	Jan-Dec	> 85	yes	MEF, DOXY, A/P
Mauritania	All, except no risk Dakhlet-Nouadhibou and Tiris-Zemmour region	Jan-Dec in all areas except Jul-Oct in Adrar and Inchiri	> 85	likely	MEF, DOXY, A/P

Mauritius	Rural areas only; no risk on Rodrigues Island	Jan-Dec [3]	0	no	CQ
Mayotte (French Territorial Collectivity)	All areas	Jan-Dec	Not reported	yes	MEF, DOXY, A/P
Mexico	Limited to areas infrequently visited by travellers, including small foci along the Guatemala and Belize borders in the states of Chiapas, Quintana Roo and Tabasco; rural areas in the states of Nayarit, Oaxaca, Sinaloa; and in an area between 24° N and 28° N latitude, and 106° W and 110° W longitude, which lies in parts of Sonora, Chihuahua, and Durango. No malaria risk exists along the United States-Mexico border. No malaria risk exists in the major resorts along the Pacific and Gulf coasts	Jan-Dec	1	no	CQ (risk is very limited; therefore, prophylaxis is not recommended for most travellers to Mexico. Travellers should use personal protection measures such as insect repellents for malaria prevention. Chemoprophylaxis is recommended for the rare traveller going to the risk areas)
Morocco (including Western Sahara)	Rural areas of Chefchaouen province; no risk in Tangier, Rabat, Casablanca, Marrakech and Fès	May-Oct	< 1	no	None (risk is very limited; therefore, prophylaxis is not recommended)
Mozambique	All areas	Jan-Dec	95	yes	MEF, DOXY, A/P
Myanmar (formerly Burma)	Rural areas throughout the country below 1,000 metres elevation; no risk in cities of Rangoon (Yangon) and Mandalay	Jan-Dec	85	yes	DOXY, A/P in the provinces of Shan, Kayah, Kachin, Kayin, and Tanintharyi. MEF, DOXY, A/P in all other areas
Namibia	The provinces of Kunene, Ohangwena, Okavango, Omaheke, Omusati, Oshana, Oshikoto, Otjozondjupa and the Caprivi Strip	Nov-Jun in: Oshana, Oshikoto, Omusati, Omaheke, Ohangwena and Otjozondjupa. Jan-Dec along the Kunene river and in Kavango and Caprivi regions.	90	yes	MEF, DOXY, A/P
Nepal	Risk below 1,200 metres in rural areas in the Tarai and Hill districts bordering India and in the areas of the inner Tarai valley areas of Udaypur Sindhupalchowk, Makwanpur, Chitwan and Dang; no risk in Kathmandu or on typical Himalayan treks	Jan-Dec	12	yes	MEF, DOXY, A/P
Nicaragua	Rural areas in outskirts of Managua	Jan-Dec	10	no	CQ
Niger	All areas	Jan-Dec	> 85	yes	MEF, DOXY, A/P
Nigeria	All areas	Jan-Dec	> 85	yes	MEF, DOXY, A/P
Oman	Limited risk in remote areas of Musandam Province	Jan-Dec [3]	90	yes	None (risk is very limited; therefore, prophylaxis is not recommended)
Pakistan	All areas, including all cities below 2,000 metres elevation.	Jan-Dec	46	yes	MEF, DOXY, A/P
Panama	Rural areas of Bocas Del Toro, Darién, San Blas provinces and San Blas Islands; no risk in Panama City or in the former Canal Zone	Jan-Dec	13	yes	CQ in Bocas Del Tora; MEF, DOXY, A/P in Darién and San Blas
Papua New Guinea	All areas below 1,800 metres	Jan-Dec	82	yes	MEF, DOXY, A/P

