CANADIAN RECOMMENDATIONS FOR THE PREVENTION AND TREATMENT OF MALARIA

AN ADVISORY COMMITTEE STATEMENT (ACS) COMMITTEE TO ADVISE ON TROPICAL MEDICINE AND TRAVEL (CATMAT)

PROTECTING CANADIANS FROM ILLNESS

Public Health Agency of Canada
Agence de la santé publique du Canada

Canada

TO PROMOTE AND PROTECT THE HEALTH OF CANADIANS THROUGH LEADERSHIP, PARTNERSHIP, INNOVATION AND ACTION IN PUBLIC HEALTH.

—Public Health Agency of Canada

Également disponible en français sous le titre :
Recommandations canadiennes pour la prévention et le traitement du paludisme (malaria) chez les voyageurs internationaux

To obtain additional information, please contact:

Public Health Agency of Canada
Address Locator 0900C2
Ottawa, ON K1A 0K9
Tel.: 613-957-2991
Toll free: 1-866-225-0709
Fax: 613-941-5366
TTY: 1-800-465-7735
E-mail: publications@hc-sc.gc.ca

This publication can be made available in alternative formats upon request.

Publication date: May 2014

Cat.: HP40-102/2014E-PDF
ISBN: 978-1-100-23458-8
Pub.: 140006

CANADIAN RECOMMENDATIONS FOR THE PREVENTION AND TREATMENT OF MALARIA

AN ADVISORY COMMITTEE STATEMENT (ACS)
COMMITTEE TO ADVISE ON TROPICAL MEDICINE AND TRAVEL (CATMAT)

TABLE OF CONTENTS

EXECUTIVE SUMMARY

The *Canadian Recommendations for the Prevention and Treatment of Malaria Among International Travellers* developed by the Committee to Advise on Tropical Medicine and Travel (CATMAT) on behalf of the Public Health Agency of Canada (the Agency), are designed for Canadian health practitioners who are preparing travellers to visit areas with malaria risk and for those who are dealing with ill returned travellers. These recommendations aim to ensure appropriate diagnosis and management of this potentially life threatening infectious disease. Many Canadian practitioners may have limited experience with this "exotic" tropical disease, it is hoped that these guidelines will be of valuable assistance.

The Public Health Agency of Canada is committed to provide evidenced-based guidelines and to make these accessible to practicing clinicians. The guidelines generally follow the same format as previous editions, addressing specifically the traveller risk assessment, drugs for prophylaxis and treatment, as well as instruction on management of malaria cases. With this edition there have been some important changes and additions.

In the risk assessment section (Chapter 2) we have introduced the use of length of stay threshold whereby optional use of chemoprophylaxis (with personal protective measures) is recommended for short stays (≤ *2 weeks*) for certain countries. This same threshold has been applied to *Appendix 1: Malaria Risk by Geographic Area*. The consensus of the authors was that this will provide practitioners with increased flexibility to better tailor their individualized risk assessment for each traveller.

There has been the addition of a new insect repellent—20% icaridin (recently registered in Canada), this is recognized as an equivalent to DEET as first-line choice for mosquito repellent (Chapter 3).

The section on malaria chemoprophylaxis (Chapter 4) has been refined, with an aim to help the practitioner assessing travellers to better navigate the drug choices available. These changes include a simplified, step-wise approach to selecting malaria prophylaxis; comprehensive listings of medications and malaria risk by country/area, presented in easy to understand tables; and expansion of the explanation about differences in approaches to malaria prophylaxis in other jurisdictions.

Chapter 5, *Malaria Issues in Special Hosts* has been expanded, recognizing the increasing numbers of travellers who may be at increased risk of acquiring malaria, having severe disease, or having more dire consequences. The special host section includes guidelines for diverse populations including children, migrants, travellers visiting friends and relatives (VFRs), management of women who are pregnant or breastfeeding, malaria prevention in expatriates and dealing with individuals with co-morbidities.

The section on treatment of malaria (Chapter 7) includes updated information on the management of severe malaria, including new information on the use of exchange transfusion.

There have been a number of changes to the section on *Drugs for the Prevention and Treatment of Malaria* (Chapter 8), which outlines the drugs used for malaria prevention and treatment. There is an update on primaquine use for malaria prophylaxis and prevention; additional up to date information on pediatric dosing of atovaquone/proguanil, as well as general updates to *Table 8.11: Drugs (generic and trade name) for the treatment and prevention of malaria*. Revisions have also been made to the following sub-sections: artemisinins, chloroquine, mefloquine (with increased emphasis on selection or avoidance of this drug based on individual tolerability), quinine/quinidine.

There has been extensive updating and editing on the appendices, especially Appendix 1.

There has been an important addition to *Appendix 1: Malaria Risk by Geographic Area*, we now present the option of personal protection measures without anti-malarial medication in some circumstances. This applies to short stays in a small number of countries where malaria risk is low.

There is a new "Malaria Card" that can be given to travellers with information about their malaria chemoprophylaxis, and an important reminder to seek medical attention in the event of a fever illness after travel.

ACKNOWLEDGEMENTS

This Statement was prepared by Boggild A, Brophy J, Charlebois P, Crockett M, Geduld J, Ghesquiere W, McDonald P, Plourde P, Teitelbaum P, Tepper M, Schofield S, and McCarthy A

CATMAT gracefully acknowledges the contribution of Manisha Kulkarni to the development of the statement.

CATMAT Members: Boggild A, Brophy J, Bui YG, Crockett M, Ghesquiere W, Greenaway C, Henteleff A, Libman M, Teitelbaum P and McCarthy A (Chair)

Liaison members: Hui C (Canadian Paediatric Society) and Gershman M (US Centers for Disease Control and Prevention).

Ex-officio members: Marion D (Canadian Forces Health Services Centre, Department of National Defence), McDonald P (Division of Anti-Infective Drugs, Health Canada), Schofield S (Directorate of Force Health Protection, Department of National Defence), and Tepper M (Directorate of Force Health Protection, Department of National Defence).

Member Emeritus: Jeanes C.W.L.

CHAPTER 1: INTRODUCTION

Malaria is a common and serious infection caused by five different species of the genus *Plasmodium*: *falciparum, vivax, ovale, malariae* and *knowlesi*. Malaria is transmitted by the bite of infected female anopheline mosquitoes. Rarely, transmission may occur through transfused blood (1), by sharing needles or from mother to fetus (2).

The disease is characterized by fever and flu-like symptoms such as myalgia, headache, abdominal pain and malaise. Rigours and chills often occur. The alternate-day or periodic fevers described above are, in fact, often not present.

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

Malaria-associated deaths are frequently the result of delays in the diagnosis and treatment of the infection (3;4). Infections caused by *P. falciparum* have the highest fatality rates but all the species have the potential to cause severe disease. The majority of deaths due to malaria are preventable.

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.

According to the World Health Organization (WHO), about 3.3 billion people were at risk of malaria in 2010, resulting in an estimated 219 million cases, of which about 80% occurred in 17 countries and about 40% were in India, Nigeria and the Democratic Republic of Congo (4). In that same year, there were 660,000 malaria-associated deaths worldwide, of which about 80% occurred in 14 countries (4). Figure 1 shows the trends in reported malaria incidence between 2000 and 2011.

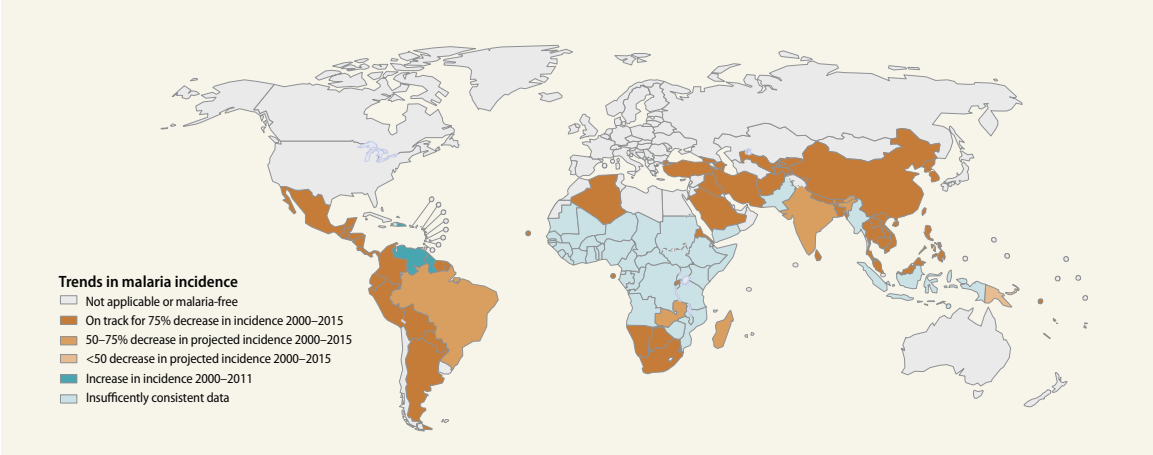
The global health goals of the Millennium Development Goals (MDGs) include a target to halt the spread of malaria by 2015 and to begin to reverse its incidence (5). A recent report on the MDGs indicates that between 2000 and 2009, malaria-associated deaths worldwide were reduced by about 20% through the use of critical interventions involving tools effective in preventing and treating the disease. The focus was on sub-Saharan Africa. Since 2000, 11 countries in Africa have reduced the number of confirmed malaria cases and deaths by 50% (5).

The Canadian Notifiable Diseases Surveillance System (CNDSS), a passive surveillance system co-ordinated by the Public Health Agency of Canada (the Agency), is used to monitor more than 40 nationally notifiable infectious diseases. Notification by provinces and territories to the federal level is voluntary, and cases are based on predetermined surveillance definitions. From 2001 to 2011, 4,254 cases of malaria were diagnosed and reported to the CNDSS; between 2009 and 2011, 18.3% of 1,387 reported cases were among those aged 19 years or less (D Taylor, unpublished data, 2013).

From 2006 to 2010, there were 7,542 malaria cases reported to the Centers for Disease Control and Prevention in the United States (annual average: 1,508 cases; range: 1,298–1,691 cases). Children (< 18 years) represented 19% of these cases (1,418) and 360 (5%) were aged 4 years or less (K Cullen and P Arguin, unpublished data, 2012).

In 2009, 35% of Canadian travellers who went to a destination other than the United States visited a country with a risk of malaria, an increase of 131% from 2000 (4;6). There were 94 cases of malaria diagnosed among returned Canadian travellers presenting to the five Canadian GeoSentinel Surveillance Network sites between September 2009 and September 2011; 60% of these cases were caused by *P. falciparum* (7).

FIGURE 1: Trends in reported malaria incidence, 2000–2011*



* This map is intended as a visual aid only; see Appendix I for specific country recommendations. Reproduced with permission from: WHO, 2013 (8).

The Canadian Malaria Network (CMN), in collaboration with the Agency and Health Canada's Special Access Programme, maintains supplies of intravenous artesunate and intravenous quinine at major medical centres across the country to facilitate rapid access to effective treatment of severe malaria. See Appendix V for information on the CMN sites.

From August 2001 to August 2012, there were 195 cases diagnosed with severe or complicated malaria reported to the CMN. Of these 195 cases, 21.1% were aged 17 years and younger and 88.2% were assumed to have acquired malaria in Africa. Where the reason for travel was known, 25.1% were visiting friends and relatives, 17.9% were immigrants, 14% were business travellers and 8% were on vacation. Parenteral quinine was requested for 62.6%, artesunate for 36.4% and both for 1.0%. There were delays in malaria management; only 19.5% presented to medical care within 24 hours of onset of symptoms, and 43.8% waited more than three days before seeking medical care. Diagnosis was delayed more than 24 hours in 33.5% of the cases (9) (Personal communication, A McCarthy and J Geduld, 2012).

Almost all malaria-associated deaths among travellers are due to *P. falciparum*. The overall case-fatality rate of imported falciparum malaria varies from about 1% to 5% and increases to 20% for those with severe malaria, even when the disease is managed in intensive care units (9;10). 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.

REFERENCE LIST

(1) Slinger R, Giulivi A, Bodie-Collins M, Hindieh F, John RS, Sher G, et al. Transfusion-transmitted malaria in Canada. CMAJ 2001 Feb 6;164(3):377–9.

(2) Davies HD, Keystone J, Lester ML, Gold R. Congenital malaria in infants of asymptomatic women. CMAJ 1992 May 15;146(10):1755–6.

(3) Bell D, Wongsrichanalai C, Barnwell JW. Ensuring quality and access for malaria diagnosis: how can it be achieved? Nat Rev Microbiol 2006 Sep;4(9 Suppl):S7–20.

(4) World Health Organization. World Malaria Report 2012. 2012.

(5) Inter-Agency and Expert Group on MDG Indicators. The Millennium Development Goals Report 2011. New York: United Nations; 2011.

(6) Geduld J, Bryson M, Straight-Caron T. Canadian Trends of International Travel and Risk of Malaria Exposure. 12th Conference of the International Society of Travel Medicine, May 8–12, 2011 Boston, U S 2011.

(7) Boggild AK, Geduld J, Libman MMA, Doyle P, Ghesquiere W, Vincelette J, et al. Travel acquired infections and illnesses in Canadians: surveillance report from CanTravNet surveillance data , 2009–2011. 2012.

(8) World Health Organization. Trends in reported malaria incidence, 2000–2011. WHO publication: World Health Organization World Malaria Report 2012.

(9) McCarthy AE, Plourde P, Kuhn S., Bodie M. Parenteral quinine for severe malaria: Five year surveillance data from the Canadian Malaria Network. 10th Conference of the International Society of Travel Medicine. 10th Conference of the International Society of Travel Medicine, [Abstract No. FC02.01]. 2007.

(10) Murphy GS, Oldfield EC, III. Falciparum malaria. Infect Dis Clin North Am 1996 Dec;10(4):747–75.

CHAPTER 2: PREVENTION AND RISK ASSESSMENT

The components of malaria prevention are often described as the ABCDs of malaria. All travellers to areas where malaria is endemic need to:

a) be aware of the risk of Acquiring malaria infection (described in this chapter),
b) know how to avoid mosquito Bites (see Chapter 3),
c) take Chemoprophylaxis, as appropriate (see Chapter 4), and
d) understand the need to be urgently Diagnosed and treated if they have a fever (see Chapters 6 and Chapter 7).

Appendix II provides a checklist for people preparing to travel to malarial areas.

RISK OF ACQUIRING MALARIA BY DESTINATION

Although data that characterize risk of malaria by destination for Canadian travellers are not currently available, there are such data for other populations (1). For example, based on case reports and volume of travel to a given country, the Centers for Disease Control and Prevention (CDC) in the United States reported that risk of acquiring malaria was highest for those travelling to west Africa and parts of Oceania; moderate for other parts of Africa, parts of South America and south Asia; and lower for much of Central America, the Caribbean, Mexico and other parts of Asia and South America (2–4). This hierarchy accords with data from other surveillance networks, including GeoSentinel (5–11), and with extrapolations from country-specific endemicity estimates (12–14). Given such consistency, the Committee to Advise on Tropical Medicine and Travel (CATMAT) considers that it is highly likely that the geographic risk stratification articulated by the CDC can be applied to Canadian travellers.

Appendix I shows a country-by-country characterization of malaria transmission areas. Regional and/or city-specific information is also sometimes provided. These data were extracted from travel-specific risk characterizations published by the World Health Organization, the CDC and the International Association for Medical Assistance to Travellers (15–17). These risk characterizations are generally consistent; the most obvious differences relate to difference in recommendations for chemoprophylaxis in areas with low endemicity. In these few countries (see Appendix 1), CATMAT uses a length-of-stay threshold and recommends *the use of* personal protective measures (PPM) and the *optional use of chemoprophylaxis* for short *stays* (see Box 2.1).

ASSESSING MALARIA RISK

Many factors can affect the risk of acquiring malaria or the development of adverse outcomes. There are also health risks, although relatively uncommon, associated with malaria interventions, particularly chemoprophylaxis. Deciding on the way to prevent malaria involves balancing these risks with expected benefits and with individual preferences. Unfortunately, there is no easy-to-follow recipe that allows for this—malaria is a disease of subtleties and its prevention is similarly nuanced. Because of this complexity, CATMAT suggests a two-component process for malaria risk assessment: an exposure assessment and a host assessment.

EXPOSURE ASSESSMENT

CATMAT defines *exposure assessment* as an evaluation of the probability that an individual will be bitten by potentially infected mosquitoes. Depending on the species and location, malaria mosquitoes can bite inside and/or out and usually between late afternoon and morning. The number of vectors (and hence transmission intensity) tends to be higher in rural areas (at least partly because of the wider availability of sites for the larvae to develop), can vary seasonally and decreases with altitude so that risk is often absent or negligible in highland areas (> 2,000 m or 6,500 ft) (see Appendix I for country-specific information on malaria risk and altitude). Although not always feasible, knowing the habits of the principal vector(s) in an area is useful for assessing exposure. The CATMAT *Statement on Personal Protective Measures to Prevent Arthropod Bites* provides additional information on this topic, and a number of publications provide information on malaria vectors by geographic area (15;18–22).

A detailed review of the travel itinerary is critical to determine whether the traveller will be visiting malaria-endemic areas (Appendix I). If so, then evaluation of the risk of exposure should be done. Factors to consider include:

- Expected level of endemicity in the area(s) in the travel itinerary: as noted above, transmission intensity is highest in west Africa and Oceania, moderate in other areas of Africa and in some areas of South America and south Asia, and low through much of the Caribbean, Central America, Mexico and other areas of South America and of Asia (2–4);
- Presence/predominance of *Plasmodium falciparum*: infections caused by *P. falciparum* have the highest fatality rates;
- Duration of exposure: longer periods of travel are generally associated with increased risk (see Box 2.1);
- Destination: rural travel is generally more likely to result in exposure than peri-urban travel, and peri-urban travel is more likely to result in exposure than urban travel. CATMAT considers the risk of malaria in urban centres of southeast Asia and Central and South America and in large resort areas in the Caribbean and Mexico to be minimal;
- Season: risk can be higher during or soon after the rainy season due to larger mosquito populations;
- Night-time exposure;
- Presence of drug-resistant malaria (see Appendix I): 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 (23). Chloroquine-*and* mefloquine-resistant *P. falciparum* has been confirmed in the Thai-Cambodia, Thai-Burma (Myanmar), China-Burma (Myanmar) and Lao-Burma (Myanmar) border areas, as well as in the western provinces of Cambodia, the eastern states of Burma (Myanmar) and southern Vietnam;
- Availability and likelihood of use of other interventions (e.g. PPM); and
- Availability of information to suggest that endemicity for a given area has changed. Health care providers providing pre-travel care should monitor appropriate sites (e.g. Public Health Agency of Canada and CDC websites, ProMed) to stay abreast of new information about malaria risks. This is especially relevant for regions considered as being minimal risk because changes might mean the difference between not recommending and recommending the use of malaria chemoprophylaxis.

HOST ASSESSMENT

CATMAT defines *host assessment* as an evaluation of the individual traveller's health as it relates to the potential hazard(s) of clinical malaria and the indications for specific malaria chemoprophylaxis. Host assessment should also involve evaluating individual preferences regarding risk management. Factors to consider include:

- General health of the individual: primary considerations include factors that might cause adverse outcomes (e.g. age, pregnancy, chronic illnesses such as HIV, etc.) or that might affect the choice of chemoprophylactic agent(s) (e.g. age, pregnancy, cardiac or neurological conditions) (see Chapters 3, 5 and 8);
- Possibility of drug-drug interactions (see Chapters 3 and 8);
- Likelihood that the traveller will be able to readily access appropriate medical care: travellers should be informed that reliable malaria diagnostics and treatments might not be available in some travel destinations (24). Self-diagnosis and concomitant treatment of malaria based on symptoms only, without laboratory diagnostic testing, is not ideal. However, some travellers going to more remote locations might have few alternatives (see Chapters 3 and 5); and
- Risk tolerance and individual-specific preferences: this is especially pertinent where malaria chemoprophylaxis might or might not be used (see Box 2.1 and Appendix 1). Indeed, for a given area and for otherwise identical exposure and host assessments, some individuals might prefer not to use chemoprophylaxis while others would. Travellers who decide not to use chemoprophylaxis have higher risk of malaria but lower risk of chemoprophylaxis-associated adverse effects; the opposite is true for those who decide to use it.

CONVERTING MALARIA RISK ASSESSMENT TO RECOMMENDATIONS FOR PREVENTIVE MEASURES

Once complete, the risk assessment can be used to help inform whether to use malaria chemoprophylaxis and which to use (Appendix I shows country/region-specific advice on malaria risk and recommended chemoprophylaxis). Nevertheless, clinical judgement remains important, for example, to select the most appropriate chemoprophylactic agent and/or to provide individual-specific preventive guidance (see Box 2.1: The CATMAT approach to recommendations for malaria chemoprophylaxis).

BOX 2.1: The CATMAT approach to recommendations for malaria chemoprophylaxis

CATMAT recommends chemoprophylaxis if there is a threat of malaria. However, where malaria risk is minimal and if the period of exposure is relatively short (i.e. ≤ 2 weeks), CATMAT considers that there is no clear indication for either using or not using chemoprophylaxis. Therefore, CATMAT's country-by-country malaria recommendations include a small number of countries for which length-of-stay thresholds have been incorporated (see Appendix 1). *CATMAT proposes the optional use of chemoprophylaxis (with PPM) for short stays in these low-risk destinations.*

- To select these countries, two CDC parameters were used:
- For countries considered by CDC as having an estimated "very low" relative risk of malaria and with a nil or low incidence of *P. falciparum*, a two-week length-of-stay threshold is recommended.

For countries with "very low" relative risk of malaria and a higher incidence of *P. falciparum*, or with a "low" malaria risk and a nil to low incidence of *P. falciparum*, a one-week length-of-stay threshold is suggested.

Of note, this approach:

- only applies to those areas where malaria presents a minimal risk;
- recognizes that exposure probably increases with time; and
- recognizes that compliance with PPM probably decreases with duration of travel thereby increasing risk.

Whether or not chemoprophylaxis is used, risk reduction through use of PPM and prompt seeking of medical assessment in the event of a fever are important for all travellers to areas that are endemic for malaria.

TABLE 2.1: Evidence-based medicine recommendations

RECOMMENDATION	EBM RATING
Travellers should receive expert advice on malaria risks and strategies to avoid mosquitoes (1).	B III
Properly used malaria chemoprophylaxis is very effective (4).	A I
A detailed review of the travel itinerary to determine the expected level of malaria endemicity and duration of exposure is essential to providing an accurate risk assessment for travellers (1;4;6).	B III
An assessment of the traveller's health and risk tolerances is also important in making malaria prevention recommendations.	B III

ABBREVIATION: EBM, evidence-based medicine.

NOTE: For a description of the categories and quality of evidence of the recommendations, see Appendix IV.

REFERENCE LIST

(1) Steffen R, deBernardis C, Banos A. Travel epidemiology—a global perspective. Int J Antimicrob Agents 2003 Feb;21(2):89–95.

(2) Mali S, Steele S, Slutsker L, Arguin PM. Malaria surveillance—United States, 2008. MMWR Surveill Summ 2010 Jun 25;59(7):1–15.

(3) Mali S, Tan KR, Arguin PM. Malaria surveillance—United States, 2009. MMWR Surveill Summ 2011 Apr 22;60(3):1–15.

(4) Centers for Disease Control and Prevention. CDC Health Information for international travel 2012. Atlanta: US Department of Health and Human Services, Public Health Service; 2012.

(5) Loutan L. Malaria: still a threat to travellers. Int J Antimicrob Agents 2003 Feb;21(2):158–63.

(6) Leder K, Black J, O'Brien D, Greenwood Z, Kain KC, Schwartz E, et al. Malaria in travelers: a review of the GeoSentinel surveillance network. Clin Infect Dis 2004 Oct 15;39(8):1104–12.

(7) Torresi J, Leder K. Defining infections in international travellers through the GeoSentinel surveillance network. Nat Rev Microbiol 2009 Dec;7(12):895–901.

(8) Freedman DO, Weld LH, Kozarsky PE, Fisk T, Robins R, von SF, et al. Spectrum of disease and relation to place of exposure among ill returned travelers. N Engl J Med 2006 Jan 12;354(2):119–30.

(9) Gautret P, Schlagenhauf P, Gaudart J, Castelli F, Brouqui P, von SF, et al. Multicenter EuroTravNet/GeoSentinel study of travel-related infectious diseases in Europe. Emerg Infect Dis 2009 Nov;15(11):1783–90.