Paraguay	The departments of Alto Paraná, Caaguazú, and Canendiyú	Oct-May [3]	4	no	CQ
Peru	Below 2,000 metres in all departments except Arequipa, Moquegua, Puno and Tacna; risk in Puerto Maldonado	Jan-Dec	15	yes	MEF, DOXY, A/P (NOTE: travellers who will visit only Lima and its vicinity, coastal areas south of Lima or the highland tourist areas [Cuzco, Machu Picchu and Lake Titicaca] are not at risk and need no prophylaxis)
Philippines	All areas below 600 metres elevation, except no risk in Bohol Island, Borocay Island, Catanduanes Island and Cebu Island. No risk is considered to exist in Manila or other urban areas.	Jan-Dec	74	yes (for *P. falciparum*)	MEF, DOXY, A/P
Rwanda	All areas	Jan-Dec	90	yes	MEF, DOXY, A/P
Sao Tome and Principe	All areas	Jan-Dec	> 85	yes	MEF, DOXY, A/P
Saudi Arabia	Al Bahah, Al Madinah, Asir (excluding the high-altitude areas above 2,000 m), Jizan, Makkah, Najran and Tabuk province. No risk in urban areas of Jeddah, Mecca, Medina and Ta'if	Jan-Dec	88	yes	MEF, DOXY, A/P
Senegal	All areas	Jan-Dec	> 85	yes	MEF, DOXY, A/P
Sierra Leone	All areas	Jan-Dec	> 85	yes	MEF, DOXY, A/P
Solomon Islands	All areas except for the southern province of Rennell and Bellona, the eastern province of Temotu, and the outer islands of Tikopia, Anuta and Fatutaka	Jan-Dec	62	yes	MEF, DOXY, A/P
Somalia	All areas	Jan-Dec	95	yes	MEF, DOXY, A/P
South Africa	The low altitude areas of the Mpumalanga Province, Northern Province Limpopo and northeastern KwaZulu-Natal as far south as the Tugela (Thukela) River; also, risk in Kruger National Park	Jan-Dec	99	yes	MEF, DOXY, A/P
Sri Lanka	All areas, except no risk in the districts of Colombo, Galle, Kalutara and Nuwara Eliya	Jan-Dec	12	yes	MEF, DOXY, A/P
Sudan	All areas	Jan-Dec	90	yes	MEF, DOXY, A/P
Suriname	All areas, except no risk in the Paramaribo and coastal districts of Nickerie, Coronie, Saramacca, Wanica, Commewijne and Marowijne north of 5° N	Jan-Dec	81	yes (also: mefloquine reistance reported)	MEF, DOXY, A/P
Swaziland	The northern and eastern lowland areas bordering Mozambique in the Lubombo district, particularly around the villages/towns of Big Bend, Mhlume, Simunye and Tshaneni	Jan-Dec	99	yes	MEF, DOXY, A/P
Syrian Arab Republic (Syria)	Along the northern border in El Hassaka province	May-Oct	0	no	CQ
Tajikistan	All areas below 2,500 elevation, particularly along the southern border in Khatlon Oblast; central (Dushanbe), western (Gorno- Badakhshan), and northern (Leninabad) areas	Jun-Oct	9	yes	MEF, DOXY, A/P
Tanzania	All areas below 1,800 metres	Jan-Dec	> 85	yes	MEF, DOXY, A/P