(10) Steffen R. Malaria prophylaxis: setting the scene. J Travel Med 2003 May;10 Suppl 1:S3–S7.

(11) van Rijckevorsel GG, Sonder GJ, Geskus RB, Wetsteyn JC, Ligthelm RJ, Visser LG, et al. Declining incidence of imported malaria in the Netherlands, 2000–2007. Malar J 2010;9:300.

(12) Guerra CA, Howes RE, Patil AP, Gething PW, Van Boeckel TP, Temperley WH, et al. The international limits and population at risk of Plasmodium vivax transmission in 2009. PLoS Negl Trop Dis 2010;4(8):e774.

(13) Guerra CA, Hay SI, Lucioparedes LS, Gikandi PW, Tatem AJ, Noor AM, et al. Assembling a global database of malaria parasite prevalence for the Malaria Atlas Project. Malar J 2007;6:17.

(14) Guerra CA, Gikandi PW, Tatem AJ, Noor AM, Smith DL, Hay SI, et al. The limits and intensity of Plasmodium falciparum transmission: implications for malaria control and elimination worldwide. PLoS Med 2008 Feb;5(2):e38.

(15) World Malaria Risk Chart. International Association for Medical Assistance to Travellers 2011

(16) Centers for Disease Control and Prevention. CDC health information for international travel 2014. Atlanta: US Department of Health and Human Services, Public Health Service; 2013.

(17) World Health Organization. International travel and health 2011 country list [Internet]. In: World Health Organization, editor. International travel and health. Available from: www.who.int/ith/chapters/en. Geneva: 2011.

(18) Sinka ME, Bangs MJ, Manguin S, Chareonviriyaphap T, Patil AP, Temperley WH, et al. The dominant Anopheles vectors of human malaria in the Asia-Pacific region: occurrence data, distribution maps and bionomic precis. Parasit Vectors 2011;4:89.

(19) Sinka ME, Bangs MJ, Manguin S, Coetzee M, Mbogo CM, Hemingway J, et al. The dominant Anopheles vectors of human malaria in Africa, Europe and the Middle East: occurrence data, distribution maps and bionomic precis. Parasit Vectors 2010;3:117.

(20) Sinka ME, Rubio-Palis Y, Manguin S, Patil AP, Temperley WH, Gething PW, et al. The dominant Anopheles vectors of human malaria in the Americas: occurrence data, distribution maps and bionomic precis. Parasit Vectors 2010;3:72.

(21) Kiszewski A, Mellinger A, Spielman A, Malaney P, Sachs SE, Sachs J. A global index representing the stability of malaria transmission. Am J Trop Med Hyg 2004;70(5):486–98.

(22) Committee to Advise on Tropical Medicine and Travel. Statement on Personal Protective Measures to Prevent Arthropod Bites. Can Commun Dis Rep 2012;38 (ASC-2):1–18.

(23) World Health Organization- Roll Back Malaria Department, United Nations Children's Fund. World Malaria Report 2005. 2005.

(24) Keystone JS. The sound of hoof beats does not always mean that it is a zebra. Clin Infect Dis 2004 Dec 1;39(11):1589–90.

CHAPTER 3: PREVENTION— MALARIA EDUCATION FOR TRAVELLERS

Adherence to prescribed antimalarial prophylactic drug regimens and use of appropriate personal protective measures (PPM) are essential for the prevention of malaria. Malaria-associated deaths among Canadian travellers are often due poor use of protective measures, in particular malaria chemoprophylaxis (1–3), or because they did not use an efficacious intervention appropriately, or because they used a non-efficacious approach.

ADHERENCE TO RECOMMENDED MEASURES— THE ACHILLES' HEEL OF MALARIA PREVENTION

Evidence suggests that non-adherence to or suboptimal use of chemoprophylaxis and other preventive interventions is common (4–11). Although a generic problem, certain subpopulations seem to be at higher risk for non-adherence, for example, backpacking travellers; immigrants who return to their country of origin to visit friends and relatives (VFRs); long-term travellers (those who travel for more than one month); travellers aged 40 years or less; and those using antimalarials that must be taken daily (4–8;12–18). Explanations for non-adherence are varied and have included: lack of knowledge that malaria was a threat; fear of or past experience with adverse effects of antimalarials; the false belief that prior malaria infections have conferred long-term immunity; the cost of medications; confusion arising from contradictory recommendations; forgetfulness; or lack of interest in taking antimalarial medications (4–6;8;12–14).

While there is ample evidence describing the problem of nonadherence, there is little information on how to enhance adherence. Interestingly, some research has evaluated text messaging as a tool for improving uptake of malaria interventions. In a seeming paradox, text messages did not improve post-travel adherence to malaria chemoprophylaxis in a group of travellers in one study (19), but was associated with improved adherence to malaria prevention clinical practice guidelines among health professionals in another (20).

While acknowledging that data supporting the assertion are lacking, Committee to Advise on Tropical Medicine and Travel (CATMAT) considers that a critical control point for malaria prevention is traveller–health care provider communication. Health care providers need to be properly informed to be able to provide appropriate guidance (21). In turn, the advice they give should be developed for each individual based on their travel itinerary and with identified risk factors for non-adherence. In terms of an ideal counselling situation, travellers who use one qualified information source, such as a family physician trained in travel medicine, are significantly more likely to be compliant with malaria prophylaxis than those who collect information from multiple sources that could contradict each other (21;22).

EARLY DIAGNOSIS AND TREATMENT

All travellers should be told that malaria could be the reason for any fever (without an identifiable etiology) that develops while they are travelling in a malaria-endemic area or up to one year[i] after returning. If a fever occurs during this period, travellers should get medical attention as soon as possible, regardless of whether they used malaria chemoprophylaxis. The febrile traveller should provide a travel history, including the fact that they are in or have recently been in a malaria-endemic area, and request that thick and thin blood films be immediately obtained and examined for malaria parasites. If the laboratory is unable to perform a reliable thick blood film, a thin blood film alone is better than nothing. If the initial blood films are negative and the traveller remains symptomatic, the blood films should be repeated at least twice over the next 12 to 24 hours. Both clinicians and patients must remember that early diagnosis and prompt initiation of appropriate treatment affect the survival of patients with *Plasmodium falciparum* malaria (2). (For more information, see Chapters 6 and 7.)

PREVENTION—PERSONAL PROTECTIVE MEASURES

GENERAL

If mosquitoes cannot bite, they cannot transmit malaria. For this reason, interventions that reduce biting are recommended. This topic is covered in detail in the CATMAT *Statement on Personal Protective Measures to Prevent Arthropod Bites* (24). Since only the most important and general of the recommendations are repeated here, readers are encouraged to refer to that article (24) as well as the most recent *Canadian Recommendations for the Prevention and Treatment of Malaria Among International Travellers*.

MALARIA MOSQUITOES

Only *Anopheles* mosquitoes transmit malaria. Usually, these mosquitoes are active during the evening and, at least for the most efficient vectors of malaria, bite and rest indoors. However, these are not universal rules; many mosquitoes that transmit malaria can or even prefer to bite outside and can feed at various times of the day, including during the late afternoon and early morning. Information about the major malaria vector(s) in a given risk area can be useful to develop risk management strategies. For example, knowing that *A. albimanus,* an important vector in parts of the New World, can bite earlier in the evening and often outside can be used to emphasize the importance of preventive modalities that are effective in that context, for example, insecticide-treated clothing and topical skin repellents.

More information on malaria mosquitoes can be found in the CATMAT *Statement on Personal Protective Measures to Prevent Arthropod Bites*, especially "Appendix 1: Summary information for some important arthropod vectors" and its references (24).

---

[i] The large majority of travel-related malaria cases diagnosed in non-endemic countries present within several months of return from an endemic area (23). However, some cases, including cases involving *Plasmodium falciparum*, will present after a longer period, i.e. 6 months or more post-exposure. For this reason, CATMAT recommends that travellers who become ill with an unexplained fever after returning (for up to 1 year – regardless of whether malaria prophylaxis was prescribed or taken) should seek immediate medical attention and tell the physician their travel history. Particular attention should be paid to fevers that develop in the 3 months following travel, the period during which > 90% of *P. falciparum*-related disease is expressed.

PREVENTING MALARIA MOSQUITOES FROM BITING

An individual can do a number of things to reduce the risk of malaria before travelling. These include planning activities for those periods when risk is reduced or going to areas where transmission is less likely, for example, urban centres. In addition, once the traveller is in a malaria-endemic area, there are a limited number of ways of preventing mosquito bites. The main approaches fall into two categories: physical or chemical barriers. These are not mutually exclusive; rather, they work together and often are combined into a single intervention. For example, treated netting and clothing provide a physical and a chemical barrier.

PHYSICAL BARRIERS

There are a variety of physical means to reduce contact between vectors and their human hosts. The principle methods recommended by CATMAT are:

- Protection of work and accommodation areas: Screening on doors, windows and eaves (the open area between the roof and wall) protects against mosquitoes as does closing holes in roofs, walls and other gaps in the building (25–27);
- Use of bed nets: In addition to being a chemical barrier (see below), bed nets are a physical barrier against mosquitoes. They also protect against other pests like bed bugs, rodents and snakes; and
- Wearing appropriate clothing: Full-length, loose-fitting and light-coloured clothing prevent mosquitoes from biting. Sleeves should be rolled down and pants legs tucked into socks (28–30).

CHEMICAL BARRIERS

Chemical barriers act in a variety of ways, including by repelling mosquitoes and/or by killing them. The main chemical modalities currently available are topical insect repellents that are applied to the skin and insecticides that impregnate bed nets and clothing. A full discussion of the various chemical barriers, including their efficacy and safety, use among specific subpopulations (e.g. children) and the evidence to support their use is given in CATMAT's *Statement on Personal Protective Measures to Prevent Arthropod Bites* (24).

The following are important recommendations regarding the use of chemical barriers:

Use topical repellents on exposed areas of skin to prevent bites and to reduce the risk of exposure to malaria-carrying mosquitoes (31;32).

Topical repellents registered in Canada that contain 20%–30% DEET or 20% icaridin should be the first choice for Canadian travellers. *DEET (N,N-diethyl-m-toluamide) has been registered in Canada for a long time, has a good safety profile and shows excellent performance against mosquitoes including malaria vectors. Icaridin (also called picaridine, KBR 3023; 1-piperidinecarboxylic acid 2-(2-hydroxyethyl)-1-methylpropylester)* was recently registered in Canada. However, the Centers for Disease Control and Prevention in the United States and the World Health Organization Pesticide Evaluation Scheme have been recommending *icaridin* as an appropriate mosquito repellent to prevent bites for some time. It has been available in the United States since 2005 (33–35).

Repellents that contain *p*-menthane-3,8-diol (a chemical originally derived from the lemon eucalyptus plant) and that are registered in Canada should be considered second-choice topical repellents.

Other active ingredients currently registered in Canada, e.g. citronella and soybean oil, are either not widely available and/or do not provide sufficiently long protection against mosquitoes. They are not recommended for travellers as protection against mosquito bites.

All travellers to foreign destinations endemic or epidemic for malaria should use pretreated insecticide-treated bed nets (36).

Travellers should use insecticide-treated clothing to protect against the bites of vectors and nuisance arthropods (37–40).

OTHER INTERVENTIONS

Do not rely on other insecticide-based approaches such as insecticide coils that are burned, insecticide vaporizers, aerosols and space sprays, and insecticide-treated bed sheets.

Avoid PPM that are either ineffective or have not been convincingly shown to be effective against arthropod vectors and related diseases. These include: electronic (ultrasonic) devices (41;42); wristbands, neckbands and ankle bands impregnated with repellents (43); electrocuting devices ("bug zappers") (41;44); odour-baited mosquito traps; *Citrosa* plant (a type of geranium houseplant) (45–47); orally administered vitamin B1 (48); and skin moisturizers that do not contain an active ingredient from an approved repellent (43).

TABLE 3.1: Evidence-based medicine recommendations

RECOMMENDATIONS	EBM RATING
It is very important to adhere to recommended malaria prevention practices, e.g. use of chemoprophylaxis and PPM (4;5;7;12–18;49).	B III
Malaria must be considered as a possible diagnosis for any febrile illness of unexplained etiology that occurs during travel or within 12 months of returning from a malaria-endemic area (2) and medical attention should be sought promptly.	B III
Early diagnosis and prompt initiation of appropriate treatment are critical for patients infected with *P. falciparum* (2).	B III
Protect work and accommodation areas against mosquitoes by using screening on doors, windows, and eaves (the open area between the roof and wall), eliminating holes in roofs and walls, and closing other gaps around a building.	B I
Wear appropriate clothing, e.g. full-length, loose-fitting and light-coloured clothing with sleeves rolled down and pants tucked in to socks or boots.	B III
Use pretreated insecticide-treated bed nets.	A I
Use insecticide-treated clothing.	B II
Use topical repellents on exposed areas of skin to prevent arthropod bites and to reduce the risk of exposure to malaria-carrying mosquitoes.	A I
Products registered in Canada and that contain 20%–30% DEET or 20% icaridin should be the first choice for Canadian travellers.	A II
Products that contain *p*-menthane-3,8-diol (a chemical originally derived from the lemon eucalyptus plant) and that are registered in Canada should be considered second-choice topical repellents.	A II
Other active ingredients currently registered in Canada, e.g. citronella and soybean oil, are either not widely available and/or do not provide sufficiently long protection times against bites. These products are not recommended for protecting travellers against the bites of vectors.	E II

Do not use/rely on other insecticide-based approaches such as insecticide coils that are burned, insecticide vaporizers, aerosols and space sprays, and insecticide-treated bed sheets.	E III
PPM that are either ineffective or that have not been convincingly shown to be efficacious against arthropod vectors and related diseases are not recommended. These include: 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 and skin moisturizers that do not contain an approved repellent active ingredient.	E II

ABBREVIATIONS: DEET, *N, N-diethyl-m-toluamide;* PPM, personal protective measures.

NOTE: For a description of the categories and quality of evidence of the recommendations, see Appendix IV.

REFERENCE LIST

(1) Humar A, Sharma S, Zoutman D, Kain KC. Fatal falciparum malaria in Canadian travellers. CMAJ 1997 Apr 15;156(8):1165–7.

(2) Kain KC, MacPherson DW, Kelton T, Keystone JS, Mendelson J, MacLean JD. Malaria deaths in visitors to Canada and in Canadian travellers: a case series. CMAJ 2001 Mar 6;164(5):654–9.

(3) Gyorkos TW, Svenson JE, MacLean JD, Mohamed N, Remondin MH, Franco ED. Compliance with antimalarial chemoprophylaxis and the subsequent development of malaria: a matched case-control study. Am J Trop Med Hyg 1995 Nov;53(5):511–7.

(4) Chatterjee S. Compliance of malaria chemoprophylaxis among travelers to India. J Travel Med 1999 Mar;6(1):7–11.

(5) Laver SM, Wetzels J, Behrens RH. Knowledge of malaria, risk perception, and compliance with prophylaxis and personal and environmental preventive measures in travelers exiting Zimbabwe from Harare and Victoria Falls International airport. J Travel Med 2001 Nov;8(6):298–303.

(6) Landry P, Iorillo D, Darioli R, Burnier M, Genton B. Do travelers really take their mefloquine malaria chemoprophylaxis? Estimation of adherence by an electronic pillbox. J Travel Med 2006 Jan;13(1):8–14.

(7) Banerjee D, Stanley PJ. Malaria chemoprophylaxis in UK general practitioners traveling to South Asia. J Travel Med 2001 Jul;8(4):173–5.

(8) Molle I, Christensen KL, Hansen PS, Dragsted UB, Aarup M, Buhl MR. Use of medical chemoprophylaxis and antimosquito precautions in Danish malaria patients and their traveling companions. J Travel Med 2000 Sep;7(5):253–8.

(9) Pistone T, Ezzedine K, Gaudin AF, Hercberg S, Nachbaur G, Malvy D. Malaria prevention behaviour and risk awareness in French adult travellers. Travel Med Infect Dis 2010 Jan;8(1):13–21.

(10) Ollivier L, Michel R, Carlotti MP, Mahe P, Romand O, Todesco A, et al. Chemoprophylaxis compliance in a French battalion after returning from malaria-endemic area. J Travel Med 2008 Sep;15(5):355–7.

(11) Queyriaux B, Texier G, Galoisy-Guibal L, Michel R, Meynard J-B, et al. Plasmodium vivax malaria among military personnel, French Guiana, 1998–2008. Emerg Infect Dis 2011;17(7):1280–2.

(12) Lobel HO, Baker MA, Gras FA, Stennies GM, Meerburg P, Hiemstra E, et al. Use of malaria prevention measures by North American and European travelers to East Africa. J Travel Med 2001 Jul;8(4):167–72.

(13) Leonard L, VanLandingham M. Adherence to travel health guidelines: the experience of Nigerian immigrants in Houston, Texas. J Immigr Health 2001 Jan;3(1):31–45.

(14) Morgan M, Figueroa-Munoz JI. Barriers to uptake and adherence with malaria prophylaxis by the African community in London, England: focus group study. Ethn Health 2005 Nov;10(4):355–72.

(15) Alon D, Shitrit P, Chowers M. Risk behaviors and spectrum of diseases among elderly travelers: a comparison of younger and older adults. J Travel Med 2010 Jul;17(4):250–5.

(16) Toovey S, Moerman F, van GA. Special infectious disease risks of expatriates and long-term travelers in tropical countries. Part I: malaria. J Travel Med 2007 Jan;14(1):42–9.

(17) Baggett HC, Graham S, Kozarsky PE, Gallagher N, Blumensaadt S, Bateman J, et al. Pretravel health preparation among US residents traveling to India to VFRs: importance of ethnicity in defining VFRs. J Travel Med 2009 Mar;16(2):112–8.

(18) Piyaphanee W, Wattanagoon Y, Silachamroon U, Mansanguan C, Wichianprasat P, Walker E. Knowledge, attitudes, and practices among foreign backpackers toward malaria risk in southeast Asia. J Travel Med 2009 Mar;16(2):101–6.

(19) Ollivier L, Romand O, Marimoutou C, Michel R, Pognant C, Todesco A, et al. Use of short message service (SMS) to improve malaria chemoprophylaxis compliance after returning from a malaria endemic area. Malar J 2009;8:236.

(20) Zurovac D, Sudoi RK, Akhwale WS, Ndiritu M, Hamer DH, Rowe AK, et al. The effect of mobile phone text-message reminders on Kenyan health workers' adherence to malaria treatment guidelines: a cluster randomised trial. Lancet 2011 Aug 27;378(9793):795–803.

(21) Ropers G, Du Ry van Beest Holle, Wichmann O, Kappelmayer L, Stuben U, Schonfeld C, et al. Determinants of malaria prophylaxis among German travelers to Kenya, Senegal, and Thailand. J Travel Med 2008 May;15(3):162–71.

(22) Held TK, Weinke T, Mansmann U, Trautmann M, Pohle HD. Malaria prophylaxis: identifying risk groups for non-compliance. Q J Med 1994 Jan;87(1):17–22.

(23) Mali S, Kachur SP, Arguin PM. Malaria surveillance—United States, 2010. MMWR Surveill Summ 2012 Mar 2;61(2):1–17.

(24) Committee to Advise on Tropical Medicine and Travel. Statement on Personal Protective Measures to Prevent Arthropod Bites. Can Commun Dis Rep 2012;38 (ASC-2):1–18.

(25) Lindsay SW, Jawara M, Paine K, Pinder M, Walraven GE, Emerson PM. Changes in house design reduce exposure to malaria mosquitoes. Trop Med Int Health 2003;8(6):512–7.

(26) Lindsay SW, Emerson PM, Charlwood JD. Reducing malaria by mosquito-proofing houses. Trends Parasitol 2002;18(11):510–4.

(27) Njie M, Dilger E, Lindsay SW, Kirby MJ. Importance of eaves to house entry by anopheline, but not culicine, mosquitoes. J Med Entomol 2009;46(3):505–10.

(28) Christophers S. Mosquito repellents; being a report of the work of the mosquito repellent inquiry, Cambridge, 1943–5. J Hyg 1947;45:176–231.

(29) Schoepke A, Steffen R, Gratz N. Effectiveness of personal protection measures against mosquito bites for malaria prophylaxis in travelers. J Travel Med 1998 Jul 28;5(4):188–92.

(30) Joy RJ. Malaria in American troops in the South and Southwest Pacific in World War II. Med Hist 1999;43(2):192–207.

(31) Maia MF, Moore SJ. Plant-based insect repellents: a review of their efficacy, development and testing. Malar J 2011;10 Suppl 1:S11.

(32) Moore SJ, Debboun M. History of insect repellents. In: Debboun M, Francis S, Strickman DA, editors. Insect repellents: principles, methods and uses. CRC Press; 2007. p. 3–29.

(33) Centers for Disease Control and Prevention. Updated information regarding insect repellents [Internet]. 2008 [cited 2011 Apr 24]. Available from: www.cdc.gov/ncidod/dvbid/westnile/RepellentUpdates.htm. Ref Type: Generic

(34) World Health Organization Pesticide Evaluation Scheme. WHO specifications for pesticides used in public health [Internet]. 2011 [cited 2011 Apr 24]. Available from: www.who.int/whopes/quality/newspecif/en. Ref Type: Generic

(35) Zielinski-Gutierrez E, Wirtz RA, Nasci RS. The Pre-Travel Consultation. Protection against mosquitoes, ticks, and other insects and arthropods. CDC health information for international travel 2012.Atlanta: U.S. Department of Health and Human Services, Public Health Service; 2011. p. 86–9.

(36) Lengeler C. Insecticide-treated bed nets and curtains for preventing malaria. Cochrane Database Syst Rev 2004;(2):CD000363.

(37) Schreck CE, Posey K, Smith D. Durability of permethrin as a potential clothing treatment to protect against blood-feeding arthropods. J Econ Entomol 1978;71(3):397–400.

(38) Schreck CE, Haile DG, Kline D. The effectiveness of permethrin and deet, alone or in combination, for protection against Aedes taeniorhynchus. Am J Trop Med Hyg 1984;33:725–30.

(39) Vaughn MF, Meshnick SR. Pilot study assessing the effectiveness of long-lasting permethrin-impregnated clothing for the prevention of tick bites. Vector Borne Zoonotic Dis 2011;11(7):869–75.

(40) Soto J, Medina F, Dember N, Berman J. Efficacy of permethrin-impregnated uniforms in the prevention of malaria and leishmaniasis in Colombian soldiers. Clin Infect Dis 1995;21(3):599–602.

(41) Surgeoner GA, Helson BV. A field evaluation of electrocutors for mosquito control in southern Ontario. Proc Entomol Soc Ontario 1977;108:53–7.

(42) Enayati AA, Hemingway J, Garner P. Electronic mosquito repellents for preventing mosquito bites and malaria infection. Cochrane Database Syst Rev 2007;(2):CD005434.

(43) Fradin MS, Day JF. Comparative efficacy of insect repellents against mosquito bites. N Engl J Med 2002 Jul 4;347(1):13–8.

(44) Nasci RS, Harris CW, Porter CK. Failure of an insect electrocuting device to reduce mosquito biting. Mosquito News 1983;43(2):180–4.

(45) Jensen T, Lampman R, Slamecka MC, Novak RJ. Field efficacy of commercial antimosquito products in Illinois. J Am Mosq Control Assoc 2000;16(2):148–52.

(46) Matsuda BM, Surgeoner GA, Heal JD, Tucker AO, Maciarello MJ. Essential oil analysis and field evaluation of the citrosa plant "Pelargonium citrosum" as a repellent against populations of Aedes mosquitoes. J Am Mosq Control Assoc 1996 Mar;12(1):69–74.

(47) Cilek JE, Schreiber ET. Failure of the "mosquito plant", Pelargonium x citrosum 'van Leenii', to repel adult Aedes albopictus and Culex quinquefasciatus in Florida. J Am Mosq Control Assoc 1994;10(4):473–6.

(48) Khan AA, Maibach HI, Strauss WG, Fenley WR. Vitamin B1 is not a systemic mosquito repellent in man. Trans St Johns Hosp Dermatol Soc 1969;55(1):99–102.

(49) Abraham C, Clift S, Grabowski P. Cognitive predictors of adherence to malaria prophylaxis regimens on return from a malarious region: a prospective study. Soc Sci Med 1999 Jun;48(11):1641–54.

CHAPTER 4: PREVENTION—CHEMOPROPHYLAXIS REGIMENS

Malaria is a severe life-threatening illness. Even with modern, effective treatments and intensive care support, the case-fatality rate for severe infections of *Plasmodium falciparum* can be as high as 20%. Thus, prevention of disease is the mainstay of reducing its impact on travellers. A variety of interventions exists to reduce this threat. Chief among these is the use of malaria chemoprophylaxis (see Chapters 5 and 8) along with personal protective measures (PPM) against insect bites (1) (see Chapter 3).

ANTIMALARIAL DRUGS

Most people who take antimalarial chemoprophylaxis will have no or only minor adverse reactions (2–8). Nevertheless, antimalarial drugs should be prescribed only after completion of an individual risk assessment (see Chapter 2) that takes into consideration the risks and benefits of chemoprophylaxis. In deciding between the various options, the health care provider should consider: the traveller's health status; other medications being taken; malaria drug effectiveness; risks for and character of adverse drug reactions; and the traveller's preferences and risk tolerances.

If adverse events do occur, they can have a significant impact on the traveller's health and on adherence to the medication regimen. One way to test for tolerability is to have a trial of the medication before travelling. To keep adverse effects to a minimum, it is essential that all travellers understand the dosing schedule, including time of day, and whether the chemoprophylaxis should be taken with food, as well as precautions regarding drug-specific side effects (e.g. sun exposure with doxycycline).

The efficacy reported for different antimalarial clinical trials assumes strict adherence to the dosing schedule as well as the use of PPM, such as insect avoidance and use of insect repellents. Some regimens (e.g. mefloquine) are more forgiving of missed doses while some need to be taken on a very regular schedule (e.g. doxycycline) to ensure maximal protection. If travellers are educated on all aspects of malaria prevention and the specific issues around their prophylactic regimen will, they may be more compliant with the treatment schedule.

SELECTION OF ANTIMALARIAL DRUGS

Selecting the most appropriate antimalarial chemoprophylaxis involves the health care provider following five steps:

a) Evaluate the traveller's exact travel itinerary to determine their malaria risk profile. Ask specific questions about timing, type of travel and destination(s). Once these are determined, the potential antimalarial regimen(s) can be reviewed with the traveller (see Appendix I). For many itineraries, there will be several options. Review the advantages and disadvantages (outlined in Table 8.11), and determine what regimen is the best fit for the individual traveller.

b) Select the appropriate dosage of the antimalarial agent, taking time to educate the traveller about proper use of the drug (outlined in Table 8.11).

c) Discuss the importance of PPM, such as insect repellents and bed nets, to help prevent malaria (see Chapter 3).

d) Discuss the importance of seeking out medical advice urgently if the traveller develops a fever while in a malaria-endemic area or within one year[ii] after returning to Canada.

SELECTION OF ANTIMALARIAL DRUGS FOR SPECIFIC REGIONS OF DRUG RESISTANCE

Travellers should know that, while antimalarial medication can markedly decrease the risk of acquiring symptomatic malaria (2;4–8;10), chemoprophylaxis does not provide complete protection. PPM complement antimalarials (1) and decrease travellers' risk of acquiring malaria (see Chapter 3).

Although minor differences in expert opinion exist between jurisdictions (i.e. United States, Europe and Canada), experts do agree that chemoprophylaxis is an essential component of malaria prevention in areas of high transmission. Differences in guidelines often relate to preferred regimens or whether to use chemoprophylaxis in areas with low levels of transmission (see below). Such differences might confuse travellers, and practitioners should therefore take care to explain these differences.

Box 4.1 summarizes the main chemoprophylactic options by resistance status (see Chapter 8 for a more complete discussion of these drugs).

BOX 4.1: Malaria chemoprophylaxis options by drug resistance status

Chloroquine-sensitive regions

Chloroquine-sensitive regions are malaria-endemic areas where chloroquine resistance has not been documented or is not widely present. These include Haiti, the Dominican Republic, Central America north of the Panama Canal, parts of Mexico, parts of South America, north Africa, parts of the Middle East, and west/central China. (See individual countries in Appendix I for 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 (11).

Chloroquine or hydroxychloroquine is taken once a week, beginning at least 1 week before entering a chloroquine-sensitive malaria-endemic region (or 2–3 weeks before to assess tolerability), during the period of exposure, and for 4 weeks after leaving the malaria-endemic region.

Alternatives: Individuals who are unable to tolerate chloroquine or hydroxychloroquine should use atovaquone-proguanil, doxycycline or mefloquine (see next section and Chapter 8).

[ii] The large majority of travel-related malaria cases diagnosed in non-endemic countries present within several months of return from an endemic area (9). However, some cases, including *P. falciparum* malaria, will present after a more protracted period, i.e. ≥ 6 months post-exposure. For this reason, CATMAT recommends that travellers who become ill with an unexplained fever within one year of returning home (regardless of whether malaria prophylaxis was prescribed or taken) should seek immediate medical attention and tell the physician their travel history. Particular attention should be paid to fevers developing in the 3 months following travel, the period during which > 90% of *P. falciparum*-related disease is expressed.

Chloroquine-resistant regions

Chloroquine-resistant regions are malaria-endemic areas where chloroquine resistance has been documented. Chloroquine-resistant regions include 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 both chloroquine-resistant and mefloquine-resistant regions (12–14) (see next section).

There are sufficient data in semi-immune and nonimmune hosts in various geographic locations to conclude that atovaquone-proguanil, doxycycline and mefloquine provide similar levels of protection against chloroquine-resistant malaria (2;4–8).

Drugs of choice: Atovaquone-proguanil, doxycycline or mefloquine (2;4–8;10).

Atovaquone-proguanil is taken daily, beginning at least 1 day before entering a malaria-endemic region (or 3–4 days before to test tolerability), during the period of exposure, and for 1 week after leaving the malaria-endemic region (15).

Doxycycline is taken daily, beginning at least 1 day before entering a malaria-endemic region (or 3–4 days before to test tolerability), during the period of exposure, and for 4 weeks after leaving the malaria-endemic region (4).

Mefloquine is taken weekly, beginning 1 week before entering a malaria-endemic region (or 3 weeks before, to assess tolerability), during the period of exposure, and for 4 weeks after leaving the malaria-endemic region (4).

Alternatives: If atovaquone-proguanil, doxycycline and mefloquine are not well tolerated, primaquine daily can be considered. Begin taking it at least 1 day before entering a malaria-endemic region (or 3–4 days before to ensure tolerability), during the period of exposure, and for 7 days after leaving the malaria-endemic region.

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

Chloroquine-and mefloquine-resistant regions

Resistance to both chloroquine and mefloquine has been reported in various countries in Asia, Africa and 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 (13;14) and Laos, as well as in southern Vietnam (12;16). While these areas are infrequently visited by travellers, use of PPM should be optimized for those travelling there (1).

Drugs of choice: Atovaquone-proguanil or doxycycline (see Chapter 8).

Atovaquone-proguanil is taken daily, beginning at least 1 day before entering a malaria-endemic region or 3–4 days before to ensure tolerability), during the period of exposure, and for 1 week after leaving the malaria-endemic region (15).

Doxycycline is taken daily, beginning at least 1 day before entering a malaria-endemic region (or 3–4 days before to ensure tolerability), during the period of exposure, and for 4 weeks after leaving the malaria-endemic region (4).

Alternatives: There are currently no alternatives for prevention in these regions.

NOTE: There are no approved drugs to prevent malaria in pregnant women or in children weighing less than 5 kg travelling to mefloquine-resistant regions. Atovaquone-proguanil (Malarone®) may be considered for women after the first trimester who cannot avoid travel to mefloquine-resistant areas (e.g. border areas between Thailand and Cambodia/Myanmar) after careful discussion of the benefits and risks (see Chapters 5 and 8) (17;18).

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 relapse 5 years or more after routine chemoprophylaxis has been discontinued (19;20). Although considered less virulent than falciparum malaria, *P. vivax* still carries the potential for significant morbidity requiring intensive care (21). Since most malaria-endemic areas of the world (except Haiti and the Dominican Republic) have either *P. vivax* or *P. ovale*, travellers to these areas have some risk of acquiring relapsing malaria. Primaquine terminal prophylaxis is administered after the traveller has left a malaria-endemic area, usually during or after the post-travel period of chemoprophylaxis. Primaquine decreases the risk of such relapse by acting against the persistent liver stages (hypnozoites) of *P. vivax* and *P. ovale*.

Data pertaining to the risk of relapse are limited. One study showed that, of 725 US Army Ranger task force soldiers stationed in Afghanistan, 38 (5.2%) had *P. vivax* malaria after leaving, 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 (21). Military personnel, long-term travellers and expatriates are groups that should be considered for terminal prophylaxis if they were in regions with high *P. vivax* or *P. ovale* endemicity. Any traveller who returns to Canada with a history of *P. vivax* or *P. ovale* diagnosis should also be considered for terminal prophylaxis (22).

Primaquine is contraindicated in pregnant women and individuals deficient in G6PD (see Chapter 8 for contraindications and precautions).

DIFFERENCES IN APPROACHES TO MALARIA CHEMOPROPHYLAXIS

Committee to Advise on Tropical Medicine and Travel (CATMAT) reviews all major sources of malaria prevention information, including World Health Organization (WHO) (23), Centers for Disease Control and Prevention (CDC) (24) and the Health Protection Agency Advisory Committee on Malaria Prevention (ACMP) (25). CATMAT also reviews recent research and national and international epidemiological data in order to provide guidelines and recommendations tailored to the Canadian context. Factors that influence recommendations include: drug licensure, Canadian-specific travel patterns and malaria epidemiology, and the anticipated values and preferences of travellers and health care providers.

Some jurisdictions (e.g. United States) have a very low risk tolerance for malaria in returning travellers (24), and thus give more weight to chemoprophylaxis. Other jurisdictions (e.g. most European countries) emphasize the potential for drug-adverse effects, and are less likely to recommend chemoprophylaxis in low-risk areas. As well, region-specific recommendations are dynamic; thus, some differences arise as a result of the age of the epidemiologic evidence on which the individual recommendation is based. In these guidelines, CATMAT has tried to balance the need for protection with the potential for adverse effects of chemoprophylaxis. For the most part, CATMAT guidelines are consistent with the WHO (23) and the CDC's *Yellow Book: Health Information for International Travel* (24), although there are still some minor differences.

CATMAT recommends chloroquine for the prevention of malaria in chloroquine-sensitive regions. In chloroquine-resistant regions, CATMAT recommends atovaquone-proguanil, doxycycline or mefloquine as three equivalent options for the prevention of malaria. This is similar to the approach of the CDC. Recommendations on when to start and stop malaria chemoprophylaxis are also consistent among major guidelines, and they also 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 (see section on emergency standby treatment for more information).

CATMAT guidelines sometimes differ from WHO and ACMP guidelines with respect to drug recommendations. For example, 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. In addition, in areas with low-to-moderate levels of malaria transmission and with 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 first-line chemoprophylaxis. However, CATMAT considers chloroquine-proguanil chemoprophylaxis to be significantly less effective compared with atovaquone-proguanil, doxycycline or mefloquine (26;27) and does not recommend this regimen.

Emergency standby therapy for short-term travellers is an option that all the guidelines include, although CATMAT and CDC have more restrictive criteria as to when to use it. CATMAT recommends standby self-treatment for selected travellers who are unable to access medical assistance within 24 hours. CDC guidelines recommend atovaquone-proguanil or artemether-lumefantrine for this use, whereas CATMAT recommends standby malaria treatment with atovaquone-proguanil or quinine and doxycycline, since artemether-lumefantrine is not available in Canada. However, CATMAT does not recommend using mefloquine for therapy under any circumstances because of the high likelihood of severe adverse reactions when using higher therapeutic doses. For more information about self-treatment, see Chapter 7.

DISCONTINUING ANTIMALARIAL DRUGS

Fatal malaria has occurred in travellers who have discontinued an effective antimalarial drug in favour of one that is less protective (11;28–30). During travel, individuals might meet other travellers and/or health care providers who suggest that they change or stop their antimalarial medication. For the most part, such advice should be ignored or questioned; medications used in other areas of the world may be less effective, may be associated with serious adverse effects or may not be manufactured to Canadian standards and are not recommended for Canadian travellers. Examples include proguanil alone (Paludrine®), pyrimethamine (Daraprim®), dapsone-pyrimethamine (Maloprim®) and mefloquine-sulfadoxine-pyrimethamine (Fansimef®).

One of the exceptions to this general rule is when the traveller is suffering significant adverse events associated with the chemoprophylactic agent. In such a situation, and when the advice is provided by a health care provider (preferably the one who provided the initial advice), changing medication is reasonable. Ideally, this would be to another agent recommended by CATMAT in these guidelines. Discontinuation of all chemoprophylaxis is NOT a reasonable option.

CO-ADMINISTRATION 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 co-administered with live attenuated bacterial oral vaccines. Mefloquine and chloroquine have shown *in vitro* inhibitory activity against an oral typhoid vaccine (31). Proguanil has some antibacterial activity, but co-administering atovaquone-proguanil with live, oral typhoid and cholera vaccines to children did not affect the

antibody response to the vaccine (32). However, co-administering of proguanil and chloroquine with live, oral typhoid and cholera vaccines decreased vaccine immunogenicity (33). Vaccine efficacy studies measuring the impact on the incidence of clinical typhoid and cholera of the co-administration of antimalarials with live, oral typhoid and cholera vaccines have not been performed. Since the data are not definitive, the cautious approach will be to complete vaccination with live oral typhoid or cholera vaccines at least 3 days before the first dose of antimalarial medication (34–36). Formalin-and/or heat-inactivated oral vaccines (such as Dukoral®) do not contain live bacteria and may be co-administered with antimalarials.

Concurrent use of chloroquine also interferes with the antibody response to intradermal administration of human diploid cell rabies vaccine (37). If intradermal rabies vaccine is administered to someone taking chloroquine, rabies serology may help confirm response to vaccination, but it is not always easily available.

During the discussion of chemoprophylaxis:

a) Tell travellers that malaria can be fatal, but that medications rarely cause serious adverse events if selected and used with care.
b) Choose a medication that is least likely to exacerbate any past or present medical problem(s).
c) Present all the options to travellers and, unless there is a contraindication, give them a choice of which chemoprophylaxis they prefer; all recommended first-line malaria chemoprophylactic regimens are equally effective.
d) Emphasize that medication should be taken in the recommended fashion to minimize significant adverse events.
e) Discuss the option of a drug trial to check for medication-associated adverse reactions before travelling.
f) Discuss strategies to change medication if serious adverse effects should arise during travel.
g) Advise travellers that if a malaria medication is tolerated well they should continue taking it regardless of negative anecdotes about the drug. There is no evidence to suggest that long-term use of currently recommended therapies for travellers will result in additional risks for severe adverse events.

TABLE 4.1: Evidence-based medicine recommendations

RECOMMENDATION	EBM RATING
Chloroquine (Aralen®) or hydroxychloroquine (Plaquenil®) is the drug of choice for travellers to areas with chloroquine-sensitive malaria (11) .	A I
Atovaquone-proguanil, doxycycline or mefloquine are drugs of choice for travellers to areas with chloroquine-resistant or mefloquine-sensitive malaria (2;4–8;10).	A I
Atovaquone-proguanil and doxycycline are drugs of choice for travellers to areas with mefloquine-resistant malaria (4;15;38).	A I
Primaquine is recommended for malaria chemoprophylaxis for travellers to regions with chloroquine resistance who are not willing or able to use atovaquone-proguanil, doxycycline or mefloquine (5).	A I
Primaquine is recommended as post-travel terminal prophylaxis for travellers who have suffered from *Plasmodium vivax* or *Plasmodium ovale* malaria while abroad (22).	B III
Standby malaria treatment with atovaquone-proguanil or quinine and doxycycline is recommended for travellers who are more than a day away from malaria diagnostic help.	C III

Doxycycline is an antibiotic and should never be co-administered with any live, oral bacterial vaccines. Vaccination with live oral typhoid or cholera vaccines should be completed at least 3 days before the first dose of antimalarial medication (34–36).	B III
Concurrent use of chloroquine interferes with antibody response to intradermal administration of human diploid cell rabies vaccine (37). 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

ABBREVIATION: EBM, evidence-based medicine.

NOTE: For a description of the categories and quality of evidence of the recommendations, see Appendix IV.

REFERENCE LIST

(1) Committee to Advise on Tropical Medicine and Travel. Statement on Personal Protective Measures to Prevent Arthropod Bites. Can Commun Dis Rep 2012;38 (ASC-2):1–18.

(2) Sanchez JL, DeFraites RF, Sharp TW, Hanson RK. Mefloquine or doxycycline prophylaxis in US troops in Somalia. Lancet 1993 Apr 17;341(8851):1021–2.

(3) Koren G, Matsui D, Bailey B. DEET-based insect repellents: safety implications for children and pregnant and lactating women. CMAJ 2003 Aug 5;169(3):209–12.

(4) Ohrt C, Richie TL, Widjaja H, Shanks GD, Fitriadi J, Fryauff DJ, et al. Mefloquine compared with doxycycline for the prophylaxis of malaria in Indonesian soldiers. A randomized, double-blind, placebo-controlled trial. Ann Intern Med 1997 Jun 15;126(12):963–72.

(5) Weiss WR, Oloo AJ, Johnson A, Koech D, Hoffman SL. Daily primaquine is effective for prophylaxis against falciparum malaria in Kenya: comparison with mefloquine, doxycycline, and chloroquine plus proguanil. J Infect Dis 1995 Jun;171(6):1569–75.

(6) Sukwa TY, Mulenga M, Chisdaka N, Roskell NS, Scott TR. A randomized, double-blind, placebo-controlled field trial to determine the efficacy and safety of Malarone (atovaquone/proguanil) for the prophylaxis of malaria in Zambia. Am J Trop Med Hyg 1999 Apr;60(4):521–5.

(7) Shanks GD, Kremsner PG, Sukwa TY, Van Der Berg JD, Shapiro TA, Scott TR, et al. Atovaquone and proguanil hydrochloride for prophylaxis of malaria. J Travel Med 1999;SUPPL 6:S21-S27.

(8) Shanks GD, Gordon DM, Klotz FW, Aleman GM, Oloo AJ, Sadie D, et al. Efficacy and safety of atovaquone/proguanil as suppressive prophylaxis for Plasmodium falciparum malaria. Clin Infect Dis 1998 Sep;27(3):494–9.

(9) Mali S, Kachur SP, Arguin PM. Malaria surveillance—United States, 2010. MMWR Surveill Summ 2012 Mar 2;61(2):1–17.

(10) Lell B, Luckner D, Ndjave M, Scott T, Kremsner PG. Randomised placebo-controlled study of atovaquone plus proguanil for malaria prophylaxis in children. Lancet 1998 Mar 7;351(9104):709–13.

(11) Newman RD, Parise ME, Barber AM, Steketee RW. Malaria-related deaths among U.S. travelers, 1963–2001. Ann Intern Med 2004 Oct 5;141(7):547–55.

(12) Arguin PM, Mali S. Malaria. In: Brunette G.W., Kozarsky PE, Magill AJ, Shlim D.R., Whatley A.D., editors. CDC Health Information for International Travel 2012.New York: Oxford University Press; 2012. p. 223–43.

(13) Wongsrichanalai C, Pickard AL, Wernsdorfer WH, Meshnick SR. Epidemiology of drug-resistant malaria. Lancet Infect Dis 2002 Apr;2(4):209–18.

(14) Wongsrichanalai C, Sirichaisinthop J, Karwacki JJ, Congpuong K, Miller RS, Pang L, et al. Drug resistant malaria on the Thai-Myanmar and Thai-Cambodian borders. Southeast Asian J Trop Med Public Health 2001 Mar;32(1):41–9.

(15) Camus D, Djossou F, Schilthuis HJ, Hogh B, Dutoit E, Malvy D, et al. Atovaquone-proguanil versus chloroquine-proguanil for malaria prophylaxis in nonimmune pediatric travelers: results of an international, randomized, open-label study. Clin Infect Dis 2004 Jun 15;38(12):1716–23.

(16) Kozarsky PE, Arguin PM, Navin A. Malaria. CDC health information for international travel, 2005–2006. Philadelphia: Elsevier Mosby; 2005.

(17) Stauffer WM, Kamat D, Magill AJ. Traveling with infants and children. Part IV: insect avoidance and malaria prevention. J Travel Med 2003 Jul;10(4):225–40.

(18) Na-Bangchang K, Manyando C, Ruengweerayut R, Kioy D, Mulenga M, Miller GB, et al. The pharmacokinetics and pharmacodynamics of atovaquone and proguanil for the treatment of uncomplicated falciparum malaria in third-trimester pregnant women. Eur J Clin Pharmacol 2005 Sep;61(8):573–82.

(19) Shwartz E, Parise M, Kozarsky P, Cetron M. Delayed onset of malaria-implications for chemoprophylaxis in travellors. N Engl J Med 2003 Oct 16;349(16):1510–6.

(20) Baird JK. Chloroquine resistance in Plasmodium vivax. Antimicrob Agents Chemother 2004 Nov;48(11):4075–83.

(21) Kotwal RS, Wenzel RB, Sterling RA, Porter WD, Jordan NN, Petruccelli BP. An outbreak of malaria in US Army Rangers returning from Afghanistan. JAMA 2005 Jan 12;293(2):212–6.

(22) Hill DR, Baire JK, Parise ME, Lewis LS, Ryan ET, Magill AJ. Primaquine: report from CDC expert meeting on malaria chemoprophylaxis I. Am J Trop Med Hyg 2006;75(3):402–15.

(23) World Health Organization. International travel and health. 2012.

(24) CDC Health Information for International Travel 2012. New York: Oxford University Press; 2012.

(25) Bradley DJ, Bannister B. Guidelines for malaria prevention in travellers from the United Kingdom for 2003. Commun Dis Public Health 2003 Sep;6(3):180–99.

(26) Lobel HO, Miani M, Eng T, Bernard KW, Hightower AW, Campbell CC. Long-term malaria prophylaxis with weekly mefloquine. Lancet 1993 Apr 3;341(8849):848–51.

(27) Steffen R, Fuchs E, Schildknecht J, Naef U, Funk M, Schlagenhauf P, et al. Mefloquine compared with other malaria chemoprophylactic regimens in tourists visiting east Africa. Lancet 1993 May 22;341(8856):1299–303.

(28) Humar A, Sharma S, Zoutman D, Kain KC. Fatal falciparum malaria in Canadian travellers. CMAJ 1997 Apr 15;156(8):1165–7.

(29) Kain KC, MacPherson DW, Kelton T, Keystone JS, Mendelson J, MacLean JD. Malaria deaths in visitors to Canada and in Canadian travellers: a case series. CMAJ 2001 Mar 6;164(5):654–9.

(30) Centers for Disease Control and Prevention. Malaria deaths following inappropriate malaria chemoprophylaxis—United States, 2001. MMWR Morb Mortal Wkly Rep 2001 Jul 20;50(28):597–9.

(31) Horowitz H, Carbonaro CA. Inhibition of the Salmonella typhi oral vaccine strain, Ty21a, by mefloquine and chloroquine. J Infect Dis 1992 Dec;166(6):1462–4.

(32) Faucher JF, Binder R, Missinou MA, Matsiegui PB, Gruss H, Neubauer R, et al. Efficacy of atovaquone/proguanil for malaria prophylaxis in children and its effect on the immunogenicity of live oral typhoid and cholera vaccines. Clin Infect Dis 2002 Nov 15;35(10):1147–54.

(33) Kollaritsch H, Que JU, Kunz C, Wiedermann G, Herzog C, Cryz SJ, Jr. Safety and immunogenicity of live oral cholera and typhoid vaccines administered alone or in combination with antimalarial drugs, oral polio vaccine, or yellow fever vaccine. J Infect Dis 1997 Apr;175(4):871–5.

(34) Mefloquine (mefloquine hydrchloride tablets) Product Monograph. 2010.

(35) Malarone Product Monograph. Mississauga: GlaxoSmithKline; 2012.

(36) Aralen Product Monograph. 2008.

(37) Pappaioanou M, Fishbein DB, Dreesen DW, Schwartz IK, Campbell GH, Sumner JW, et al. Antibody response to preexposure human diploid-cell rabies vaccine given concurrently with chloroquine. N Engl J Med 1986 Jan 30;314(5):280–4.

(38) Krudsood S, Patel SN, Tangpukdee N, Thanachartwet W, Leowattana W, Pornpininworakij K, et al. Efficacy of atovaquone-proguanil for treatment of acute multidrug-resistant Plasmodium falciparum malaria in Thailand. Am J Trop Med Hyg 2007 Apr;76(4):655–8.