Thailand	In rural areas that border Cambodia, Laos and Myanmar (Burma); risk in Koh Phangan. No risk in cities and no risk in major tourist resorts. No risk in Bangkok, Chiang Mai, Chiang Rai, Pattaya, Phuket Island and Ko Samui	Jan-Dec	56	yes (also: mefloquine resistance reported from areas near the borders with Cambodia and Myanmar)	DOXY, A/P
Timor Leste (East Timor)	All areas	Jan-Dec	Predominates[2]	yes	MEF, DOXY, A/P
Togo	All areas	Jan-Dec	> 85	yes	MEF, DOXY, A/P
Turkey	The provinces of Adana, Adryaman, Batman, Bingol, Bitlis, Diyarbakar, Elazig, Gaziantep, Hakkari, Hatay, Icel, Kahraman Maras, Kilis, Mardin, Mus, Osmaniyeh, , Sanliurfa, Siirt, Sirnak and Van; no risk on the Incirlik U.S. Air Force base and on typical cruise itineraries	May-Oct	0	no	CQ
Turkmenistan	Southeast Mary Region and in the flood plains between the Murgab and Tedzhen Rivers	Jun-Oct	0	no	CQ
Uganda	All areas	Jan-Dec	> 85	yes	MEF, DOXY, A/P
Uzbekistan	Sporadic cases reported in Uzunskiy, Sariassiskiy and Shurchinskiy districts (Surkhanda-Rinskaya Region)	Typically May-Oct [(4)]	0	no	CQ
Vanuatu	All areas	Jan-Dec	62	yes	MEF, DOXY, A/P
Venezuela	Rural areas of the following states: Apure, Amazonas, Barinas, Bolivar, Sucre, Tachira and Delta Amacuro; risk in Angel Falls	Jan-Dec	10	yes	MEF, DOXY, A/P
Viet Nam	Rural areas, except no risk in the Red River Delta and the coastal plain north of Nha Trang.; no risk in Hanoi, Ho Chi Minh City (Saigon), Da Nang, Nha Trang, Qui Nhon and Haiphong	Jan-Dec[(3)]	72	yes (also: mefloquine resistance reported)	DOXY, A/P in the southern part of the country in the provinces of Tay Ninh, Song Be, Lam Dong, Ninh Thuan, Khanh Hoa, Dac Lac, Gia Lai and Kon Tum. All other areas MEF, DOXY, A/P.
Yemen	All areas below 2,000 metres; no risk in Sana'a	Jan-Dec	95	yes	MEF, DOXY, A/P
Zambia	All areas	Jan-Dec	90	yes	MEF, DOXY, A/P
Zimbabwe	All areas, except no risk in cities of Harare and Bulawayo	Nov-Jun in areas below 1,200 m; Jan-Dec in the Zambezi valley	97	yes	MEF, DOXY, A/P

References

1 from World Health Organization (WHO) country nomenclature at **http://www.who.int/ith/countries/en/** (last accessed: 23 April 2009)
2 from US Centers for Disease Control and Prevention, Health Information for International Travel, 2007-2008 (last accessed: 13 April 2009)
3 from International Association for Medical Assistance to Travellers at **http://www.iamat.org/pdf/WorldMalariaRisk.pdf** (last accessed: 13 April 2009)
4 from sources other than WHO
5 from sources other than IAMAT

Appendix II

Checklist for Advising Travellers to Malarial Areas

The following is a checklist of key issues to be considered in advising travellers.

☐ **Assess the Risk of Malaria** (see Chapter 2 and Appendix I)

- Destination and distribution of malaria within destination country
- Is the malaria in the destination country seasonal?
- What species of malaria is/are present at the destination?
- Is drug resistance documented?

Travellers should be informed about their individual risk of malaria infection and the presence of drug-resistant *P. falciparum* malaria in their travel destinations.

Those who are pregnant, travelling with young children or who have medical conditions that put them at increased risk (see Chapter 5) should carefully evaluate the risks/benefits of choosing a malaria-endemic destination.

☐ **Chemoprophylaxis Recommendations**

- Does the traveller have any drug allergies?
- Does the traveller have any contraindications to antimalarial agents?
- Does the traveller have any medical conditions that would influence the choice of antimalarial agents?
- Does the traveller have any prior experience with antimalarial agents?
- Does the traveller have any strong opinions for, or against, a particular agent?

☐ **Provide Education Regarding Malaria Chemoprophylaxis**

- Start chemoprophylaxis before travel as directed.
- Use chemoprophylaxis continuously while in malaria-endemic areas and for 4 weeks after leaving such areas (except for atovaquone/proguanil and primaquine, which are taken for 1 week after leaving such areas).
- Be aware that all antimalarial drugs can cause side effects; most minor side effects abate even with continued use of the drugs and should not prompt discontinuation of chemoprophylaxis. If side effects persist, medical advice should be sought.
- If serious side effects occur, medical advice should be sought promptly and use of the drug discontinued.
- Travellers who discontinue antimalarial medications because of side effects should take an effective alternative drug.
- Travellers should be aware that they may acquire malaria even if chemoprophylaxis is used.
- Travellers should be advised that they may receive conflicting information regarding antimalarial drugs from almost any source, including other travellers, websites and health providers in endemic countries. Such advice is often inaccurate or based on an understanding of malaria in semi-immune populations. Travellers should continue their prescribed medication unless they are experiencing at least moderate to severe adverse effects.