CHAPTER 5: MALARIA ISSUES IN SPECIAL HOSTS

5.1 PREVENTION IN SPECIAL HOSTS—CHILDREN

MALARIA PREVENTION IN CHILDREN

Health care providers should clearly advise travellers of the risks of taking young children to areas with *Plasmodium falciparum* malaria. The majority of the over 650,000 deaths per year due to malaria are among children (1). A study found that malaria was the most common cause of febrile illness (35%) among returned pediatric travellers, and the most common single diagnosis overall (8%) (2); however these findings cannot be generalized to all children travelling internationally. Travel to sub-Saharan Africa accounts for the vast majority of childhood cases of falciparum malaria, with most travellers visiting friends and relatives (2–4). Malaria also disproportionately affects children. Of the Canadians diagnosed with malaria who were reported to the Public Health Agency of Canada from 1998 to 2008, 23% were 19 years old or younger whereas only 8.7% of international travellers in 2011 were in that age group (5). From August 2001 to August 2012, 195 cases of severe or complicated malaria were reported to the Canadian Malaria Network (CMN). Of these, 21.1% were children (< 18 years old), and 11.6% were 0 to 4 years old (Personal communication, A. McCarthy and J. Geduld, 2012).

Of the 7,542 malaria cases reported between 2006 and 2010 to the Centers for Disease Control and Prevention (CDC) in the United States, 1,418 (18.0%) were children (< 18 years old) and 360 (4.8%) were aged 0 to 4 years old (Personal communication, K. Cullen and P. Arguin, 2012; Domestic Response Unit, Malaria Branch, Division of Parasitic Diseases, CDC and Prevention, United States).

Malaria can present with nonspecific symptoms that mimic other common childhood diagnoses, leading to delays in diagnosis. Severe or complicated malaria, such as cerebral malaria, severe anemia, shock or even death, may develop more quickly in children (6). CMN data from June 2001 to September 2011 indicate that 22% of the complicated malaria cases requiring treatment with intravenous quinine or artesunate were in children, the majority of whom were foreign-born (61%) (7).

To reduce the risk of infection when travel to malaria-endemic areas is unavoidable, all children should be well protected against mosquito bites (see Chapter 3) and receive appropriate malaria chemoprophylaxis (7;8). Infants do not receive sufficient medication through breast milk to protect them and should be prescribed antimalarial drugs even if their mother is taking antimalarials (9;10).

Making sure 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. Prescribe sufficient tablets to allow a few doses to be vomited or spat out, with clear instructions as to when doses that were not successfully ingested should be repeated. Health care providers should consider enlisting the help of compounding pharmacies that can either pre-cut tablets and/or crush and insert portions into capsules to increase the accuracy and ease of dosing.

Deaths due to inadvertent overdose have been reported; these medications should, therefore, be kept out of reach of infants and children and stored in childproof containers (11).

Families who are travelling over the long term should be told how to adjust the dose of medications to allow for an increase in children's weight over time.

CHEMOPROPHYLAXIS FOR CHILDREN

Chloroquine is the preferred chemoprophylactic agent in areas with chloroquine-sensitive malaria (see Appendix I for specific recommendations for areas). Chloroquine sulfate (e.g. Nivaquine®) is widely available as a syrup in malaria-endemic areas, and this is often more easily administered to children than are tablets. However, it is not available in Canada, and those purchasing products outside of Canada need to take care to minimize the risk of counterfeit medication (see "Preventing Malaria in the Long-Term Traveller or Expatriate"). If parents plan to use this syrup, inform them 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 (see Appendix I for specific recommendations for different areas); however, there are no studies that analyze its bioavailability and rate of metabolism in children. Although the manufacturer recommends that mefloquine not be given to children smaller than 5 kg (11 lb), mefloquine should be considered for all children at high risk of acquiring chloroquine-resistant *P. falciparum*, at a dose of 5 mg base/kg once weekly (12). Young children are less likely to suffer major neuropsychiatric side effects from mefloquine (13) but may be more likely to have emesis (14).

While chloroquine and mefloquine may exacerbate seizure disorders, in which case other agents should be used, there is no evidence that febrile seizures in children are a contraindication to these drugs.

Atovaquone-proguanil is licensed for the prophylaxis and treatment of malaria in children weighing 11 kg (25 lb) or more or who are older than 3 years (15). Clinical trials using atovaquone-proguanil to treat malaria in children weighing as low as 5 kg (11 lb) suggest it may be safe for infants of this size when required (16). Daily doses for small infants have been extrapolated from those used in treatment trials (one-quarter of the treatment dose, or 5 mg/kg/doses and 2 mg/kg/doses of the atovaquone and proguanil components, respectively). Based on a pediatric tablet of 62.5 mg atovaquone/25 mg proguanil, the daily doses are half of a pediatric tablet for those children weighing 5 kg to 8 kg (11–17 lb) and three-quarters of a pediatric tablet for those children weighing 8 kg to 10 kg (17–22 lb) (16).

Doxycycline has been studied as pediatric prophylactic medication (17). It can be used at a daily dose of 2 mg/kg (maximum: 100 mg/d) in children aged 8 years and older (9;18). Primaquine can be given to children 9 years and older who are unable to take any of the first-line prophylactic agents (19), although it is not licensed in Canada for this indication. As there is no age limit for primaquine when used for radical cure of *P. vivax* or *P. ovale,* it may be an option for children of any age as long as they have been screened for adequate glucose-6-phosphate dehydrogenase (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.

TABLE 5.1.1: Evidence-based medicine recommendations

RECOMMENDATION	EBM RATING
Young children should avoid travel to areas with significant malaria transmission, particularly of chloroquine-resistant malaria (9).	C III
Effective PPM should be used by all children who travel to malaria-endemic areas (20).	A I
For children travelling to or residing in chloroquine-resistant areas, mefloquine, doxycycline (≥ 8 years) and atovaquone-proguanil (≥ 5 kg) are the drugs of choice for chemoprophylaxis (12;15;17;21).	A I
Primaquine chemoprophylaxis may be suitable for children who are unable to take any of the first-line prophylactic agents (19).	B II

ABBREVIATION: EBM, evidence-based medicine; PPM, personal protective measures.

NOTE: For a description of the categories and quality of evidence of the recommendations, see Appendix IV.

REFERENCE LIST

(1) World Health Organization. World Malaria Report 2011. 2011.

(2) Hagmann S, Neugebauer R, Schwartz E, Perret C, Castelli F, Barnett ED, et al. Illness in children after international travel: analysis from the GeoSentinel Surveillance Network. Pediatrics 2010 May;125(5):e1072–e1080.

(3) Ladhani S, Aibara RJ, Riordan FA, Shingadia D. Imported malaria in children: a review of clinical studies. Lancet Infect Dis 2007 May;7(5):349–57.

(4) Stager K, Legros F, Krause G, Low N, Bradley D, Desai M, et al. Imported malaria in children in industrialized countries, 1992–2002. Emerg Infect Dis 2009 Feb;15(2):185–91.

(5) Statistics Canada. Characteristics of International Travelers: Custom Extraction. 2011.

(6) Maitland K, Marsh K. Pathophysiology of severe malaria in children. Acta Trop 2004 Apr;90(2):131–40.

(7) McCarthy AE, Plourde P, Kuhn S., Bodie M. Parenteral quinine for severe malaria: Five year surveillance data from the Canadian Malaria Network. 10th Conference of the International Society of Travel Medicine. 10th Conference of the International Society of Travel Medicine, [Abstract No. FC02.01]. 2007.

(8) Committee to Advise on Tropical Medicine and Travel. Statement on personal protective measures to prevent arthropod bites. Can Commun Dis Rep 2012;38 (ASC-3):1–18.

(9) American Academy of Pediatrics. Red Book: 2009 Report of the Committee on Infectious Diseases, 28th ed. Illinois: American Academy of Pediatrics; 2009.

(10) Martindale. The Complete Drug Reference. 32nd Ed. ed. London: Pharmaceutical Press; 2008.

(11) Smith ER, Klein-Schwartz W. Are 1–2 dangerous? Chloroquine and hydroxychloroquine exposure in toddlers. J Emerg Med 2005 May;28(4):437–43.

(12) Centers for Disease Control. Information for health care providers: preventing malaria in infants and children. 2006.

(13) Luxemburger C, Price RN, Nosten F, Ter Kuile FO, Chongsuphajaisiddhi T, White NJ. Mefloquine in infants and young children. Ann Trop Paediatr 1996 Dec;16(4):281–6.

(14) Stauffer WM, Kamat D, Magill AJ. Traveling with infants and children. Part IV: insect avoidance and malaria prevention. J Travel Med 2003 Jul;10(4):225–40.

(15) Camus D, Djossou F, Schilthuis HJ, Hogh B, Dutoit E, Malvy D, et al. Atovaquone-proguanil versus chloroquine-proguanil for malaria prophylaxis in nonimmune pediatric travelers: results of an international, randomized, open-label study. Clin Infect Dis 2004 Jun 15;38(12):1716–23.

(16) Boggild AK, Parise ME, Lewis LS, Kain KC. Atovaquone-proguanil: report from the CDC expert meeting on malaria chemoprophylaxis (II). Am J Trop Med Hyg 2007 Feb;76(2):208–23.

(17) Pang LW, Limsomwong N, Boudreau EF, Singharaj P. Doxycycline prophylaxis for falciparum malaria. Lancet 1987 May 23;1(8543):1161–4.

(18) Rietveld AE. Special groups: pregnant women, infants, and young children. In: Schlagenhauf P, editor. Traveller's medicine. 315 ed. Hamilton: BC Decker Inc; 2001.

(19) Weiss WR, Oloo AJ, Johnson A, Koech D, Hoffman SL. Daily primaquine is effective for prophylaxis against falciparum malaria in Kenya: comparison with mefloquine, doxycycline, and chloroquine plus proguanil. J Infect Dis 1995 Jun;171(6):1569–75.

(20) Fradin MS, Day JF. Comparative efficacy of insect repellents against mosquito bites. N Engl J Med 2002 Jul 4;347(1):13–8.

(21) Overbosch D, Schilthuis H, Bienzle U, Behrens RH, Kain KC, Clarke PD, et al. Atovaquone-proguanil versus mefloquine for malaria prophylaxis in nonimmune travelers: results from a randomized, double-blind study. Clin Infect Dis 2001 Oct 1;33(7):1015–21.

5.2 PREVENTION IN SPECIAL HOSTS—PREGNANCY AND BREASTFEEDING

MALARIA PREVENTION IN PREGNANCY AND DURING BREASTFEEDING

Malaria increases the risk of maternal and neonatal death, miscarriage and stillbirth. In addition, low birth-weight infants are more commonly born to women taking ineffective prophylaxis (1). In addition, pregnant women are twice as likely to be bitten by mosquitoes, probably as a result of increased body surface temperature, increased CO_2 production and the greater chance of leaving the protection of the bed net at night due to increased urinary frequency (2).

Pregnant women should defer travel to malaria-endemic areas and particularly to those regions with drug-resistant falciparum malaria. If travel cannot be avoided, special care should be taken. Personal protective measures (PPM) to avoid mosquito bites are the same for pregnant women as for other adults—use topical repellents and insecticide-treated bed nets (see Chapter 3) (3). In addition, effective chemoprophylaxis (outlined below) should be selected. Refer to the CATMAT *Statement on Pregnancy and Travel* for a more detailed description of malaria in pregnant travellers or those who are breastfeeding (4).

SELECTING ANTIMALARIALS FOR PREGNANT TRAVELLERS FOR SPECIFIC REGIONS OF DRUG RESISTANCE

CHLOROQUINE-SENSITIVE DESTINATIONS

Chloroquine is safe in pregnancy and is the drug of choice for pregnant travellers travelling to chloroquine-sensitive malaria-endemic destinations (see Appendix I).

CHLOROQUINE-RESISTANT DESTINATIONS

Atovaquone-proguanil: Proguanil has long been considered safe in pregnancy; however, data are lacking on atovaquone. Small malaria treatment trials using atovaquone-proguanil 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 (4–6). 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.

Chloroquine–proguanil: While chloroquine and proguanil are both safe in pregnancy, the combination is ineffective in preventing chloroquine-resistant malaria and is not recommended.

Doxycycline: Doxycycline is contraindicated for malaria prophylaxis during pregnancy because of adverse effects on the fetus, including discolouration and dysplasia of the teeth, and inhibition of bone growth. Attempting to become pregnant should be avoided for a week after completing doxycycline prophylaxis to allow for complete excretion.

Mefloquine: Mefloquine can be used safely for chemoprophylaxis throughout most of pregnancy. While treatment doses five-fold greater than prophylaxis doses may be associated with an increased risk of stillbirth (7), the majority of observational and clinical trial data have concluded that mefloquine does not lead to an increased risk of either stillbirth or congenital malformations at prophylactic doses when used during the second and third trimesters (7–9). Surveillance data of more than 1,500 pregnant women found no evidence of increased risk of either teratogenicity or spontaneous abortion when mefloquine was used at any time from before conception up to and including the third trimester (10). Although there does not appear to be a concern early in

pregnancy, the data for the first trimester are limited. While the use of mefloquine at the time of conception or during the first trimester is not an indication for therapeutic abortion (8;11), highly risk-averse travellers may choose to avoid pregnancy for up to three months after discontinuing mefloquine because of the long half-life of the drug (approximately three weeks). For expatriates or other long-term travellers in malaria-endemic areas, it is safer for both fetus and mother if she uses effective chemoprophylaxis, given the ongoing risk of disease and the increased risk of severe disease and death during pregnancy (1).

Primaquine: Primaquine is contraindicated during pregnancy[iii] because the glucose-6-phosphate dehydrogenase (G6PD) status of the fetus cannot be established and the drug can be passed across the placenta (12). Whenever radical cure or terminal prophylaxis for vivax malaria is indicated in a pregnant woman, chloroquine can be given once a week until delivery, at which time primaquine may be given postpartum.

TABLE 5.2.1: Evidence-based medicine recommendations

RECOMMENDATION	EBM RATING
Pregnant women should avoid travel to areas with significant transmission of malaria (1).	C III
The use of PPM, including appropriate topical repellents and insecticide-treated bed nets, are strongly encouraged for all pregnant women who travel to malaria-endemic areas (3).	A I
Pregnant women travelling to or living in chloroquine-sensitive areas should use chloroquine as chemoprophylaxis.	A I
Where exposure to chloroquine-resistant falciparum malaria is unavoidable, mefloquine is recommended from conception through the first trimester (A II), as well as during the second and third trimesters (A I) (7–9).	A II, A I
There are no currently approved antimalarials for pregnant women travelling to mefloquine-resistant regions. Atovaquone-proguanil after the first trimester in women who cannot avoid travel to mefloquine-resistant areas (e.g. border areas between Thailand and Cambodia or Burma [Myanmar], see Appendix I) may be considered after careful discussion of the benefits and risks (5;6).	B II
Although safe in pregnancy, the combination of chloroquine and proguanil is inadequate as an antimalarial and cannot be recommended for chloroquine-resistant areas (13).	E I

ABBREVIATION: EBM, evidence-based medicine; PPM, personal protective measures.

NOTE: For a description of the categories and quality of evidence of the recommendations, see Appendix IV.

PROPHYLAXIS WHILE BREASTFEEDING

The availability of antimalarial medication in breast milk is insufficient to protect breastfeeding infants against malaria; therefore, infants requiring chemoprophylaxis should receive a recommended dose of appropriate antimalarial drug. Breastfeeding is not contraindicated for the use of medications that are safe in infancy (chloroquine, mefloquine, atovaquone-proguanil in infants weighing ≥ 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 administered to a breastfeeding woman.

[iii] Category C of US Food and Drug Administration Use-in-Pregnancy Ratings (see Perinatology webpage for rating details.)

Because of the lack of data on the safety and efficacy of atovaquone in infants weighing less than 5 kg, atovaquone-proguanil should not be given to a woman who is breastfeeding 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 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 (14).

TABLE 5.2.2: Evidence-based medicine recommendations

RECOMMENDATION	EBM RATING
Infants who are at risk of malaria and who are being breastfed should receive their own appropriate chemoprophylaxis (15).	A III
Atovaquone-proguanil should be avoided, if possible, in a woman who is breastfeeding a child weighing less than 5 kg (15).	C II
Limited data suggest that doxycycline absorption through breast milk is negligible and that breastfeeding is not an absolute contraindication to maternal use (14).	C III

ABBREVIATION: EBM, evidence-based medicine.

NOTE: For a description of the categories and quality of evidence of the recommendations, see Appendix IV.

REFERENCE LIST

(1) Shulman CE, Dorman EK. Importance and prevention of malaria in pregnancy. Trans R Soc Trop Med Hyg 2003 Jan;97(1):30–5.

(2) Lindsay S, Ansell J, Selman C, Cox V, Hamilton K, Walraven G. Effect of pregnancy on exposure to malaria mosquitoes. Lancet 2000 Jun 3;355(9219):1972.

(3) McGready R, Hamilton KA, Simpson JA, Cho T, Luxemburger C, Edwards R, et al. Safety of the insect repellent N,N-diethyl-M-toluamide (DEET) in pregnancy. Am J Trop Med Hyg 2001 Oct;65(4):285–9.

(4) Committee to Advise on Tropical Medicine and Travel (CATMAT). Statement on pregnancy and travel. Can Commun Dis Rep 2010;36(ACS-2):1–43.

(5) Stauffer WM, Kamat D, Magill AJ. Traveling with infants and children. Part IV: insect avoidance and malaria prevention. J Travel Med 2003 Jul;10(4):225–40.

(6) Na-Bangchang K, Manyando C, Ruengweerayut R, Kioy D, Mulenga M, Miller GB, et al. The pharmacokinetics and pharmacodynamics of atovaquone and proguanil for the treatment of uncomplicated falciparum malaria in third-trimester pregnant women. Eur J Clin Pharmacol 2005 Sep;61(8):573–82.

(7) Nosten F, Vincenti M, Simpson J, Yei P, Thwai KL, de VA, et al. The effects of mefloquine treatment in pregnancy. Clin Infect Dis 1999 Apr;28(4):808–15.

(8) Balocco RB, Bonati M. Mefloquine prophylaxis against malaria for female travelers of childbearing age. Lancet 1992 Aug 1;340(8814):309–10.

(9) Steketee RW, Wirima JJ, Slutsker L, Roberts JM, Khoromana CO, Heymann DL, et al. Malaria parasite infection during pregnancy and at delivery in mother, placenta, and newborn: efficacy of chloroquine and mefloquine in rural Malawi. Am J Trop Med Hyg 1996;55(1 Suppl):24–32.

(10) Vanhauwere B, Maradit H, Kerr L. Post-marketing surveillance of prophylactic mefloquine (Lariam) use in pregnancy. Am J Trop Med Hyg 1998 Jan;58(1):17–21.

(11) Nosten F, ter KF, Maelankiri L, Chongsuphajaisiddhi T, Nopdonrattakoon L, Tangkitchot S, et al. Mefloquine prophylaxis prevents malaria during pregnancy: a double-blind, placebo-controlled study. J Infect Dis 1994 Mar;169(3):595–603.

(12) Rietveld AE. Special groups: pregnant women, infants, and young children. In: Schlagenhauf P, editor. Traveller's medicine. 315 ed. Hamilton: BC Decker Inc; 2001.

(13) Hogh B, Clarke P, Camus D, Nothdurft HD, Overbosch D, Gunther M, et al. Atovaquone-proguanil versus chloroquine-proguanil for malaria prophylaxis in non-immune travellers: a randomised, double-blind study. Lancet 2000;356(9245):1888–94.

(14) Ward RM, Bates BA, Benitz WE, Burchfield DJ. The transfer of drugs and other chemicals into human milk. Pediatrics 2001;108(3):776–89.

(15) Boggild AK, Parise ME, Lewis LS, Kain KC. Atovaquone-proguanil: report from the CDC expert meeting on malaria chemoprophylaxis (II). Am J Trop Med Hyg 2007 Feb;76(2):208–23.

5.3 PREVENTION IN SPECIAL HOSTS—LONG TERM OR EXPATRIATE

PREVENTING MALARIA IN THE LONG-TERM TRAVELLER OR EXPATRIATE

The particular concerns that relate to preventing malaria in long-term travellers (those who travel for more than one month) and expatriates include: safety of chemoprophylactic drugs and fear of toxic effects with prolonged use of medication; cost of long-term medication; use of locally procured drugs that may be counterfeit; conflicting counsel about appropriate chemoprophylaxis and self-treatment; and lack of adherence to chemoprophylaxis and personal protective measures (PPM).

Modern prevention strategies have had a significant positive impact on the risk of malaria-related mortality in long-term expatriates. Mortality was reported to be as high as 60% among missionaries in west Africa during the 20th century (1). However, developing unique, evidence-based guidelines for the long-term traveller or expatriate has been limited by a lack of medical literature in this area, as well as the variability in risk based on location, occupation, lifestyle and activities (2). The risk of malaria associated with location, or the entomological inoculation rate, may vary depending on the season, as well as whether the location is rural, peri-urban or urban.

The advice of health care providers may compete with the opinions of travellers who assume that their personal experience with drug-related adverse events is representative of the general population (3). Some researchers have observed that the incidence of malaria may be greater among veteran expatriates than among their less experienced counterparts. The veteran expatriates may have unreasonable confidence in their clinical self-diagnosis (4) compounded by false-positive laboratory errors (5). The use of counterfeit drugs can also lead to drug resistance or, more immediately, treatment failures. Users may then generalize the resultant failure of response of a specific medication to all malaria medications (6).

ADVERSE EVENTS

A survey of over 2,700 Peace Corps volunteers found that 62% reported one or more adverse events, with 9% reporting serious adverse events and 23% changing malaria prophylaxis due to adverse events (7).

There is no evidence to suggest that long-term use of therapies currently recommended for short-stay travellers results in additional risk of severe adverse events. Chloroquine may be an exception; the risk of chloroquine retinopathy requires an ophthalmologic exam at least every two years for travellers using chloroquine long-term (8). However, this drug is seldom indicated because of extensive drug resistance. Although the data supporting long-term use of doxycycline for chemoprophylaxis are limited, the drug and the related minocycline is in use for extended periods of time for other indications (9).

Mefloquine tolerance improves over time, possibly associated with the relatively early onset of adverse events experienced by those who use mefloquine for prophylaxis (5). Consequently, there does not appear to be increased risk with long-term use (10). Although there are few data on prolonged use of atovaquone-proguanil, the individual components have been used for extended periods of time (8).

CURRENT MALARIA PREVENTION PRACTICE AMONG EXPATRIATES

Malaria chemoprophylaxis use in expatriates is suboptimal. Only 69% of expatriate households in Nigeria appropriately picked up their chemoprophylaxis from the pharmacy, and among those that did, 58% were nonadherent, resulting in an overall nonadherence rate of 61% (11). A study of expatriates in western Ghana found that duration of stay was inversely proportional to adherence to malaria chemoprophylaxis; 80% of those who had been in western Ghana for three months or less were taking malaria chemoprophylaxis, compared to none of the workers who had been there for over a year (12). A review of health behaviours among expatriate workers for the International Committee of the Red Cross reported 65% adherence to recommended malaria chemoprophylaxis (13). Finally, a survey of expatriate health care workers in Equatorial Guinea found that only 31% adhered to their malaria chemoprophylaxis regimen (14).

Data collected from deployed military troops also suggest poor adherence to recommended malaria chemoprophylaxis. Of over 1,000 French soldiers assigned to missions in sub-Saharan Africa, only 61% reported taking their chemoprophylaxis (15). A more recent report only 45% compliance with malaria prophylaxis among 575 French soldiers stationed in Ivory Coast (16). This is comparable to the outcome of an anonymous, post-deployment survey of United States Army Rangers returned from 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. In this group 82% reported treating uniforms with permethrin, and 29% for the application of insect repellent (17).

SUPPORT FOR ESTABLISHED GUIDELINES

In general, guidelines for preventing malaria in long-term travellers or expatriates should be very similar to standard recommendations for the short-term traveller, though cost may limit the use of more expensive drugs such as atovaquone-proguanil. However, given how poorly long-term travellers tend to adhere to malaria chemoprophylaxis, pre-travel advice regarding malaria precautions should also include a description of malaria symptoms and emphasis on the need for early diagnosis and treatment; a discussion of the need to develop a plan for accessing competent medical care in the event of illness; detailed advice regarding PPM (see Chapter 3); the use of standby emergency therapy (self-treatment), if applicable; and the possibility of counterfeit malaria drugs procured locally (10).

Data on the incidence of malaria in long-term travellers are limited; also limited are data on the effectiveness and tolerance of currently recommended regimens. Studies conducted in chloroquine-resistant regions consistently demonstrate that mefloquine is more effective than chloroquine and proguanil and its long-term use and that it is well tolerated (5;18–20). Better knowledge about malaria seems to benefit compliance: a preventive malaria program for nonimmune expatriates working in malaria-endemic areas resulted in significant increase in knowledge about malaria and improved practices including greater adherence to chemoprophylaxis (19). Another program that included instruction on Canadian guidelines, PPM and self-treatment with self-administered positive rapid diagnostic tests was instituted for a cohort of expatriates in Ghana, among whom the incidence of malaria ranged from 1/50 to 1/25 per month between 1993 and 1999 (2%–4%). Subsequent surveillance data indicated that the monthly incidence of malaria decreased from 4/1,000 in 2000 to 1.7/1,000 in 2002 (0.4%–0.17%) (unpublished data, K. Gamble).

INSECTICIDE-TREATED BED NETS

CATMAT recommends that all travellers to malaria-endemic regions use insecticide-treated bed nets as part of their PPM (see Chapter 3)**.** For the majority of travellers, conventional **insecticide-treated bed nets** provide sufficiently long-lasting protection. However, long-term travellers face additional challenges: the insecticide that is in most nets starts to lose its effect after 6 months. Thus, where travel to a malaria-endemic area is frequent and/or is expected to be for 6 months or longer, conventionally treated bed nets are inadequate and long-lasting insecticide-treated nets would be preferable (21). **Currently there are no Canadian** long-lasting **insecticide-treated nets registrations**, nor is there a specific policy that permits their sale in Canada for use abroad; in addition, liquid permethrin (an insecticide used to treat bed nets) is not available in Canada. Nevertheless, insecticide-treated bed nets can be obtained from some Canadian travel health clinics and other domestic and international suppliers (21).

Long-term travellers also need to know about seasonal changes in weather that affect malaria risk and loss of effect of the insecticide-impregnating bed nets. This means that the start of rainy seasons requires the renewal of this insecticide in bed nets.

RAPID DIAGNOSTIC TESTS

Without adequate training of laboratory staff, the usefulness of rapid diagnostic tests (RDTs) may be no better than that shown in the general travel population (22;23) (see Chapter 6 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, however; there are few data from controlled studies on the use of RDTs in the long-term traveller or expatriate populations. An evaluation of a preventive malaria program for expatriates in malaria-endemic areas, which included RDTs and standby treatment, found that 15% of participants had difficulty performing the RDTs and 22% used standby treatment despite having a negative RDT (24).

COUNTERFEIT DRUGS

The production, distribution and sale of counterfeit antimalarial, antiretroviral and other medications are widespread throughout many parts of Asia and Africa (25–27). One-third to one-half of artesunate tablets in southeast Asia have been found to have no active ingredient (25). Many expatriates buy their antimalarial drugs over the counter, and they do not have the ability to evaluate the authenticity of these drugs. Unfortunately, simply encouraging expatriates and long-term travellers to purchase brand names may be insufficient (25–27).

The counterfeit drug problem is especially important for long-term travellers because they are dependent on local pharmacies for renewal of their antimalarial chemoprophylaxis prescriptions and often for standby malaria self-treatment drugs (25–27). Warn all travellers, and especially long-term travellers, expatriates and missionaries, about counterfeit drugs and encourage them to buy a supply of medication in countries where strict quality control measures are in place. If Coartem® (artemether-lumefantrine), which is not yet licensed for distribution in Canada but is recommended by the World Health Organization as first-line treatment for *P. falciparum* malaria in Africa, is recommended, travellers should buy it in countries where counterfeiting is unlikely (e.g. in Europe or the USA) (28). Although long-term atovaquone-proguanil prophylaxis may be too expensive for most long-term travellers and expatriates, long-term travellers may choose to purchase enough for one or two self-treatment courses to keep in their medical kit (29).

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—Chemoprophylaxis Regimens").

TABLE 5.3.1: Evidence-based medicine recommendations

RECOMMENDATION	EBM RATING
Guidelines for the prevention of malaria in long-term travellers or expatriates should not deviate considerably from recommendations for short-term travellers (30).	B III
Training in the use of RDTs is reasonable for long-term travellers (23;30).	C III
Education about counterfeit antimalarial medications is important for long-term travellers who are more likely to buy drugs in countries without quality controls (25–27).	C II
Consider primaquine for terminal prophylaxis (see Chapter 8) for military personnel, long-term travellers or expatriates returned from regions with *P. vivax* transmission (17;28;30).	A I

ABBREVIATION: EBM, evidence-based medicine; RDT, rapid diagnostic test.

NOTE: For a description of the categories and quality of evidence of the recommendations, see Appendix IV.

REFERENCE LIST

(1) Frame JD, Lange WR, Frankenfield DL. Mortality trends of American missionaries in Africa, 1945–1985. Am J Trop Med Hyg 1992 Jun;46(6):686–90.

(2) Toovey S, Moerman F, van GA. Special infectious disease risks of expatriates and long-term travelers in tropical countries. Part I: malaria. J Travel Med 2007 Jan;14(1):42–9.

(3) Schneider G. Malaria prevention for long-term workers overseas, choice or necessary evil? Dissertation University of London, London School of Hygiene and Tropical Medicine; 1998.

(4) Adera T, Wolfe MS, Guire-Rugh K, Calhoun N, Marum L. Risk factors for malaria among expatriates living in Kampala, Uganda: the need for adherence to chemoprophylactic regimens. Am J Trop Med Hyg 1995 Mar;52(3):207–12.

(5) Lobel HO, Varma JK, Miani M, Green M, Todd GD, Grady K, et al. Monitoring for mefloquine-resistant Plasmodium falciparum in Africa: implications for travelers' health. Am J Trop Med Hyg 1998 Jul;59(1):129–32.

(6) Onwujekwe O, Kaur H, Dike N, Shu E, Uzochukwu B, Hanson K, et al. Quality of anti-malarial drugs provided by public and private healthcare providers in south-east Nigeria. Malar J 2009;8:22.

(7) Korhonen C, Peterson K, Bruder C, Jung P. Self-reported adverse events associated with antimalarial chemoprophylaxis in peace corps volunteers. Am J Prev Med 2007 Sep;33(3):194–9.

(8) Schlagenhauf P, Tschopp A, Johnson R, Nothdurft HD, Beck B, Schwartz E, et al. Tolerability of malaria chemoprophylaxis in non-immune travellers to sub-Saharan Africa: multicentre, randomised, double blind, four arm study. BMJ 2003 Nov 8;327(7423):1078.

(9) Knobloch J. Long-term malaria prophylaxis for travelers. J Travel Med 2004 Nov;11(6):374–8.

(10) Schlagenhauf P, Petersen E. Malaria chemoprophylaxis: strategies for risk groups. Clin Microbiol Rev 2008 Jul;21(3):466–72.

(11) Berg J, Visser LG. Expatriate chemoprophylaxis use and compliance: past, present and future from an occupational health perspective. J Travel Med 2007 Sep;14(5):357–8.

(12) Hamer DH, Ruffing R, Callahan MV, Lyons SH, Abdullah AS. Knowledge and use of measures to reduce health risks by corporate expatriate employees in western Ghana. J Travel Med 2008 Jul;15(4):237–42.

(13) Dahlgren AL, Deroo L, Avril J, Bise G, Loutan L. Health risks and risk-taking behaviors among International Committee of the Red Cross (ICRC) expatriates returning from humanitarian missions. J Travel Med 2009 Nov;16(6):382–90.

(14) Neuberger A, Klement E, Reyes CM, Stamler A. A cohort study of risk factors for malaria among healthcare workers in equatorial Guinea: stay away from the ground floor. J Travel Med 2010 Sep;17(5):339–45.

(15) Machault V, Orlandi-Pradines E, Michel R, Pages F, Texier G, Pradines B, et al. Remote sensing and malaria risk for military personnel in Africa. J Travel Med 2008 Jul;15(4):216–20.

(16) Mayet A, Lacassagne D, Juzan N, Chaudier B, Haus-Cheymol R, Berger F, et al. Malaria outbreak among French army troops returning from the Ivory Coast. J Travel Med 2010 Sep;17(5):353–5.

(17) Kotwal RS, Wenzel RB, Sterling RA, Porter WD, Jordan NN, Petruccelli BP. An outbreak of malaria in US Army Rangers returning from Afghanistan. JAMA 2005 Jan 12;293(2):212–6.

(18) Lobel HO, Bernard KW, Williams SL, Hightower AW, Patchen LC, Campbell CC. Effectiveness and tolerance of long-term malaria prophylaxis with mefloquine. Need for a better dosing regimen. JAMA 1991 Jan 16;265(3):361–4.

(19) Lobel HO, Miani M, Eng T, Bernard KW, Hightower AW, Campbell CC. Long-term malaria prophylaxis with weekly mefloquine. Lancet 1993 Apr 3;341(8849):848–51.

(20) Ohrt C, Richie TL, Widjaja H, Shanks GD, Fitriadi J, Fryauff DJ, et al. Mefloquine compared with doxycycline for the prophylaxis of malaria in Indonesian soldiers. A randomized, double-blind, placebo-controlled trial. Ann Intern Med 1997 Jun 15;126(12):963–72.

(21) Committee to Advise on Tropical Medicine and Travel. Statement on personal protective measures to prevent arthropod bites. Can Commun Dis Rep 2012;38 (ASC-3):1–18.

(22) Schlagenhauf P, Steffen R, Tschopp A, Van Damme P., Mittelholzer ML, Leuenberger H, et al. Behavioural aspects of travellers in their use of malaria presumptive treatment. Bull World Health Organ 1995;73(2):215–21.

(23) Funk M, Schlagenhauf P, Tschopp A, Steffen R. MalaQuick versus ParaSight F as a diagnostic aid in travellers' malaria. Trans R Soc Trop Med Hyg 1999 May;93(3):268–72.

(24) Roukens AH, Berg J, Barbey A, Visser LG. Performance of self-diagnosis and standby treatment of malaria in international oilfield service employees in the field. Malar J 2008;7:128.

(25) Dondorp AM, Newton PN, Mayxay M, Van DW, Smithuis FM, Yeung S, et al. Fake antimalarials in Southeast Asia are a major impediment to malaria control: multinational cross-sectional survey on the prevalence of fake antimalarials. Trop Med Int Health 2004 Dec;9(12):1241–6.

(26) Newton P, Proux S, Green M, Smithuis F, Rozendaal J, Prakongpan S, et al. Fake artesunate in southeast Asia. Lancet 2001 Jun 16;357(9272):1948–50.

(27) Cockburn R, Newton PN, Agyarko EK, Akunyili D, White NJ. The global threat of counterfeit drugs: why industry and governments must communicate the dangers. PLoS Med 2005 Apr;2(4):e100.

(28) World Health Organization. Guidelines for the treatment of malaria, Second edition. 2010.

(29) Bryan JP. Cost considerations of malaria chemoprophylaxis including use of primaquine for primary or terminal chemoprophylaxis. Am J Trop Med Hyg 2006 Sep;75(3):416–20.

(30) Chen LH, Wilson ME, Schlagenhauf P. Prevention of malaria in long-term travelers. JAMA 2006 Nov 8;296(18):2234–44.

5.4 PREVENTION IN SPECIAL HOSTS—TRAVELLERS WITH CO-MORBIDITIES

The prevention, diagnosis and management of malaria in travellers with underlying medical conditions present a number of challenges. Deleterious interactions between malaria and underlying conditions may result in increased susceptibility to and severity of malaria or risk of complications of the underlying condition. Drug interactions with chronic-use medications must be considered when prescribing malaria chemoprophylaxis or treatment. Some underlying health conditions may be exacerbated by or preclude the use of one or more antimalarial medications.

The potential for adverse drug interactions should always be considered when recommending malaria chemoprophylaxis. A drug interaction check should be undertaken routinely unless the travellers' medications are known to be safe with the proposed antimalarial agent.

IMMUNOCOMPROMISED HOSTS

i. HIV/AIDS: There is a significant and complex interaction between human immunodeficiency virus (HIV) and *P. falciparum*. Acute malaria stimulates HIV-1 replication, resulting in increased viral loads that may hasten disease progression (1;2) and increase transmission risk. HIV infection impairs immune responses to malaria and increases both the incidence and severity of malaria (2;3). HIV infection may increase the risk of malaria treatment failure (4) with risk increasing as CD4 counts decline (5–7). Women who are co-infected with HIV and malaria may have a higher risk of mother-to-child HIV transmission as well as an increased risk of congenital malaria (8–10).

The potential for drug interactions between antimalarial and antiretroviral agents must be considered whenever an antimalarial prophylaxis or treatment is prescribed to an HIV-infected person on antiretroviral therapy. Protease inhibitors and non-nucleoside reverse transcriptase inhibitors may interact with antimalarials, resulting in toxicity or reduced effectiveness of either drug (11). Table 1 summarizes general antiretroviral and antimalarial drug interactions. Despite the limited information available, it is recommended that specific drug interactions be reviewed whenever antimalarials are prescribed for a traveller taking antiretroviral compounds.

TABLE 5.4.1: General antiretroviral and antimalarial drug interactions (11)

	SUMMARY OF INTERACTIONS
Chloroquine	No documented significant interactions Ritonavir: potential increase in chloroquine levels
Mefloquine	Non-nucleoside reverse transcriptase inhibitors (NNRTIs): may decrease mefloquine levels Protease inhibitors (PIs): possible decrease in mefloquine or PI levels
Doxycycline	No interactions with NNRTIs or PIs ddI—avoid use with tablets / oral suspension (Videx EC® capsules: no interaction)
Atovaquone-proguanil	Azidothymidine (AZT): increased AZT levels, routine dose adjustment not required NNRTIs and PIs: avoid co-administration due to risk of sub therapeutic atovaquone levels

In addition to assessing for drug interactions, consideration must also be given to the risk of overlapping adverse effect profiles (11). Consultation with a travel or tropical medicine expert in conjunction with the traveller's HIV specialist is recommended.

ii. Asplenia: Asplenia increases the risk, magnitude and duration of parasitemia, even among partially immune individuals in malaria-endemic countries (12), and severe and fatal malaria has been reported in travellers with asplenia (13). 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 5.3) including section on stand-by emergency treatment). Fever in an asplenic individual may represent malaria or infection with an encapsulated bacterial organism, so antibacterial standby treatment should also be discussed/provided (14). Given the risk of postsplenectomy bacterial sepsis, use of doxycycline for malarial prophylaxis may be preferred over other options due to its antibacterial activity (15).

iii. Other immunosuppressive conditions: There is limited information about the natural history of malaria in individuals with other immunocompromising conditions and treatments, such as biologic agents. The severity and mortality of malaria may be increased and therefore immune compromised travellers should receive extra attention directed at securing optimal adherence to both personal protective measures against arthropod exposure and malaria chemoprophylaxis. The potential for adverse drug interactions must be considered when prescribing malaria chemoprophylactic agents to travellers using immunosuppressive medications. The major interactions between antimalarials and anti-rejection drugs are listed in Table 2. Collaboration between transplant specialists and travel medicine prescribers and, in some cases, a pre-travel trial with monitoring of drug levels, may be beneficial to optimize malaria chemoprophylaxis for these patients.

TABLE 5.4.2: Potential interactions between anti-rejection drugs and antimalarials

ANTIMALARIAL	ANTIREJECTION AGENT	POTENTIAL EFFECT
Chloroquine	Tacrolimus	Prolonged QT
	Cyclosporine	Increased cyclo levels
Mefloquine	Cyclosporine	Prolonged QT
	Tacrolimus	Prolonged QT
Doxycycline	Mycophenolate	Decreased myco levels
Atovaquone	No reported interactions to date	

OTHER CONDITIONS

i. Cardiovascular: Mefloquine has not been confirmed to be linked to arrhythmias when used for prophylaxis in a small research study (16), although aberrant atrioventricular conduction was reported in a case study (17). There are reports of mefloquine, doxycycline and proguanil potentiating warfarin, resulting in abnormal coagulation and sometimes bleeding (16;18–21). If these medications are used (including proguanil as a component of Malarone®), a medication trial should be done several weeks in advance of travel and serial testing of the International Normalized Ratio should be done to allow adjustment of the anticoagulant dose both before and after travel.

ii. Neurologic disorders:

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 dosage adjustment (21) (see Chapter 8).

Myasthenia gravis: Acute infections, including malaria, may trigger exacerbations of myasthenia gravis; therefore optimal malaria prevention through adherence to chemoprophylaxis and effective use of insect personal protective measures should be reinforced. Chloroquine, mefloquine and doxycycline have all been associated with worsening of myasthenic symptoms and should be avoided although doxycycline has less frequently been associated with worsening myasthenic symptoms compared to chloroquine and mefloquine and a trial of therapy prior to travel may be considered in stable patients, particularly for those with only ophthalmologic symptoms. Although atovaquone-proguanil has not been linked with worsening of myasthenic symptoms, proguanil monotherapy has been reported to worsen symptoms (22) and a trial of therapy prior to travel would be prudent. Both proguanil and doxycycline have the benefit of a short half-life, compared to other prophylactic choices, thus potentially limiting the duration of worsened symptoms compared to long acting agents. Primaquine has not been associated with myasthenic symptoms; therefore, it may be an option for prophylaxis of *P. falciparum* infection (after ruling out G6PD deficiency) in myasthenic travellers who are unable to tolerate doxycycline and atovaquone-proguanil.

If an acute episode of malaria occurs, treatment options may be limited, and it may be difficult to determine if deterioration in myasthenic symptoms is due to the effects of acute malaria or malaria treatment. Quinine has been reported to cause a myasthenia-like syndrome (23) and deterioration in patients with myasthenia (24). Lumefantrine and the artemesinin derivatives have not been reported to trigger or worsen myasthenic symptoms but there are also no reports of use of these agents in myasthenic patients. Because of the risk of severe decompensation with respiratory compromise, travellers with active myasthenia gravis should avoid travelling to areas where tertiary care may be difficult to access in a timely manner and should ensure they carry adequate medical evacuation insurance.

iii. Psychiatric disorders: Dose related neuropsychiatric adverse effects are well recognized with mefloquine and to a lesser extent with chloroquine (25;26). Predisposing factors for possible significant adverse neuropsychiatric events include: female gender, low body mass index, prior history of adverse neuropsychiatric reactions to mefloquine, and previous significant psychiatric diagnoses (27). Although the link between mefloquine and serious mental reactions has not been clearly established, mefloquine should not be prescribed for travellers before completing a careful assessment of history of depression, generalized anxiety disorder or psychosis (28;29). There are no data demonstrating that attention deficit disorder increases the risk of neuropsychiatric side effects; however, it is prudent to ensure that psychiatric conditions such as those noted above do not co-exist (30).

iv. Hepatic or renal dysfunction: Moderate to severe hepatic or renal dysfunction may result in significant alteration in antimalarial medication levels. If the course of action is unclear after review of a standard reference, consultation with a travel/tropical medicine expert is recommended. Table 3 outlines antimalarial drug considerations for individuals with renal or hepatic disease.

TABLE 5.4.3: Antimalarial Drug considerations for individuals with renal or hepatic disease (31–35)

	RENAL	HEPATIC	RECOMMENDATIONS
Chloroquine	95% excreted in urine	Partial hepatic metabolism	Caution for use in hepatic impairment, (dose adjustment may be required) and in presence of concurrent use of hepatotoxic agents. Caution for use in renal impairment—dosage adjustment may be required.
Mefloquine	9% excreted unchanged in urine	Metabolized in liver (CYP 3A4) and excreted predominantly in bile and feces	Caution for use in hepatic impairment. No dose adjustments required for renal failure or dialysis.
Doxycycline	30–50% excreted unchanged, does not accumulate in renal insufficiency	Partial hepatic metabolism—prolonged half- life may occur with significant hepatic impairment.	No dose adjustment in renal failure or dialysis. Dose adjustment may be required for hepatic disease. Avoid in severe liver dysfunction.
Proguanil	< 40% excreted unchanged in urine	Partial hepatic metabolism of proguanil (CYP 2C19). Metabolites excreted in urine	No dose change for mild to moderate renal impairment. Contraindicated if creatinine clearance is < 30 mls. / min due to potential drug accumulation. No change for mild to moderate hepatic impairment. Not studied in patients with severe hepatic impairment—use with caution.
Atovaquone	Minimal	> 90% Excreted unchanged in feces	

v. Miscellaneous conditions:

Psoriasis: Antimalarials, particularly chloroquine and hydroxychloroquine, have been reported to trigger acute flares of psoriasis; however there is no consensus on whether this constitutes a contraindication for the use of these agents (36;37). When making recommendations for malaria chemoprophylaxis in the presence of psoriasis, chloroquine should generally be avoided and alternative agents recommended. There is insufficient evidence to consider psoriasis an absolute contraindication to the use of chloroquine, however, if chloroquine is chosen, travellers with psoriasis should be made aware of the potential risk of exacerbation. The risk of exacerbation of psoriasis with use of mefloquine, atovaquone/ proguanil and doxycycline is not substantiated based on current literature.

Glucose-6-phosphate dehydrogenase deficiency (G6PD): While G6PD deficiency may impart a degree of resistance to malaria infection, this is not absolute and effective malaria prevention is important. Use of primaquine is contraindicated in the presence of G6PD deficiency due to high risk of hemolysis, which can be life threatening. Chloroquine is considered contraindicated by the manufacturer in the presence of G6PD deficiency, although significant hemolysis is unlikely at prophylactic doses. Hemolysis is not a concern for use of other antimalarials when used in prophylactic doses.

Porphyria: With the exception of atovaquone proguanil, all of the first line malaria chemoprophylactic agents are considered possibly porphyrinogenic and are recommended for use with precaution and only if no safer alternative exists. Atovaquone proguanil is considered "probably not porphyrinogenic" and may be used without special precautions (38). Evidence for safety of doxycycline in porphyria is conflicting (38).

TABLE 5.4.4: Evidence-based medicine recommendations

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 prior to travel (39).	B III
Potential drug interactions and overlapping toxicities warrant careful review before antimalarial drugs are prescribed for individuals with chronic medical conditions, including HIV infection (12).	A I
HIV-infected individuals who are pregnant or have advanced immune suppression should be encouraged to choose non malaria endemic locations or defer travel until after pregnancy or restoration of immune function.	BIII
Standby antimalarial therapy should be provided to asplenic travellers who may experience delays in accessing appropriate care for febrile illness.	AII
A pre-travel trial with INR testing should be done if mefloquine, doxycycline or proguanil (including atovaquone-proguanil) are to be used in individuals taking warfarin (18–21).	AII
Chloroquine and mefloquine should be avoided in the presence of a chronic seizure disorder.	EII
Chloroquine and mefloquine should be avoided in travellers with myasthenia gravis.	EIII
Mental health history should be carefully reviewed prior to recommending use of mefloquine to ensure that psychotic, depressive or anxiety disorders are absent (28).	AI
Travellers with psoriasis should be aware of the potential risk of exacerbation of psoriasis with malaria chemoprophylaxis.	BIII
Mefloquine, doxycycline and atovaquone-proguanil should be preferred over chloroquine for use in patients with underlying psoriasis.	BIII
Primaquine should not be used as chemoprophylaxis in the presence of G6PD deficiency.	EII
Atovaquone-proguanil may be the preferred choice for malaria prophylaxis in the presence of porphyria.	BIII

ABBREVIATION: EBM, evidence-based medicine; PPM, personal protective measures.

NOTE: For a description of the categories and quality of evidence of the recommendations, see Appendix IV.

REFERENCE LIST

(1) Kublin JG, Patnaik P, Jere CS, Miller WC, Hoffman IF, Chimbiya N, et al. Effect of Plasmodium falciparum malaria on concentration of HIV-1-RNA in the blood of adults in rural Malawi: a prospective cohort study. Lancet 2005 Jan 15;365(9455):233–40.

(2) Abu-Raddad LJ, Patnaik P, Kublin JG. Dual infection with HIV and Malaria fuels the spread of both diseases in sub-saharan Africa. Science 2006 Dec 8;314(5805):1603–6.

(3) Patnaik P, Jere CS, Miller WC, Hoffman IF, Wirima J, Pendame R, et al. Effects of HIV-1 serostatus, HIV-1 RNA concentration, and CD4 cell count on the incidence of malaria infection in a cohort of adults in rural Malawi. The Journal of infectious diseases 2005;192(6):984–91.

(4) Kamya MR, Gasasira AF, Yeka A, Bakyaita N, Nsobya SL, Francis D, et al. Effect of HIV-1 infection on antimalarial treatment outcomes in Uganda: a population-based study. J Infect Dis 2006 Jan 1;193(1):9–15.