- Travellers should be advised that some popular antimalarial measures (e.g., papaya tea and others) promoted in endemic areas have not been proven effective and should not be used as a substitute for chemoprophylactic agents with documented efficacy.

☐ **Provide Education Regarding Personal Protective (Anti-mosquito) Measures**
Travellers should be instructed on how to protect themselves against mosquito bites.

- All travellers to endemic areas should be encouraged to use insecticide-impregnated bednets if not in air-conditioned sleeping accommodation.
- DEET is the most effective available mosquito repellent. Extended-duration DEET preparations are recommended for malaria-endemic areas. If extended-duration formulations are not available, products containing 30%-35% DEET should be used.
- DEET should be evenly applied to all exposed skin and should be reapplied if biting activity is observed prior to the recommended reapplication interval noted on the product label.
- Alternatives when DEET cannot be used include Picaridin (Bayrepel™), lemon eucalyptus oil and soybean oil 2%. Since the duration of action of these products varies, product use instructions should be consulted and followed carefully.
- Many other non-DEET repellents are of limited efficacy and usually provide only transient protection. Avoid using citronella oil-based repellents because of very short durations of action.

Refer to CATMAT Statement on Personal Protective Measures to Prevent Arthropod Bites for more detailed information: **http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/05vol31/asc-dcc-4/index.html**

☐ **Provide Education About Malaria Illness** (see Chapter 6)

- Symptoms of malaria may be mild and non-specific, and malaria should be considered in any **unexplained fever** or "**flu-like**" illness during or after travel to endemic areas.
- Travellers should advise health care providers of their travel to malaria-endemic areas.
- Diagnosis of malaria requires laboratory testing (blood smears, PCR or rapid diagnostic tests). Diagnosis based on symptoms alone is highly inaccurate.
- Medical help should be sought promptly if malaria is suspected, and diagnostic testing should be done on one or more occasions. If the patient is travelling when symptoms develop, they should request blood smears that can be brought home for review.
- Malaria may become severe and/or lead to death if treatment is delayed. Progression from mild to life-threatening disease can occur at any point in the illness and within hours.
- Self-treatment (if prescribed) should be taken only if prompt medical care is not available. Medical advice should still be sought as soon as possible after self-treatment.
- Chemoprophylaxis should be continued even if malaria occurs (proven or suspect case).

☐ **Special Travellers** (see Chapters 4 and 5)

- Pregnant women, young children and those with underlying medical conditions require special attention because of the potential effects of malaria illness and the contraindication of certain drugs (e.g., doxycycline in pregnant women and young children).

- Pregnant women (or women who may become pregnant while travelling or residing in endemic areas) should be advised that pregnancy is a time of heightened risk for malaria infection and adverse consequences to both mother and fetus.
- Individuals who have spent many years in malaria-endemic areas often consider themselves immune to malaria. Such individuals who return to endemic areas often choose not to take malaria precautions and are at risk of infection and severe disease. Immunity to malaria is strain specific, short-lived and always incomplete. Even those with extensive past exposure to malaria should use effective malaria prevention, including chemoprophylaxis.
- Long-term travellers may choose to discontinue malaria chemoprophylaxis because of concerns about long-term drug use or a misguided attempt to "build up immunity to malaria". Such travellers should be advised that they remain at risk of malaria (including severe malaria) and that there is no limit on the duration of antimalarial chemoprophylaxis for individuals who are tolerating the medication without significant side effects.

(Adapted from *International Travel and Health*, World Health Organization, Geneva, 2006).

Appendix III

Frequently Asked Questions (FAQS) About Malaria

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1. Is malaria a serious infection for healthy people?

Malaria is a major killer worldwide and is the principal life-threatening infectious disease for Canadians travelling to areas of malaria risk globally. Canadian travellers who were born, grew up or previously lived in malarial areas are NOT protected from malaria and remain at risk regardless of past exposures and episodes of illness. Between 400 and 1,000 cases of malaria are reported among Canadian travellers annually, with one to two malaria deaths annually.