(5) Shah SN, Smith EE, Obonyo CO, Kain KC, Bloland PB, Slutsker L, et al. HIV immunosuppression and antimalarial efficacy: sulfadoxine-pyrimethamine for the treatment of uncomplicated malaria in HIV-infected adults in Siaya, Kenya. J Infect Dis 2006 Dec 1;194(11):1519–28.

(6) Birku Y, Mekonnen E, Bjorkman A, Wolday D. Delayed clearance of Plasmodium falciparum in patients with human immunodeficiency virus co-infection treated with artemisinin. Ethiop Med J 2002 Apr;40 Suppl 1:17–26.

(7) Van Geertruyden JP, Mulenga M, Mwananyanda L, Chalwe V, Moerman F, Chilengi R, et al. HIV-1 immune suppression and antimalarial treatment outcome in Zambian adults with uncomplicated malaria. J Infect Dis 2006 Oct 1;194(7):917–25.

(8) Brahmbhatt H, Kigozi G, Wabwire-Mangen F, Serwadda D, Sewankambo N, Lutalo T, et al. The effects of placental malaria on mother-to-child HIV transmission in Rakai, Uganda. AIDS 2003 Nov 21;17(17):2539–41.

(9) Ladner J, Leroy V, Simonon A, Karita E, Bogaerts J, De Clercq A, et al. HIV infection, malaria, and pregnancy: a prospective cohort study in Kigali, Rwanda. The American journal of tropical medicine and hygiene 2002;66(1):56–60.

(10) Perrault SD, Hajek J, Zhong K, Owino SO, Sichangi M, Smith G, et al. Human immunodeficiency virus co-infection increases placental parasite density and transplacental malaria transmission in Western Kenya. Am J Trop Med Hyg 2009 Jan;80(1):119–25.

(11) Khoo S, Back D, Winstanley P. The potential for interactions between antimalarial and antiretroviral drugs. AIDS 2005 Jul 1;19(10):995–1005.

(12) Bach O, Baier M, Pullwitt A, Fosiko N, Chagaluka G, Kalima M, et al. Falciparum malaria after splenectomy: a prospective controlled study of 33 previously splenectomized Malawian adults. Trans R Soc Trop Med Hyg 2005 Nov;99(11):861–7.

(13) Demar M, Legrand E, Hommel D, Esterre P, Carme B. Plasmodium falciparum malaria in splenectomized patients: two case reports in French Guiana and a literature review. Am J Trop Med Hyg 2004 Sep;71(3):290–3.

(14) Baker H. The influence of chloroquine and related drugs on psoriasis and keratoderma blenorrhagicum. Br J Dermatol 1966;78:161–6.

(15) Davidson RN, Wall RA. Prevention and management of infections in patients without a spleen. Clin Microbiol Infect 2001 Dec;7(12):657–60.

(16) Touze JE, Heno P, Fourcade L, Deharo JC, Thomas G, Gohan S, et al. The effects of antimalarial drugs on ventricular repolarizaiton. Am J Trop Med Hyg 2002;67(1):54–60.

(17) Richter J, Burbach G, Hellgren U, Dengler A, Bienzle U. Aberrant atrioventricular conduction triggered by antimalarial prophylaxis with mefloquine. Lancet 1997 Jan 11;349(9045):101–2.

(18) Westfall LK, Mintzer DL, Wiser TH. Potentiation of warfarin by tetracycline. Am J Hosp Pharm 1980 Dec;37(12):1620, 1625.

(19) Armstrong G, Bed MF, Scahill S. Warfarin potentiated by proguanil. BMJ 1991;303:789.

(20) Loefler I. Mefloquine and anticoagulant interaction. J Travel Med 2003 May;10(3):194–5.

(21) Doxycycline: Cautions (Drug Interactions). 2007. Report No.: 10–4–0007.

(22) Fischer PR, Walker E. Myasthenia and malaria medicines. J Travel Med 2002 Sep;9(5):267–8.

(23) Karbwang J, Tin T, Rimchala W, Sukontason K, Namsiripongpun V, Thanavibul A, et al. Comparison of artemether and quinine in the treatment of severe falciparum malaria in south-east Thailand. Trans R Soc Trop Med Hyg 1995 Nov;89(6):668–71.

(24) Bateman DN, Dyson EH. Quinine toxicity. Adverse Drug React Acute Poisoning Rev 1986;5(4):215–33.

(25) Barrett PJ, Emmins PD, Clarke PD, Bradley DJ. Comparison of adverse events associated with use of mefloquine and combination of chloroquine and proguanil as antimalarial prophylaxis: postal and telephone survey of travellers. BMJ 1996 Aug 31;313(7056):525–8.

(26) Akhtar S, Mukherjee S. Chloroquine induced mania. Int J Psychiatry Med 1993;23(4):349–56.

(27) van Riemsdijk MM, Sturkenboom MC, Ditters JM, Tulen JH, Ligthelm RJ, Overbosch D, et al. Low body mass index is associated with an increased risk of neuropsychiatric adverse events and concentration impairment in women on mefloquine. Br J Clin Pharmacol 2004 Apr;57(4):506–12.

(28) Schlagenhauf P. Mefloquine for malaria chemoprophylaxis 1992–1998: a review. J Travel Med 1999 Jun;6(2):122–33.

(29) Schlagenhauf P, Adamcova M, Regep L, Schaerer MT, Rhein HG. The position of mefloquine as a 21st century malaria chemoprophylaxis. Malar J 2010;9(357):1–15.

(30) Stauffer WM, Kamat D, Magill AJ. Traveling with infants and children. Part IV: insect avoidance and malaria prevention. J Travel Med 2003 Jul;10(4):225–40.

(31) Amet S, Zimner-Rapuch S, Launay-Vacher V, Janus N, Deray G. Malaria prophylaxis in patients with renal impairment: a review. Drug Saf 2013;36(2):83–91.

(32) Malarone Product Monograph. Mississauga: GlaxoSmithKline; 2012.

(33) Agwuh KN, MacGowan A. Pharmacokinetics and pharmacodynamics of the tetracyclines including glycylcyclines. J Antimicrob Chemother 2006 Aug;58(2):256–65.

(34) Plaquenil (hydroxychloroquine sulfate) Product Monograph. 20120 Oct 16.

(35) Mefloquine (mefloquine hydrchloride tablets) Product Monograph. 20100 May 27.

(36) Kuflik EG. Effect of antimalarial drugs on psoriasis. Cutis 1980 Aug;26(2):153–5.

(37) Fry L, Baker BS. Triggering psoriasis: the role of infections and medications. Clin Dermatol 2007 Nov;25(6):606–15.

(38) The Drug Database for Acute Porphyria. 2012 April 16 [cited 2012 Apr 4]; Available from: www.drugs-porphyria.org/monograph.php?id=4079

(39) Arguin PM, Mali S. Malaria. In: Brunette G.W., Kozarsky PE, Magill AJ, Shlim D.R., Whatley A.D., editors. CDC Health Information for International Travel 2012.New York: Oxford University Press; 2012. p. 223–43.

5.5 PREVENTION IN SPECIAL HOSTS—MIGRANTS AND THOSE VISITING FRIENDS AND RELATIVES (VFR)

MIGRANTS

Risk for malaria exists for migrants after their arrival in Canada from a malaria-endemic country. While some refugees may receive pre-departure pre-emptive treatment for malaria in refugee camps, such treatment is by no means universal. Most cases of malaria will develop within three months of last exposure, but residual risk may persist for one year or longer, with the longest reported relapses occurring decades later. As such, the diagnosis of malaria should be considered for migrants new to Canada for at least 12 months after their arrival.

Recent clinical guidelines published in Canada include chapters on migrant malaria (1;2). Overall, there are no data on the number of migrant malaria cases diagnosed in Canada; however, there are limited data on severe malaria cases reported to the Canadian Malaria Network. Between 2001 to 2012, just under 20% of all cases of severe malaria in Canada had reported immigration as the reason for travel, and 65.7% of these cases were under 18 years old (Personal communication, A. McCarthy and J. Geduld, Domestic Response Unit, Malaria Branch—Division of Parasitic Diseases, US Centers for Disease Control and Prevention, 2012).

VISITING FRIENDS AND RELATIVES

According to the 2007 Census, almost 20% of the Canadian population is made up of people not born in Canada (3), and large numbers are part of families who came to Canada in recent generations. The increased ease of international travel means that that more travellers can and do return to their country of origin to visit friends and relatives. Those visiting friends and relatives (VFRs) are a unique group with distinct characteristics and behaviours, and resultant risks of disease acquisition while travelling. Malaria is a specific risk for VFRs, with some studies suggesting as much as a 4.5-fold greater risk of malaria for VFRs compared with tourist travellers (4). VFRs routinely represent a significant proportion (21%–68%) of the cases of imported malaria in various countries (5). Canada does not have data on the overall numbers of VFR cases seen. However, VFRs account for approximately 25.1% of cases of severe malaria from 2001 to 2012, and 8.8% (4 of 45 cases) were among those aged less than 18 years (Personal communication, A. McCarthy and J. Geduld, 2012).

In the United States 2,483 malaria cases reported to the Centers for Disease Control and Prevention (CDC) between 2006 and 2010 were VFRs, representing 32.9% of all cases. Among these travellers, 15.8% were aged 18 years and under (Personal communication, K. Cullen and P. Arguin, 2012). In the same timeframe, 8.1% (n = 616) of all the malaria cases reported to the CDC were among immigrants or refugees, and 45.0% were among those 18 years of age or under.

Characteristics of the travel destination, the traveller, and travel health beliefs and behaviours predispose VFRs to a heightened risk of malaria acquisition (5). VFRs tend to travel to destinations different to those travelled to by tourists: they often go to rural locations with a higher transmission risk of malaria (and of other tropical diseases) than in urban centres (6). Accommodations are more likely to be with local family members than in air-conditioned and well-screened hotels (6). VFRs tend to be younger and often travel with their Canadian-born children, remaining in their countries of origin for longer than tourist travellers travel to their destinations (6). Sometimes, travel plans are made at the last minute because of urgent situations such as returning to visit a sick relative or to attend a funeral (6). They also tend to be less likely to seek out or comply with preventive travel health advice (7–9), including malaria chemoprophylaxis and personal protective measures (PPM) (5;7), possibly because of financial or time restrictions, misconceptions about immunity against

malaria and reliance on advice from family members or local providers at their destination (6;10–13). For these reasons, risk of malaria acquisition in VFRs can sometimes approach that of local residents, but the risk of severe disease is higher due to loss of partial immunity after having lived abroad (6).

TABLE 5.5.1: Evidence-based medicine recommendations

RECOMMENDATION	EBM RATING
Test for malaria in migrants with unexplained fever for at least for at least 12 months after their arrival in Canada.	C III
Consider malaria screening in asymptomatic new arrivals from highly endemic areas, with treatment of those cases who have parasitemia (apart from the presence of gametocytes only) in blood smears.	C III
Ask migrants from malaria-endemic countries about future travel plans. Doing so may provide the opportunity for anticipatory guidance about malaria (6).	C III
Inform Canadian VFRs travelling to malaria-endemic countries of the risk of malaria, including the loss of partial immunity from living abroad and the increased risk for severe disease in children and pregnant women (6).	C III
Counsel Canadian VFRs travelling to malaria-endemic countries about PPM (repellants, bed nets, behavioural choices) and chemoprophylaxis (6).	C III
Discuss the affordability of chemoprophylaxis with Canadian VFRs travelling to malaria-endemic countries, taking cost into account in the weighing of different choices (6).	C III

ABBREVIATION: EBM, evidence-based medicine; PPM, personal; protective measures; VFR, visiting friends and relatives.

NOTE: For a description of the categories and quality of evidence of the recommendations, see Appendix IV.

REFERENCE LIST

(1) Pottie K, Greenaway C, Feightner J, Welch V, Swinkels H, Rashid M, et al. Evidence-based clinical guidelines for immigrants and refugees. CMAJ 2011 Sep 6;183(12):E824–E925.

(2) McCarthy AE, Varghese S, Duggan A, Campbell G, Pottie K, Kuhn S. Appendix 9: Malaria: evidence review for newly arriving immigrants and refugees. CMAJ 2011.

(3) Statistics Canada.2007. Population by immigrant status and period of immigration, 2006 counts, for Canada and census metropolitan areas and census agglomerations - 20% sample data (table). Immigration and Citizenship Highlight Tables, 2006 Census. Ottawa.; 2012. Report No.: Statistics Canada Catalogue no. 97-557-XWE2006002.

(4) Leder K, Tong S, Weld L, Kain KC, Wilder-Smith A, von SF, et al. Illness in travelers visiting friends and relatives: a review of the GeoSentinel Surveillance Network. Clin Infect Dis 2006 Nov 1;43(9):1185–93.

(5) Pavli A, Maltezou HC. Malaria and travellers visiting friends and relatives. Travel Med Infect Dis 2010 May;8(3):161–8.

(6) Bacaner N, Stauffer B, Boulware DR, Walker PF, Keystone JS. Travel medicine considerations for North American immigrants visiting friends and relatives. JAMA 2004 Jun 16;291(23):2856–64.

(7) dos Santos CC, Anvar A, Keystone JS, Kain KC. Survey of use of malaria prevention measures by Canadians visiting India. CMAJ 1999 Jan 26;160(2):195–200.

(8) Van HK, Van DP, Castelli F, Zuckerman J, Nothdurft H, Dahlgren AL, et al. Knowledge, attitudes and practices in travel-related infectious diseases: the European airport survey. J Travel Med 2004 Jan;11(1):3–8.

(9) Hagmann S, Neugebauer R, Schwartz E, Perret C, Castelli F, Barnett ED, et al. Illness in children after international travel: analysis from the GeoSentinel Surveillance Network. Pediatrics 2010 May;125(5):e1072–e1080.

(10) Centers for Disease Control and Prevention. CDC Health Information for international travel 2012. Atlanta: US Department of Health and Human Services, Public Health Service; 2012.

(11) Angell SY, Behrens RH. Risk assessment and disease prevention in travelers visiting friends and relatives. Infect Dis Clin North Am 2005 Mar;19(1):49–65.

(12) Campbell H. Imported malaria in the UK: advice given by general practitioners to British residents travelling to malaria endemic areas. J R Coll Gen Pract 1987 Feb;37(295):70–2.

(13) McCarthy M. Should visits to relatives carry a health warning? Lancet 2001 Mar 17;357(9259):862.

CHAPTER 6: MALARIA DIAGNOSIS

Plasmodium falciparum malaria can be rapidly fatal, particularly in a nonimmune host. It is the most urgent diagnosis to confirm or exclude in the febrile traveller who has been in a malaria-endemic zone. Although other signs and symptoms may be present in people 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 (1). Clinical assessment, even by experts, cannot reliably confirm or exclude a diagnosis of malaria (2). Most cases of *P. falciparum* malaria present within 2 to 3 months of exposure, although clinical presentation may be delayed in travellers who have taken chemoprophylaxis. Other malaria species, for example, *P. ovale* and *P. vivax*, may present as late as several years after exposure.

The large majority of travel-related malaria cases diagnosed in nonendemic countries present within several months of return from an endemic area (3). However, some cases, including *P. falciparum*, will present after a longer period, that is, six months or more postexposure. For this reason, Committee to Advise on Tropical Medicine and Travel (CATMAT) recommends that travellers who become ill with an unexplained fever within a year of returning home (regardless of whether malaria prophylaxis was prescribed or taken) should seek immediate medical attention and tell the physician their travel history. Particular attention should be paid to fevers that develop in the three months following travel, the period during which more than 90% of falciparum malaria is expressed.

Health care providers should inform travellers of this as part of their pre-travel assessment, and physicians should include a travel history in the assessment of febrile patients.

MICROSCOPY

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 examination of a blood smear 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 (4), whereas diagnosis in low-income countries is often hampered by problems with the quality of microscopes or stains and with supervision and quality control in the laboratory (5). For example, among US Peace Corps volunteers whose malaria was diagnosed by blood smear in local clinics in sub-Saharan Africa, the diagnosis could be confirmed in only 25% of cases (6).

When malaria is suspected, a Canadian laboratory should be able to confirm the presence of the parasite and, in most cases, identify the species within 1 to 2 hours of receiving a blood specimen (5). In very few cases, when the level of parasitemia is low, an initial smear may be falsely negative. Thus, one or two additional smears are required every 12 to 24 hours 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 (7).

An essential element of interpreting malaria smears is the speciation of the parasite. Correct speciation may be critical to choosing the appropriate life-saving treatment and making other decisions, for example, about hospitalization. Quantitating parasitemia is also important to determine the need for parenteral treatment or, exceptionally, the need for exchange transfusion and for admission to an intensive care unit. In addition, it is important for monitoring treatment of *P. falciparum* infection.

RAPID DIAGNOSTIC TESTS

Rapid diagnostic tests (RDTs) do not require microscopy or specialized laboratory skills and can play a valuable adjunctive role in diagnosing malaria (8). A variety of RDTs are licensed by Health Canada for use in Canada and can be reviewed in the Medical Devices Active License Listing. RDTs are immunochromatographic assays that use monoclonal antibodies to capture malaria antigens in a blood 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 indicates an invalid test, but the presence of a visible control band does not assure reliability (9).

RDTs 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* (*Pf*HRP-2) or enzymes from the parasite glycolytic pathway, for example, parasite-specific lactate dehydrogenase (pLDH) or *Plasmodium* aldolase (also called panmalarial antigen). Lactate dehydrogenase-based tests may detect all species of malaria or may be specific for *P. falciparum* or *P. vivax*. Aldolase tests are panspecific and cannot differentiate between any of the types of malaria.

The World Health Organization lists 96 different tests that can be categorized into seven different types (10). 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* / non-falciparum species. To date, tests specific for *P. malariae* and *P. ovale* are not available (10;11). Recent studies have shown that *P. knowlesi* possess both *Pf*HRP-2 and pLDH, and therefore tests falsely report *P. falciparum* or *P. vivax* (12;13).

Although some RDTs were originally developed for use by travellers without access to effective malaria diagnosis, they have proved to be unreliable in this setting. Significant proportions of travellers are unable to complete the test procedure or interpret the results correctly (14;15), and the rates of false-negative results are unacceptable (16). 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) (8).

In general, RDTs are best at detecting *P. falciparum*, with sensitivities between 88% and 100% and specificities between 92% and 95% (17). A recent meta-analysis found that RDTs based on *Pf*HRP-2 had a higher sensitivity but lower specificity in assessing for *P. falciparum* in high endemic regions compared with those based on pLDH (95.0% and 95.2% vs. 93.2% and 98.5%) (10). An earlier meta-analysis of RDTs in returned travellers found that tests based on *Pf*HRP-2 were more accurate than those on pLDH (8). Sensitivity is decreased at parasite densities below 100/µL, with sensitivities of less than 70% at densities less than 50/µL (18). 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) (14).

RDTs are not recommended for assessing the response to antimalarial therapy. *Pf*HRP-2 persists for prolonged periods after the asexual stage parasites have cleared from blood, with 68% positivity at 7 days and 27% positivity at 28 days after initiation of therapy (18). Parasite aldolase-based tests also remain positive after clearance of asexual stage parasites and may remain positive even longer than *Pf*HRP-2-based tests.

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

The presence of autoantibodies, such as rheumatoid factor, heterophile antibodies and anti-mouse antibodies, has 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 people with high levels of parasitemias are likely due to prozone in which an excess of antigen masks the test antibody (8;19).

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 (17). Geographic variation between *P. falciparum* strains could also affect test sensitivity (20).

POLYMERASE CHAIN REACTION

Although not practical for immediate care because of its limited availability, PCR is emerging as the gold standard for high sensitivity and specificity in speciation (Table 6.1). It is being increasingly used for quality control. PCR techniques (e.g. real-time PCR) that provide more rapid results are likely to become more available in the near future (21–23).

TABLE 6.1: Comparison of diagnostic tests for malaria

	APPROXIMATE PARASITE DENSITY THRESHOLD, PER µL (%)	SPECIATION	ACCESSIBILITY	RESISTANCE DETECTION
Microscopy—thick films	50 (0.001)	Fair	Limited	No
Microscopy—thin films	> 100 (0.002)	Good	Limited	No
RDT	> 100 (0.002	+/- (Limited)	Good	No
PCR	5 (0.0001)	Good	Poor	Yes

ABBREVIATIONS: PCR, polymerase chain reaction; RDT, rapid diagnostic test.

TABLE 6.2: Evidence-based medicine recommendations

RECOMMENDATION	EBM RATING
Suspected malaria should be considered a medical emergency, particularly if there is evidence of organ dysfunction, as well as altered mental state (24–27).	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, at any time while travelling and during the first year after returning. Travellers should always inform their health care provider of their travel history (27).	A III
Malaria should be suspected in any febrile person with a history of travel to a malaria-endemic area and a history of or finding of fever (2).	A III
Blood should be examined immediately for malaria if it is suspected. If expertise in reading malaria smears is not available, 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 blood taking (8).	A III
If the initial smears are negative, two additional smears should be taken and examined 12 hours and 24 hours later (28).	B III
Before declaring the smears negative for malaria, someone experienced in smear analysis should examine a thin smear under oil emersion for 15–20 minutes (200–300 oil immersion fields at 100× magnification) and a thick smear for 5–10 minutes (200–300 oil immersion fields at 100× magnification) (29;30).	A III
A laboratory should interpret the blood smear as positive or negative and quantify any parasites within 1–2 hours of receiving the blood, and should provide speciation within 12 hours, if this is not possible immediately (28;29).	B III
RDTs are essential diagnostic tools in regions of Canada where malaria microscopy results are not available within 2 hours (27).	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 (31;32).	A II
RDTs should not be used to assess response to therapy (33;34).	E II
RDTs should not be routinely recommended to travellers (14;27;35).	D II

ABBREVIATION: EBM, evidence-based recommendation; PCR, polymerase chain reaction; RDT, rapid diagnostic test.

NOTE: For a description of the categories and quality of evidence of the recommendations, see Appendix IV.

REFERENCE LIST

(1) Svenson JE, MacLean JD, Gyorkos TW, Keystone J. Imported malaria. Clinical presentation and examination of symptomatic travelers. Arch Intern Med 1995 Apr 24;155(8):861–8.

(2) Svenson JE, Gyorkos TW, MacLean JD, . Diagnosis of malaria in the febrile traveler. Am J Trop Med Hyg 1995;53(5):518–21.

(3) Mali S, Kachur SP, Arguin PM. Malaria surveillance—United States, 2010. MMWR Surveill Summ 2012 Mar 2;61(2):1–17.

(4) Kain KC, Harrington MA, Tennyson S, Keystone JS. Imported malaria: prospective analysis of problems in diagnosis and management. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 1998;27(1):142–9.

(5) Reyburn H, Mbatia R, Drakeley C, Carneiro I, Mwakasungula E, Mwerinde O, et al. Overdiagnosis of malaria in patients with severe febrile illness in Tanzania: a prospective study. BMJ 2004 Nov 20;329(7476):1212.

(6) Lobel HO, Varma JK, Miani M, Green M, Todd GD, Grady K, et al. Monitoring for mefloquine-resistant Plasmodium falciparum in Africa: implications for travelers' health. Am J Trop Med Hyg 1998 Jul;59(1):129–32.

(7) Strickland GT. Hunter's tropical mediine and emerging infectious diseases. 8 ed. philadelphia: W.B. Saunders Company; 2000.

(8) Marx A, Pewsner D, Egger M, Nuesch R, Bucher HC, Genton B, et al. Meta-analysis: accuracy of rapid tests for malaria in travelers returning from endemic areas. Ann Intern Med 2005 May 17;142(10):836–46.

(9) Bell D, Wongsrichanalai C, Barnwell JW. Ensuring quality and access for malaria diagnosis: how can it be achieved? Nat Rev Microbiol 2006 Sep;4(9 Suppl):S7–20.

(10) Abba K, Deeks JJ, Olliaro P, Naing CM, Jackson SM, Takwoingi Y, et al. Rapid diagnostic tests for diagnosing uncomplicated *P. falciparum* malaria in endemic countries. Cochrane database of systematic reviews (Online) 2011;(7):CD008122.

(11) Farcas GA, Zhong KJ, Lovegrove FE, Graham CM, Kain KC. Evaluation of the binax NOW ICT test versus polymerase chain reaction and microscopy for the detection of malaria in returning travelers. Am J Trop Med Hyg 2003;69(6):589–92.

(12) McCutchan TF, Piper RC, Makler MT. Use of malaria rapid diagnostic test to identify Plasmodium knowlesi infection. Emerging Infectious Diseases 2008;14(11):1750–2.

(13) Kawai S, Hirai M, Haruki K, Tanabe K, Chigusa Y. Cross-reactivity in rapid diagnostic tests between human malaria and zoonotic simian malaria parasite Plasmodium knowlesi infections. Parasitol Int 2009;58(3):300–2.