2. Do all travellers to the tropics need malaria prophylaxis?

Many destinations in the tropics are either free of malaria, or the risk is so low that malaria prophylaxis is not needed. Furthermore, some travellers to countries with known malaria risk may not need to take malaria prophylaxis because malaria transmission may be confined to particular areas of a country (usually rural areas) or may be seasonal. For example, most individuals travelling only to major urban centres or resort areas in Central and South America or Southeast Asia do not require malaria prophylaxis. However, ALL travellers (adults and children) to any area with any risk of malaria should use personal protective measures, such as treated mosquito nets and insect repellents, to avoid mosquito bites. The risk of malaria can change rapidly in malaria-free zones within malaria risk countries. Therefore up-to-date information is essential in determining risk.

3. What if I don't see any mosquitoes when I reach my destination? Can I stop taking preventative medications or using mosquito precautions?

No, even if you do not notice mosquitoes you should continue taking malaria prevention medications. The mosquitoes that pass malaria infection to humans typically rest during the day and become active at night and during twilight hours when they are difficult to see. In addition, these species of mosquitoes are inaudible to humans.

4. Should pregnant women, babies and children receive malaria prophylaxis?

Pregnant women, babies and small children are at particular risk of severe malaria or complications. If they must go to high-risk areas, the best available malaria prevention medications should be used, along with rigorous attention to personal protective measures. Several effective prevention regimens are known to be safe in these groups. It is important to remember that drugs taken by nursing mothers will not provide protection for the nursing child.

5. Do most people who take malaria prophylaxis have serious side effects?

For travellers to high-risk areas, the risk of acquiring malaria and dying is significantly greater than the risk of experiencing a serious side effect from malaria prophylaxis. The great majority of people taking malaria prophylaxis (95% to 99%) have either no side effects or only mild and temporary ones. In most studies, only 1% to 6% of people change to an alternative drug because of side effects. Reactions to malaria prevention medications are almost always reversible. Death from malaria, however, is not.

The final choice of which antimalarial drug to use should be based on an individual risk assessment from a knowledgeable travel medicine provider, which should include issues such as the drug's effectiveness, the traveller's willingness to accept potential side effects, the convenience of dosing (weekly versus daily), the cost and the traveller's medical history, including contraindications to antimalarial drugs.

6. Are there safer and/or more effective antimalarial drugs available?

For high-risk regions of the world with chloroquine-resistant malaria, three drugs that are equally effective are currently licensed in Canada: atovaquone/proguanil (Malarone®), doxycycline and mefloquine (Lariam®). Each has advantages and disadvantages. Travellers should be aware that cheaper, locally available drugs, such as chloroquine, proguanil (Paludrine®), amodiaquine (Camoquine®), pyrimethamine (Daraprim®), pyrimethamine plus sulfadoxine (Fansidar®) and pyrimethamine plus dapsone (Maloprim®), may be ineffective, counterfeit, more toxic or inappropriate for high-risk individuals. Travellers may obtain advice from many different sources, including websites, other travellers and residents or health care workers in endemic countries. However, before departure, travellers should consult a health care provider with knowledge of travel medicine for an informed recommendation regarding malaria prophylaxis for their planned itinerary.

7. If I take preventive medications for malaria, is there still a chance I can get sick with malaria?

Proper use of an effective preventive medication for malaria provides a high degree of protection and can reduce the risk of malaria illness by more than 90%, but no preventive medication is 100% effective. Therefore, even if you have taken preventive medication, malaria is still possible and should be considered if you develop an illness with fever during or after travel to malarial areas.

8. If I take prophylaxis, won't it be harder to diagnose malaria if I get it?

Use of malaria prophylaxis may reduce the severity of symptoms and the number of parasites in the blood and therefore could – rarely – result in a minor delay in making a definitive diagnosis by some methods. However, properly used prophylactic drugs will prevent the vast majority of malaria episodes, reduce the risk of severe disease and will not prevent a definitive diagnosis if proper testing is done. The small risk of a slight delay in diagnosis must be contrasted with the significant benefit of preventing disease and reducing the risk of severe disease.