(14) Jelinek T, Amsler L, Grobusch MP, Nothdurft HD. Self-use of rapid tests for malaria diagnosis by tourists. Lancet 1999 Nov 6;354(9190):1609.

(15) Whitty CJM, Armstrong M, Behrens RH. Self-testing for falciparum malaria with antigen-capture cards by travelers with symptoms of malaria. Am J Trop Med Hyg 2000 Nov;63(5–6):295–7.

(16) Trachsler M, Schlagenhauf P, Steffen R. Feasibility of a rapid dipstick antigen-capture assay for self-testing of travellers' malaria. Trop Med Int Health 1999 Jun;4(6):442–7.

(17) Chilton D, Malik AN, Armstrong M, Kettelhut M, Parker-Williams J, Chiodini PL. Use of rapid diagnostic tests for diagnosis of malaria in the UK. J Clin Pathol 2006 Aug;59(8):862–6.

(18) Iqbal J, Siddique A, Jameel M, Hira PR. Persistent histidine-rich protein 2, parasite lactate dehydrogenase, and panmalarial antigen reactivity after clearance of Plasmodium falciparum monoinfection. J Clin Microbiol 2004 Sep;42(9):4237–41.

(19) Jelinek T, Grobusch MP, Schwenke S, Steidl S, von SF, Nothdurft HD, et al. Sensitivity and specificity of dipstick tests for rapid diagnosis of malaria in nonimmune travelers. J Clin Microbiol 1999 Mar;37(3):721–3.

(20) Lee N, Baker J, Andrews KT, Gatton ML, Bell D, Cheng Q, et al. Effect of sequence variation in Plasmodium falciparum histidine-rich protein 2 on binding of specific monoclonal antibodies: Implications for rapid diagnostic tests for malaria. J Clin Microbiol 2006 Aug;44(8):2773–8.

(21) Farcas GA, Soeller R, Zhong K, Zahirieh A, Kain KC. Real-time polymerase chain reaction assay for the rapid detection and characterization of chloroquine-resistant Plasmodium falciparum malaria in returned travelers. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2006;42(5):622–7.

(22) Hawkes M, Kain KC. Advances in malaria diagnosis. Expert Rev Anti Infect Ther 2007 Jun;5(3):485–95.

(23) Farcas GA, Zhong KJY, Mazzulli T, Kain KC. Evaluation of the RealArt Malaria LC real-time PCR assay for malaria diagnosis. Journal of clinical microbiology 2004;42(2):636–8.

(24) Legros F, Bouchaud O, Ancelle T, Arnaud A, Cojean S, Le Gras J, et al. Risk factors for imported fatal Plasmodium falciparum malaria, France, 1996–2003. Emerg Infect Dis 2007 Jun;13(6):883–8.

(25) Bruneel R, Hocqueloux L, Alberti C, Wolff M, Chevret S, Bedos JP, et al. The clinical spectrum of severe imported falciparum malaria in the intensive care unit: report of 188 cases in adults. Am J Respir Crit Care Med 2003 Mar 1;167(5):684–9.

(26) Marsh K, Forster D, Waruiru C, Mwangi I, Winstanley M, Marsh V, et al. Indicators of life-threatening malaria in African children. N Engl J Med 1995 May 25;332(21):1399–404.

(27) Kain KC, Harrington MA, Tennyson S, Keystone JS. Imported malaria: prospective analysis of problems in diagnosis and management. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 1998;27(1):142–9.

(28) Lalloo DG, Shingadia D, Pasvol G, Chiodini PL, Whitty CJ, Beeching NJ, et al. UK malaria treatment guidelines. J Infect 2007 Feb;54(2):111–21.

(29) Yu B. Examination of blood smears for malaria parasites. Laboratories Branch, Ontario Ministry of Health and Long-term Care; 2005.

(30) Garcia LS, Johnston SP, Linscott AJ, Shimizu RY. Laboratory procedures for diagnosis of blood-borne parasitic diseases. Washington: American Society of Microbiology Press; 2008.

(31) Craig MH, Bredenkamp BL, Williams CH, Rossouw EJ, Kelly VJ, Kleinschmidt I, et al. Field and laboratory comparative evaluation of ten rapid malaria diagnostic tests. Trans R SocTrop Med Hyg 2002 May;96(3):258–65.

(32) Bigaillon C, Fontan E, Cavallo JD, Hernandez E, Spiegel A. Ineffectiveness of the Binax NOW malaria test for diagnosis of plasmodium ovale malaria. J Clin Microbiol 2005 Feb;43(2):1011.

(33) Mueller I, Betuela I, Ginny M, Reeder JC, Genton B. The sensitivity of the OptiMAL rapid diagnostic test to the presence of Plasmodium falciparum gametocytes compromises its ability to monitor treatment outcomes in an area of Papua New Guinea in which malaria is endemic. J Clin Microbiol 2007 Feb;45(2):627–30.

(34) Swarthout TD, Counihan H, Senga RK, van den Broek I. Paracheck-Pf accuracy and recently treated Plasmodium falciparum infections: is there a risk of over-diagnosis? Malar J 2007;6:58.

(35) Funk M, Schlagenhauf P, Tschopp A, Steffen R. MalaQuick versus ParaSight F as a diagnostic aid in travellers' malaria. Trans R Soc Trop Med Hyg 1999 May;93(3):268–72.

CHAPTER 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: treatment will, in cases of *Plasmodium falciparum*, help prevent progression to severe disease. When choosing treatment regimens, it is important to consider drug tolerability, adverse effects of drugs and the speed of the therapeutic response.

Severe or complicated malaria refers to symptomatic malaria with hyperparasitemia (≥ 2%) or evidence of end organ damage or complications, as listed in Table 7.1; as well as those without severe falciparum malaria who cannot tolerate oral medication, since they are at risk of progressing to severe disease. The primary objective of treatment is to prevent death. For cerebral malaria, prevention of neurological deficits is also an important objective. When treating severe malaria in pregnancy, saving the life of the mother is the primary objective. Preventing recrudescence and avoiding minor adverse effects are secondary objectives.

In a case of *P. falciparum* asexual parasitemia and no other obvious cause of symptoms, the presence of one or more of the clinical or laboratory features in Table 7.1 classifies the person as having severe malaria.

TABLE 7.1: Criteria for severe falciparum malaria

CLINICAL MANIFESTATION	LABORATORY TEST
Prostration / impaired consciousness	Severe anemia (hematocrit < 15%; Hb ≤ 50 g/L)
Respiratory distress	Hypoglycemia (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) (1)
Pulmonary edema (radiological)	Hyperlactatemia
Abnormal bleeding	Hyperparasitemia (≥ 2%)
Jaundice	—
Hemoglobinuria	—

Adapted from: *Guidelines for the Treatment of Malaria*, World Health Organization, 2010 (2).

In Canada, everyone (and especially children) with *P. falciparum* malaria should be considered for admission to hospital or should receive initial treatment in an observation unit. This is to ensure that treatment can be tolerated and to confirm decreasing parasitemia with treatment. Severe or complicated disease (Table 7.1) or the inability to tolerate oral therapy requires parenteral therapy and close clinical monitoring, preferably in an intensive care unit (ICU).

The Canadian Malaria Network (CMN) can assist in the management of malaria cases in the appropriate area (see Appendix V).

GENERAL PRINCIPLES OF MANAGEMENT

The initial management of the patient depends on many factors, including the species and the severity of infection, the age of the patient, 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, three questions need to be answered:

1) Is this infection caused by *P. falciparum*?
   Treatment varies according to the species of malaria (see below). *P. falciparum* can cause life-threatening disease in a nonimmune host. Falciparum malaria is a medical emergency.
2) Is this a severe or complicated infection? (See Table 7.1)
   Severe or complicated malaria, regardless of causative species, requires parenteral therapy and sometimes an exchange transfusion. Parenteral artesunate and/or quinine are available through the CMN (see Appendix V).
3) Was the infection acquired in an area of known drug-resistant malaria? (See Appendix I)
   Adjust treatment accordingly. Malarial parasites in most of the world are drug resistant. When in doubt, treat all *P. falciparum* malaria as drug resistant.

MANAGEMENT OF FALCIPARUM MALARIA

The following guidelines were derived, in part, from the World Health Organization (WHO) *Guidelines for the Treatment of Malaria* (1;2) and *Management of Severe Malaria* (3). Please refer to these documents for a more detailed discussion.

Consider admitting nonimmune patients and all children with *P. falciparum* malaria, severe or uncomplicated, to hospital to ensure that antimalarial drugs are tolerated and to detect complications or early treatment failure. If hospital admission is decided against, all patients must be observed in the emergency department during their first dose of therapy to ensure that the drug is tolerated. To prevent adverse outcomes, provide further doses of treatment before discharge or direct the person to a pharmacy that can fill the prescription appropriately.

An algorithm for the management of malaria (see Figure 1) is based on two essential requirements: a parasitology laboratory result within two hours, and the availability of an appropriate antimalarial drug within one to two hours. (See below for malaria management when these prerequisites are not available.) Treatment of malaria does not stop with the selection of appropriate antimalarial medications. Clinically assess all patients daily until fever ends and at any time that symptoms recur; for *P. falciparum* cases, repeat malaria smears daily until these are negative.

SEVERE MALARIA

Severe malaria is usually due to *P. falciparum* infection. However, *P. vivax* can very occasionally lead to severe disease, including severe anemia, severe thrombocytopenia, pancytopenia, jaundice, splenic rupture, acute renal failure and acute respiratory distress syndrome (3–7). In addition, *P. knowlesi*, a simian malaria parasite, has emerged in southeast Asian countries including Brunei, Burma (Myanmar), Indonesia, Malaysia, the Philippines, Singapore, Thailand and Vietnam. *P. knowlesi* can also cause a severe and fatal infection (8;9). Prompt and effective treatment and case management of knowlesi malaria should be the same as for severe falciparum malaria.

Severe *P. falciparum* infections may have a mortality rate of 20% or higher. Immediately hospitalize cases of *P. falciparum* infection and provide urgent, intensive medical management, ideally in an ICU (10). Conduct clinical observations as frequently as possible; include vital sign monitoring, with accurate assessment of respiratory rate and pattern, coma score and urine output. Monitor blood glucose using rapid stick tests every four hours or more frequently, especially in unconscious patients. Treat seizures promptly with benzodiazepines; however, there is no role for prophylactic antiseizure medication (2). Individuals with severe falciparum malaria are at risk of all the adverse outcomes listed in Table 7.1, as well as 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 the artemisinin derivatives (artesunate, artemether and artemotil). A 2005 report of an open-labeled, randomized controlled trial in 1,461 patients with severe falciparum malaria in Asia demonstrated a 35% reduction in mortality in patients receiving artesunate (15%) versus 22% in those receiving quinine (11). The authors of the report, along with WHO, advocate that artesunate become the treatment of choice for severe falciparum malaria in adults (2;11).

All patients with severe *P. falciparum* infections and all those who are unable to tolerate drugs orally should receive parenteral therapy. For patients meeting criteria for severe malaria, artesunate is the treatment of choice.

If the only indication for parenteral therapy is vomiting or inability to tolerate oral therapy, without any criteria for severe malaria, request parenteral quinine, since supplies of artesunate are limited. However, parenteral artesunate can also be used for those without severe malaria who cannot tolerate intravenous quinine.

Intravenous artesunate and/or quinine are available 24 hours per day through the CMN (see Appendix V).

Many ancillary treatments have been suggested for the management of severe malaria, but few have been shown to improve outcome (2). Individualize fluid resuscitation based on 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. Check for hypoglycemia (potentially exacerbated by quinine therapy, which stimulates insulin release) in any patient who deteriorates suddenly, and treat this immediately. Avoid using steroids to treat severe or cerebral malaria since these have been associated with worse outcomes (2;12). Correct bleeding and coagulopathy in severe malaria using blood products and injection of vitamin K (2). Evidence of shock should prompt exclusion of bacteremia through blood cultures and empiric use of broad-spectrum antibiotics (2).

In cases of severe or complicated *P. falciparum* infection with high parasitemia ($\geq$ 10%), consider exchange transfusion as a potentially life-saving procedure. The rationale for exchange blood transfusion includes: the removal of infected red blood cells (RBCs) from the circulation, thereby reducing the parasite load; the rapid reduction of the antigen load and burden of parasite-derived toxins and metabolites; the removal of host-derived toxic mediators; and the replacement of rigid unparasitized RBCs with normal-functioning cells, 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 either the indications or the volume of blood that needs to be exchanged; however, anticipate 5 to 10 PRBC units (13;14).

Committee to Advise on Tropical Medicine and Travel (CATMAT) strongly recommends consulting with an infectious or tropical disease expert when managing a patient with severe falciparum malaria. See Appendix V for CMN contact information.

BOX 7.1: Chemotherapy of severe or complicated *P falciparum* malaria

Parenteral artesunate therapy and/or quinine are available 24 hours per day through the CMN. For contact information, see Appendix V.

NOTE: If the only indication for parenteral therapy is vomiting or the inability to tolerate oral therapy, without any criteria for severe malaria, request parenteral quinine. For patients meeting criteria for severe malaria, artesunate is preferred.

NOTE: All patients on parenteral therapy should switch to oral therapy as soon as possible. Patients who meet criteria for severe malaria should have at least 24 hours of parenteral therapy before switching to oral therapy.

PARENTERAL ARTESUNATE

Give artesunate over 1–2 minutes as a 2.4 mg/kg intravenous bolus at 0, 12, 24 and 48 hours. Continue therapy 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 artesunate)

Atovaquone-proguanil (do not use as follow-on oral therapy if used as malaria chemoprophylaxis):

Adults: 4 tablets (1000 mg atovaquone and 400 mg proguanil) daily for 3 days;

Pediatric: 20 mg/kg atovaquone and 8 mg/kg proguanil once daily for 3 days

OR

Doxycycline (do not use as follow-on oral therapy if used as malaria chemoprophylaxis; contraindications: pregnancy, breastfeeding, age < 8 years):

Adults: 100 mg orally twice daily for 7 days;

Pediatric: 2 mg/kg (to a maximum of 100 mg) twice daily

OR

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

PARENTERAL QUININE

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). Repeat once every 8 hours until the patient can swallow, and then administer quinine tablets to complete 7 days of treatment or change to full dose of oral atovaquone proguanil (see below).

NOTE: Do not use loading dose if the patient received quinine or quinidine within preceding 24 hours or mefloquine within the preceding 2 weeks. Switch to oral therapy as soon as possible. If the patient requires > 48 hours of parenteral therapy, reduce the quinine maintenance dose by one-third to one-half.

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). Repeat once every 8 hours until the patient can swallow, and then administer quinine tablets to complete 7 days of treatment or change to full dose of oral atovaquone proguanil (see below).

NOTE: Do not use loading dose if the patient received quinine or quinidine within preceding 24 hours or mefloquine within the preceding 2 weeks. Switch to oral therapy as soon as possible. If the patient requires > 48 hours of parenteral therapy, reduce the quinine maintenance dose by one-third to one-half.

PLUS (either concurrently or immediately after quinine)

Atovaquone-proguanil (do not use as follow-on oral therapy if used as malaria chemoprophylaxis):

Adults: 4 tablets once daily for three days;

Pediatric: see, Table 8.11

OR

Doxycycline (do not use as follow-on oral therapy if used as malaria chemoprophylaxis; contraindications: pregnancy, breastfeeding, age < 8 years):

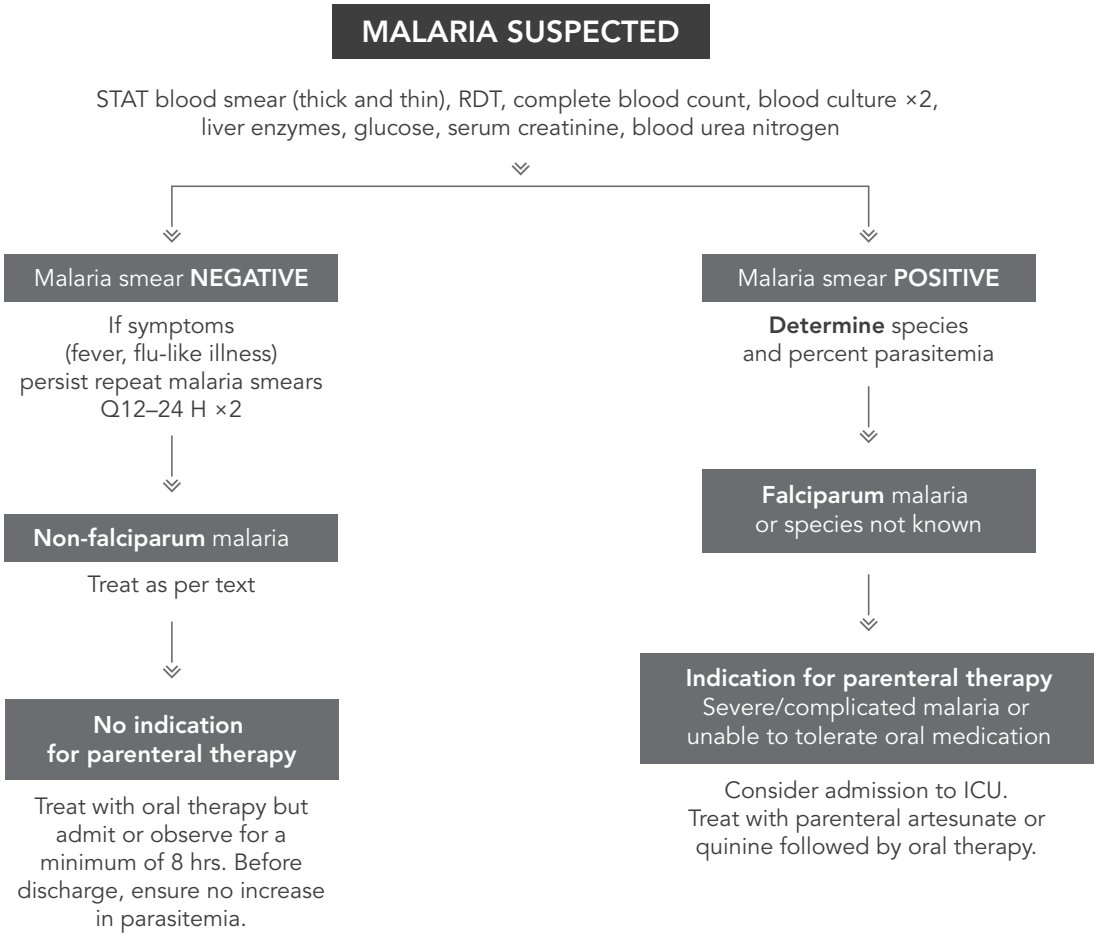
Adults: 100 mg orally twice daily for 7 days;

Pediatric: 2 mg/kg (to a maximum of 100 mg) twice daily

OR

Clindamycin (only if the patient is unable to take doxycycline or atovaquone-proguanil): 10 mg/kg (loading dose) intravenously, followed by 5 mg/kg every 8 hours for 7 days.

FIGURE 7.1: Algorithm for the management of malaria



ABBREVIATIONS: ICU—intensive care unit; RDT—rapid diagnostic test; STAT—with no delay.

UNCOMPLICATED *P. FALCIPARUM*

Uncomplicated cases of *P. falciparum* can progress to severe malaria if not properly treated and monitored. Treat infections acquired in a chloroquine-sensitive zone with chloroquine alone (see Table 8.11). WHO advocates oral combination therapy containing artemisinin derivatives as the first choice for oral therapy (2). Until these agents are available in Canada, treat infections possibly or definitely acquired in drug-resistant regions (most of the cases of *P. falciparum* malaria seen in Canada) with atovaquone-proguanil or quinine and a second drug (preferably doxycycline). If the person can tolerate quinine orally as well as doxycycline, administer quinine and doxycycline simultaneously or sequentially, starting with quinine; if doxycycline is contraindicated, administer oral quinine and clindamycin simultaneously or sequentially. If oral medication is not tolerated, administer parenteral artesunate or quinine as per Table 8.11.

MANAGEMENT OF NON-FALCIPARUM MALARIA

Chloroquine remains the treatment of choice for non-falciparum malaria (caused by *P. vivax, P. ovale, P. malariae* or *P. knowlesi*) outside of New Guinea (Papua New Guinea and Papua [Irian Jaya]) as per Table 8.11. In the case of non-falciparum malaria, conduct a clinical assessment daily until fever ends and whenever symptoms recur. Recurrence of asexual parasitemia less than 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, Burma [Myanmar] and Guyana) (15). 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, though a seven-day course of quinine is often required to cure this *P. vivax* infection (16). Mefloquine and halofantrine have been shown to be efficacious in small clinical trials, but each is limited by safety issues associated with therapeutic doses (2).

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; however, these doses have failed in cases from Guyana. Limited data also suggest that a combination of standard dose atovaquone-proguanil (4 tablets daily x 3 days) with primaquine (0.5 mg base/kg daily x 14 days) may be effective (17). Get expert advice on the management of these cases from an infectious or tropical disease specialist (see Appendix V for CMN contact information).

MANAGEMENT OF MALARIA WHEN LABORATORY RESULTS OR TREATMENT DRUGS ARE DELAYED

If fever, travel history and initial laboratory findings (low white blood count and/or platelets) suggest a diagnosis of malaria but the malaria smear is delayed for more than 2 hours, start a therapeutic antimalarial.

When a severe or complicated *P. falciparum* infection is diagnosed and parenteral quinine or artesunate is indicated but not available for more than an hour, start quinine orally (after a dose of gravol or by nasogastric tube if necessary) until the parenteral drug is available.

PRIMAQUINE TREATMENT

Primaquine 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), though it is not routinely recommended to prevent relapsing malaria in asymptomatic returning travellers (terminal prophylaxis; primaquine antirelapse therapy). For terminal prophylaxis, primaquine is administered after the traveller has left the malaria-endemic area, usually during or after the last two weeks of chemoprophylaxis (see Chapter 4 and Table 8.11 for dosage recommendations).

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 after exposure (occasionally, up to five years), even in the absence of primary symptomatic malaria infection. None of the currently recommended chemoprophylaxis regimens will prevent relapses due to these two species of *Plasmodium*. To reduce the risk of relapse following the treatment of symptomatic *P. vivax* or *P. ovale* infection, primaquine is indicated to provide "radical cure" (as per Table 8.11).

Exclude glucose-6-phosphate dehydrogenase (G6PD) deficiency before giving antirelapse therapy with primaquine. G6PD deficiency is classified based on the level of residual enzyme activity in the red blood cells (RBC): Class I is the most severe form, and Classes II to IV having diminishing degrees of deficiency. 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%), Hispanic females (1.2%) and Asian females (0.9%). The rates among Caucasians were low (0.3% of males and 0% 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 (18).

In cases with known or suspected G6PD deficiency, seek expert medical advice because primaquine may cause hemolysis in G6PD deficiency. Because the G6PD status of the fetus is unknown, primaquine is contraindicated in pregnancy. *P. vivax* or *P. ovale* infections during pregnancy should be treated with standard treatment doses of chloroquine (see Table 8.11). Relapses can also be prevented by weekly chemoprophylaxis with chloroquine until after delivery, when primaquine can be safely used by mothers with normal G6PD levels.

P. vivax isolates with a decreased responsiveness to primaquine are well documented in southeast Asia, in particular Papua New Guinea and Papua. Failure of primaquine radical treatment has been recently reported from Thailand, Somalia and elsewhere (19). As a result, 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 8.11).

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. Thus, people who have recently been in southeast Asia and have parasite levels over 1% and a parasite morphology resembling that of *P. malariae* can be diagnosed as having *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, (20;21) and potentially, parenteral therapy with artesunate.

TABLE 7.2: Evidence-based recommendations

RECOMMENDATION	EBM RATING
The treatments of choice for uncomplicated *P. falciparum* malaria include: Oral atovaquone-proguanil (2) Oral quinine combined with oral doxycycline or clindamycin Combination therapy with an artemisinin derivative (not yet available in Canada) (2)	BIII
To prevent *P. vivax* and *P. ovale* malaria relapses, primaquine phosphate (30 mg base daily for 2 weeks) should follow a chloroquine treatment of (22).	B I
Parenteral artesunate is recommended as first-line treatment for severe *P. falciparum* malaria, with parenteral quinine as an alternative (23).	A I
Exchange transfusion may have benefits for treating hyperparasitemic cases of *P. falciparum* (14).	C III
The use of steroids to treat severe or cerebral malaria has been associated with worse outcomes and should be avoided (12).	E I

NOTE: For a description of the categories and quality of evidence of the recommendations, see Appendix IV.