9. If I take prophylaxis, will the malaria I get be more resistant to treatment?

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

10. Is there a limited period in which one can take prophylaxis safely?

There is no absolute time limit on how long one can take any antimalarial prophylactic drug. The few individuals who experience significant side effects from antimalarial drugs usually do so within the first few weeks of use. If side effects are significant, then an alternative drug for malaria prevention should be used. Many mild side effects tend to diminish over time, even with continued use of the drug. Travellers who are concerned about their ability to tolerate medications may wish to consult a travel medicine practitioner well before the travel date and consider a trial of the malaria preventive medication before departure. Long-term travellers should not discontinue a well-tolerated and effective preventive drug simply because they have been taking it for any arbitrary period of time.

11. Is it true that some malaria cannot be treated?

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

12. Once you are infected with malaria, are you are infected for life?

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

13. Is it true that individuals born and raised in a malaria country are immune for life?

Individuals raised in areas where malaria is common often suffer repeated attacks of malaria in childhood (and many die from severe malaria). Those who survive slowly develop a partial degree of immunity to malaria that results in a decreased frequency and severity of attacks. However, this immunity never fully protects them from malaria infection (or severe disease) and diminishes quickly once an individual leaves a malarial area. Travellers returning to a malaria-risk birth country after a period of absence are at high risk of infection and severe disease from malaria and should take both personal protective precautions against mosquito bites as well as malarial prevention medications.

14. How would I know if I develop malaria?

Any individual who has travelled to malarial areas and subsequently develops fever should urgently seek medical advice (even if the fever appears many months after returning to Canada) and request testing to rule out malaria. Early symptoms include headache, muscle or joint aches, backache, fatigue, nausea and low appetite. The classic symptoms of malaria (a cyclical pattern of severe shaking chills, high fever and sweats) are often absent in mild or early cases. Symptoms may mimic other common diseases such as minor viral infections, influenza, gastroenteritis and pneumonia, and the diagnosis of malaria can easily be overlooked if specific testing is not done.

15. Why do I need to continue taking medications even after I have left the malaria-risk area?

Most malaria preventive medications do not actually prevent the initial stages of infection when the parasites are found in the liver but, rather, work only once the parasite has completed its development in the liver and entered the blood stream. The initial phase of infection in the liver can last from 8 days to several months, although the majority of malaria cases occur within the first month after leaving the malarial area. Most prevention medications (chloroquine, mefloquine, doxycycline) must be continued for 4 weeks after exposure ceases to prevent disease caused by parasites, which are in the liver stage when the traveller leaves the malaria-endemic area.

Several malaria prevention medications (atovaquone/proguanil, primaquine) are effective against the liver stages of infection, and these medications may be discontinued several days to 1 week after leaving the malaria-risk area. When malaria prevention medication is prescribed, you will be advised as to how long it should be taken after leaving the malaria-risk area.

Further information on issues related to travel medicine is available through the Travel Health Program of the Public Health Agency of Canada at: **http://www.phac-aspc.gc.ca/travelhealth.**

Appendix IV

Strength and Quality of Evidence Summary

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

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

Appendix IV

Canadian Malaria Network: Accessing Parenteral Artesunate or Quinine

Contact Information for the Canadian Malaria Nework

The Canadian Malaria Network (CMN), in collaboration with Health Canada's Special Access Program and the Public Health Agency of Canada, maintains strategically-located supplies of intravenous artesunate and quinine at major medical centres across the country to facilitate rapid access to effective treatment for severe malaria. These life-saving drugs are available 24 hours per day by contacting the pharmacies listed below.

Severe malaria is not a common disease in Canada, with an average of 14 cases per year (range 8-20 cases annually from 2001-2008). However, these cases were dispersed across the country, and attest to the need for distribution of these scarce drugs across the country. Please see Chapter 7 for more information on management of malaria. As well, each of the participating centers has a designated physician with experience in treating malaria who is willing to assist in patient care, if needed. For after-hours assistance please contact the infectious disease consultant on call at the respective center.

Each treatment dose will be accompanied by dispensing information and surveillance forms (FORM A and FORM B). These forms should be completed by the treating physician at the time of access/request of intravenous artesunate or quinine (FORM A); and at discharge/end of malaria therapy (FORM B). This information is vital to inform policy for distribution of these drugs, and required by the organizations supplying these drugs for notification of any drug related adverse event.

To obtain parenteral artesunate or quinine, please contact the listed pharmacy in your area.

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