SELF-TREATMENT OF PRESUMPTIVE MALARIA

Self-treatment of malaria has received little study, yet it is a frequent topic of discussion with travellers. It is particularly important to know about self-treatment if going to sub-Saharan Africa where 90% of global morbidity and mortality from malaria occurs.

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 like to use self-treatment rather than long-term prophylaxis (24–27). If presumptive self-therapy is prescribed, the traveller should be told the following:

- Travellers to high-risk regions should never rely exclusively on a self-treatment regimen (25;28–30).
- Individuals at risk of malaria and unable to seek medical care within 24 hours or adequate malaria treatment drugs should carry effective medication for self-treatment of presumptive malaria (25;30).
- The signs and symptoms of malaria are nonspecific; many other diseases, including influenza, dengue, typhoid, meningitis and febrile gastroenteritis, mimic malaria.
- Neither expatriates nor physicians can definitively diagnose malaria without a laboratory test for malaria (31–33).
- Both false-negative and false-positive malaria smears are reported to varying degree by all malaria diagnostic laboratories.
- Self-treatment is not definitive; it is a temporary, life-saving measure for 24 hours while seeking medical attention.
- Presumptive treatment requires a different drug if the traveller is taking something for chemoprophylaxis, except in chloroquine-sensitive regions (see Appendix 1) (25;27;34).

TABLE 7.3: Evidence-based recommendations

RECOMMENDATION	EBM RATING
Individuals in chloroquine-sensitive regions should self-treat with chloroquine and then resume or start chloroquine prophylaxis (25;31;35).	C III
In chloroquine- and/or chloroquine and mefloquine-resistant *P. falciparum* regions, self-treatment should consist of a drug different to that used for prophylaxis, choosing from one of the following: a. atovaquone-proguanil (Malarone®) or b. oral quinine and doxycycline or c. artemether-lumefantrine (Coartem®), ideally purchased from a country with high standards of quality control (e.g. in Europe or the United States) so as to minimize the likelihood of using counterfeit products (31;35–37).	C III
A number of antimalarials are contraindicated for treatment of malaria (self-treatment or otherwise): a. mefloquine (38;39) b. pyrimethamine-sulfadoxine (Fansidar) (40) c. mefloquine-Fansidar (39) d. halofantrine (2) e. chloroquine-Fansidar (26)	E II

REFERENCE LIST

(1) Mishra SK, Das BS. Malaria and acute kidney injury. Semin Nephrol 2008 Jul;28(4):395–408.

(2) World Health Organization. Guidelines for the treatment of malaria, 2nd ed. Geneva: World Health Organzation; 2010.

(3) World Health Organization. Management of severe malaria: a practical handbook. 3nd Ed. ed. Geneva: World Health Organization; 2013.

(4) Lomar AV, Vidal JE, Lomar FP, Barbas CV, de Matos GJ, Boulos M. Acute respiratory distress syndrome due to vivax malaria: case report and literature review. Braz J Infect Dis 2005 Oct;9(5):425–30.

(5) Muhlberger N, Jelinek T, Gascon J, Probst M, Zoller T, Schunk M, et al. Epidemiology and clinical features of vivax malaria imported to Europe: sentinel surveillance data from TropNetEurop. Malar J 2004 Mar 8;3:5.

(6) Ozen M, Gungor S, Atambay M, Daldal N. Cerebral malaria owing to Plasmodium vivax: case report. Ann Trop Paediatr 2006 Jun;26(2):141–4.

(7) Tanios MA, Kogelman L, McGovern B, Hassoun PM. Acute respiratory distress syndrome complicating Plasmodium vivax malaria. Crit Care Med 2001 Mar;29(3):665–7.

(8) Cox-Singh J, Davis TM, Lee KS, Shamsul SS, Matusop A, Ratnam S, et al. Plasmodium knowlesi malaria in humans is widely distributed and potentially life threatening. Clin Infect Dis 2008 Jan 15;46(2):165–71.

(9) Kantele A, Jokiranta TS. Review of Cases With the Emerging Fifth Human Malaria Parasite, Plasmodium knowlesi. Clin Infect Dis 2011;52(11):1356–62.

(10) Trampuz A, Jereb M, Muzlovic I, Prabhu RM. Clinical review: Severe malaria. Crit Care 2003 Aug;7(4):315–23.

(11) Dondorp A, Nosten F, Stepniewska K, Day N, White N. Artesunate versus quinine for treatment of severe falciparum malaria: a randomised trial. Lancet 2005 Aug 27;366(9487):717–25.

(12) Prasad K, Garner P. Steroids for treating cerebral malaria. Cochrane Database Syst Rev 2000;(2).

(13) Nieuwenhuis JA, Meertens JH, Zijlstra JG, Ligtenberg JJ, Tulleken JE, van der Werf TS. Automated erythrocytapheresis in severe falciparum malaria: A critical appraisal. Acta Trop 2006 Jul;98(3):201–6.

(14) Riddle MS, Jackson JL, Sanders JW, Blazes DL. Exchange transfusion as an adjunct therapy in severe Plasmodium falciparum malaria: a meta-analysis. Clin Infect Dis 2002 May 1;34(9):1192–8.

(15) Baird JK. Chloroquine resistance in Plasmodium vivax. Antimicrob Agents Chemother 2004 Nov;48(11):4075–83.

(16) World Health Organization. Management of severe malaria: a practical handbook. 2nd Ed. ed. Geneva: World Health Organization; 2000.

(17) Lacy MD, Maguire JD, Barcus MJ, Ling J, Bangs MJ, Gramzinski R, et al. Atovaquone/proguanil therapy for plasmodium falciparum and plasmodium vivax malaria in Indonesians who lack clinical immunity. Clin Infect Dis 2002 Nov 1;35(9):e92–5.

(18) Chinevere TD, Murray CK, Grant E Jr, Johnson GA, Duelm F, Hospenthal DR. Prevalence of glucose-6-phosphate dehydrogenase deficiency in U.S. Army personnel. Mil Med 2006 Sep;171(9):905–7.

(19) Smoak BL, DeFraites RF, Magill AJ, Kain KC, Wellde BT. Plasmodium vivax infections in U.S. army troops: failure of primaquine to prevent relapse in studies from Somalia. Am J Trop Med Hyg 1994 Feb;56(2):231–4.

(20) White NJ. Plasmodium knowlesi: the fifth human malaria parasite. Clin Infect Dis 2008 Jan 15;46(2):172–3.

(21) Singh B, Kim Sung L, Matusop A. A large focus of naturally acquired Plasmodium knowlesi infections in human beings. Lancet 2004 Mar 27;363(9414):1017–24.

(22) Leslie T, Mayan I, Mohammed N, Erasmus P, Kolaczinski J, Whitty CJ, et al. A randomised trial of an eight-week, once weekly primaquine regimen to prevent relapse of plasmodium vivax in northwest frontier province, Pakistan. PLoS ONE 2008 Aug 6;3(8):e2861.

(23) Sinclair D, Donegan S, Lalloo DG. Artesunate versus quinine for treating severe malaria. Cochrane Database Syst Rev 2011;3:CD005967.

(24) Schlagenhauf P, Petersen E. Malaria chemoprophylaxis: strategies for risk groups. Clin Microbiol Rev 2008 Jul;21(3):466–72.

(25) Schlagenhauf P, Petersen E. Standby emergency treatment of malaria in travelers: experience to date and new developments. Expert Rev Anti Infect Ther 2012 May;10(5):537–46.

(26) Chen LH, Wilson ME, Schlagenhauf P. *Controversies and misconceptions in malaria chemoprophylaxis for travelers.* JAMA 2007 May 23;297(20):2251–63.

(27) Chen LH, Wilson ME, Schlagenhauf P. Prevention of malaria in long-term travelers. JAMA 2006 Nov 8;296(18):2234–44.

(28) Swales CA, Chiodini PL, Bannister BA. New guidelines on malaria prevention: a summary. J Infect 2007 Feb;54(2):107–10.

(29) Quach C, Kain K, MacPherson D, Mendelson J, MacLean J. Malaria deaths in Canadian travellers. Can Commun Dis Rep 1999 Mar 15;25(6):50–3.

(30) Centers for Disease Control and Prevention. CDC health information for international travel 2012. Atlanta: US Department of Health and Human Services, Public Health Service; 2012.

(31) Nothdurft HD, Jelinek T, Pechel SM, Hess F, Maiwald H, Marschang A, et al. Stand-by treatment of suspected malaria in travellers. Trop Med Parasitol 1995 Sep;46(3):161–3.

(32) Schlagenhauf P, Steffen R, Tschopp A, Van Damme P., Mittelholzer ML, Leuenberger H, et al. Behavioural aspects of travellers in their use of malaria presumptive treatment. Bull World Health Organ 1995;73(2):215–21.

(33) World Health Organization. WHO expert committee on malaria: twentieth report. Geneva, Switzerland: WHO; 2000. Report No.: 892.

(34) Centers for Disease Control and Prevention. CDC Health Information for international travel 2012. Atlanta: US Department of Health and Human Services, Public Health Service; 2012.

(35) Schlagenhauf P, Steffen R. Stand-by treatment of malaria in travellers: a review. J Trop Med Hyg 1994 Jun;97(3):151–60.

(36) Newton P, Proux S, Green M, Smithuis F, Rozendaal J, Prakongpan S, et al. Fake artesunate in southeast Asia. Lancet 2001 Jun 16;357(9272):1948–50.

(37) Cockburn R, Newton PN, Agyarko EK, Akunyili D, White NJ. The global threat of counterfeit drugs: why industry and governments must communicate the dangers. PLoS Med 2005 Apr;2(4):e100.

(38) Weinke T, Trautmann M, Held T, Weber G, Eichenlaub D, Fleischer K, et al. Neuropsychiatric side effects after the use of mefloquine. Am J Trop Med Hyg 1991 Jul;45(1):86–91.

(39) Luxemburger C, Price RN, Nosten F, Ter Kuile FO, Chongsuphajaisiddhi T, White NJ. Mefloquine in infants and young children. Ann Trop Paediatr 1996 Dec;16(4):281–6.

(40) World Health Organization and Unicef, World Malaria Report 2005, Geneva: World Health Organization, 2005.

CHAPTER 8: DRUGS FOR THE PREVENTION AND TREATMENT OF MALARIA

A health care provider should prescribe drugs for the prevention of malaria after an individual risk assessment (see Chapter 2) to ensure that only those travellers truly at risk of malaria infection receive chemoprophylaxis. Any drugs taken for malaria chemoprophylaxis should be used in conjunction with personal protective measures to prevent mosquito bites (see Chapter 3).

Like all drugs, antimalarials have the potential to cause adverse effects, though most people using chemoprophylaxis will have no or only minor adverse effects. Careful adherence to dosing guidelines, precautions and contraindications can minimize any adverse effects. To assess drug tolerance and if time permits, start the antimalarial regiment several days or weeks (depending on the antimalarial prescribed) before travel (see Chapter 4).

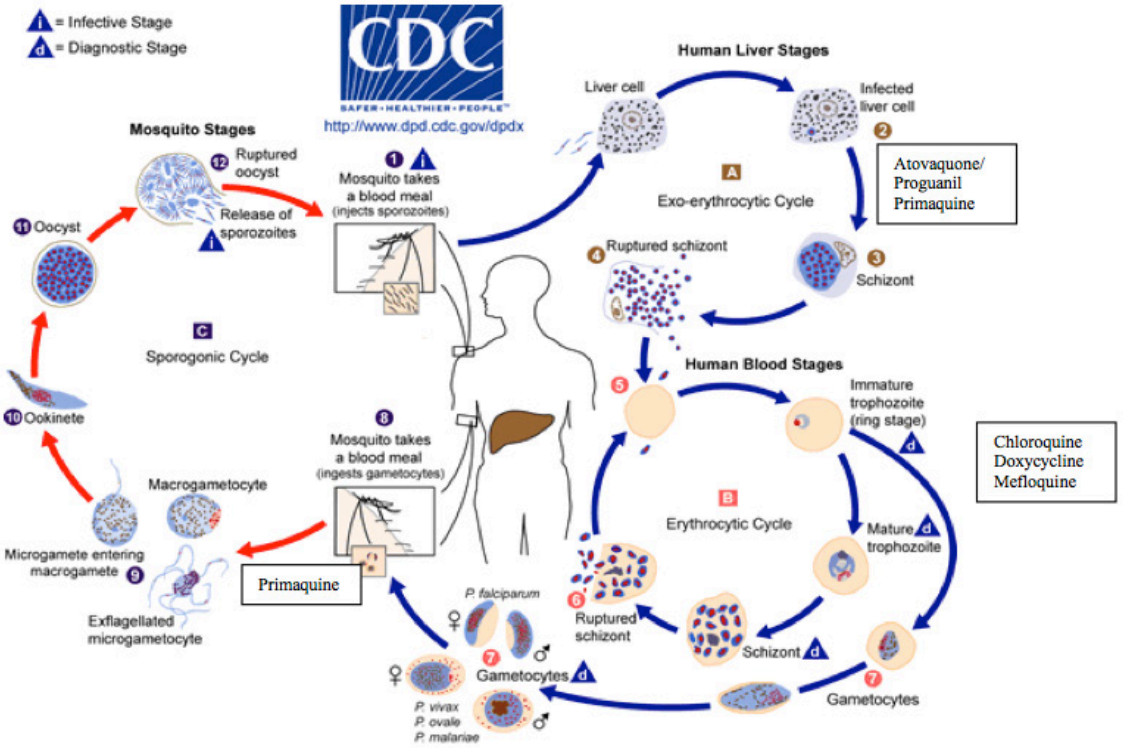
In light of the increasing prevalence of counterfeit medications in some countries and the potentially serious consequences of inadequate antimalarial prophylaxis or treatment, travellers should buy their antimalarials before leaving Canada (see Chapter 5, section on counterfeit drugs in "Preventing Malaria in the Long-Term Traveller or Expatriate").

This chapter reviews the drugs (in alphabetical order) used for the prevention and treatment of malaria. This information is not comprehensive. Note that product recommendations are subject to change, and health care providers should consult up-to-date information, including recent drug monographs, for any updates, particularly with respect to compatibility, adverse reactions, contraindications and precautions. (See also Chapters 3, 4, 5 and 7.)

Table 8.10 provides information on the base/salt equivalents of selected antimalarial drugs, and Table 8.11 summarizes information, including doses, for the antimalarial drugs routinely used in Canada.

Figure 8.1 depicts the malaria lifecycle and the sites of action of chemoprophylactic agents.

FIGURE 8.1: Malaria life cycle and primary areas of drug activity*



* Adapted from the Centers for Disease Control and Prevention DPDx website

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 *Plasmodium vivax* and *Plasmodium 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 one 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 four weeks after departure from a malaria-endemic area.

ARTEMISININ AND DERIVATIVES

Artemisinin (quinghaosu) is an endoperoxide-containing natural antimalarial from sweet wormwood (*Artemisia annua*). The semi-synthetic analogues of artemisinin, including artesunate, artemether, arteether and dihydroartesinin, are available in oral, parenteral and suppository formulations. They are all metabolized to a biologically active metabolite, dihydroartemisinin (DHA), and exert their antiparasitic effects on the younger, ring-forming parasites (erythrocytic phase), thus decreasing 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 generally produce rapid clearance of parasitemia and rapid resolution of symptoms. The artemisinin derivatives are effective against drug-resistant *P. falciparum* strains but have high recrudescence rates (about 10% to 50%) when used as monotherapy for fewer than five days. Studies have examined longer durations of therapy (seven days), and artemisinin-based combination therapy of artemisinin derivatives with mefloquine, lumefantrine, amodiaquine or tetracycline–doxycycline to prevent recrudescence. Combination therapy results in higher than 90% cure rates of primary and recrudescent *P. falciparum* infections. While efficacy remains high in many areas of the world, prolonged parasite clearance times following treatment with some artemisinin-based combination therapy , and also with seven-day artemisinin therapy, have been observed on the Thai/Cambodian border (1).

Coartemether (Riamet® in Europe, Coartem® in Africa and the United States) is a combination of artemether and lumefantrine. Coartemether is licensed in some European countries and in the United States and is becoming widely distributed in Africa for the treatment of malaria. A six-dose regimen of artemether-lumefantrine appears more effective than antimalarial regimens not containing artemisinin derivatives (2). Available data suggest that mefloquine plus artesunate is as effective and possibly superior to artemether-lumefantrine (3).

Randomized controlled trials comparing parenteral artesunate and quinine for the treatment of severe malaria in both adults and children and in different regions of the world clearly show the benefits of artesunate (4;5).

Artemisinin and its derivatives are generally well tolerated (Table 6) Neurologic lesions involving the brainstem have been seen in rats, dogs and primates given repeated doses of artemisinin derivatives, in particular the lipid-soluble derivatives (8). Such effects have not been observed with oral administration of any artemisinin derivative or with intravenous (IV) artesunate. However, neurotoxicity may be caused in humans with inappropriate dose regimens (9). Cases of delayed hemolytic anemia (either recurrent or persistent) following use of parenteral artesunate (8 to 32 days after therapy) for severe malaria have been reported worldwide. Patients with high pre-treatment parasitaemia may be at a higher risk. Although possibly attributable to the disease itself, there have been cases reported with the drug distributed through the CMN. Due to this risk, Health Canada and the CMN recommend a CBC be performed weekly for 4 weeks following treatment with parenteral artesunate to monitor patients for anemia. In addition, patients treated with IV artesunate should be counselled to report signs of hemolysis, such as dark urine, yellowing of skin or whites of eyes, fever, abdominal pain, pallor, fatigue, shortness of breath and/or chest pain. Treatment of uncomplicated malaria with coartemether may be associated with hearing loss in some people, possibly from synergy between potentially ototoxic agents in combination (10). 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 fetal loss or abnormalities when used in late pregnancy (8;11). 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 (11). Although there is good evidence that therapy with artemisinin compounds is generally safe, questions about cumulative neurologic toxicity of intramuscular preparations still require resolution. Additional studies to monitor subtle neurologic changes and hearing loss are required, especially in people undergoing repetitive treatment.

Artemisinin-based combination therapy (ART) is the recommended first-line treatment for uncomplicated falciparum malaria and for the treatment of malaria when the causative species has not been identified (8). Parenteral artesunate is recommended by the World Health Organization (WHO) as the treatment of first choice for severe or complicated malaria (8). 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 Canadian Malaria Network (CMN) (see Appendix V). Note that IV artesunate should be reserved for those who have severe malaria, where it has been proven superior to quinine. Parenteral quinine is the preferred agent ONLY for those who do not meet WHO criteria for severe malaria and who are unable to tolerate oral therapy. Both IV artesunate and IV quinine are available through the CMN.

Orally administered artemisinin drug combinations, such as the combination artemisinin-lumefantrine (Coartem®), are recommended by WHO as the treatment of choice for uncomplicated falciparum malaria. Oral artemisinin derivatives are not yet licensed or available in Canada but have been approved in the United States by the Food and Drug Administration.

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 (12) (see Chapter 5, section on counterfeit drugs in "Preventing Malaria in the Long-Term Traveller or Expatriate").

TABLE 8.1: Artemisinin and derivatives: evidence-based medicine recommendations

RECOMMENDATION	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 6-dose regimen of artemether-lumefantrine appears more effective than antimalarial regimens not containing artemisinin derivatives (2;3)	A I
Parenteral artesunate is recommended as the first-line treatment of severe *P. falciparum* malaria (4). Parenteral administration of artesunate should be followed by a full course of one of the following: atovaquone-proguanil (Malarone®), doxycycline (clindamycin in pregnant women or children < 8 years), or ART (8).	A I
On the basis of their short half-life, artemisinin compounds should not be used for chemoprophylaxis	D III

ABBREVIATIONS: ART, artemisinin-based combination therapy; EBM, evidence-based medicine; *P, Plasmodium*.

NOTE: For a description of the categories and quality of evidence of the recommendations, see Appendix IV.

ATOVAQUONE-PROGUANIL

Trade Name: Malarone®, Malarone Pediatric®

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 (13) (see Chapter 5 for dosage in children weighing between 5 and 11 kg). Two formulations of Malarone® are 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 its causal effects, atovaquone-proguanil can be discontinued one week after departure from a malaria-endemic area.

INDICATIONS AND EFFICACY

For malaria chemoprophylaxis, atovaquone-proguanil is equally effective (96%–100%) as doxycycline and mefloquine against chloroquine-resistant falciparum malaria (14). It is also effective along the borders of Thailand, where chloroquine and mefloquine resistance is documented (15;16). Daily atovaquone-proguanil can now be considered as first-line chemoprophylaxis in areas with multidrug-resistant falciparum malaria (with attention to contraindications and precautions) (see Appendix I) (16;17).

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 three days) exceeded 94% (18). In addition, published case reports have documented that it successfully treated multidrug-resistant malaria that failed to respond to other therapies (19). Being an effective and well-tolerated therapy, atovaquone-proguanil is considered first-line treatment of uncomplicated *P. falciparum* infection, including multidrug-resistant *P. falciparum* (20), provided that it was not used as chemoprophylaxis during travel. There have been sporadic documented cases of atovaquone-proguanil clinical failures (21), some of which have been related to atovaquone-proguanil-resistant *P. falciparum* malaria acquired in sub-Saharan Africa (22–24).

There is insufficient evidence at this time to recommend atovaquone-proguanil for the routine treatment of non-falciparum malaria, although limited trial data suggest efficacy for the treatment of *P. vivax* malaria when atovaquone-proguanil is combined with primaquine (beginning immediately after the three days of treatment with atovaquone-proguanil) (25–27). In clinical cases when there is a possibility of *P. falciparum* infection and *P. vivax* cannot be definitively confirmed, atovaquone-proguanil can be used for initial treatment. There is more danger to incorrectly treating chloroquine-resistant *P. falciparum*.

ADVERSE EFFECTS, CONTRAINDICATIONS AND PRECAUTIONS

Compared with other standard antimalarial regimens, the atovaquone-proguanil combination for chemoprophylaxis has demonstrated excellent safety and tolerability (6).

At prophylactic doses, the most frequently cited adverse drug reactions are gastrointestinal reactions (e.g. nausea, vomiting, diarrhea) and headache. In four of six placebo-controlled trials evaluating the safety and tolerability of atovaquone-proguanil prophylaxis, there was no difference between atovaquone-proguanil and placebo arms with respect to adverse drug reactions (21). Compared with mefloquine prophylaxis, atovaquone-proguanil has fewer associated adverse events, gastrointestinal adverse effects and neuropsychiatric adverse events (28).

During treatment, the most frequent adverse events are also 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, as are adverse drug reactions that limit treatment. Atovaquone has been associated with fever and rash in HIV-infected people, 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). Atovaquone increases the plasma concentration of zidovudine (AZT) and lowers serum levels of azithromycin. Proguanil is well tolerated; 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 (29).

Severe renal insufficiency (creatinine clearance < 30 mL/min) and hypersensitivity to either component is a contraindication to atovaquone-proguanil use. Atovaquone-proguanil is also contraindicated during pregnancy due to a lack of available safety data. A recent cohort study evaluated the risk of major birth defects among children born to pregnant travellers who were exposed to atovaquone-proguanil during the first trimester (30). Atovaquone-proguanil exposure during any of the first 12 weeks of pregnancy was not associated with increased risk of any major birth defect (30). Three small published trials have reported on the safety and efficacy of atovaquone-proguanil used in conjunction with artesunate for rescue therapy in cases of multidrug-resistant *P. falciparum* infection in pregnant women (31–33). There were no serious adverse drug events, and adverse drug reactions that were mild-to-moderate in nature were similar between comparator groups. There was no excess risk of prematurity, intrauterine growth retardation, low birth weight or congenital anomalies attributable to atovaquone-proguanil use (31–33). Thus, preliminary data suggest that atovaquone-proguanil appears to be safe, well tolerated and of no increased toxicity to the fetus in pregnant women being prophylaxed or treated for malaria. Additional data will be required before atovaquone-proguanil use in pregnancy is no longer contraindicated.

It is unknown whether atovaquone is excreted in human breast milk (21). Proguanil is excreted in small quantities. Thus, the use of atovaquone-proguanil in nursing women is recommended only if the infant weighs more than 5 kg (21).

TABLE 8.2: Malarone®: evidence-based medicine recommendations

RECOMMENDATION	EBM RATING
ATQ-PG prophylaxis has high-level efficacy (96%–100%) against chloroquine-resistant falciparum malaria (17;19).	A I
Daily ATQ-PG can now be considered as first-line chemoprophylaxis in areas with multidrug-resistant falciparum malaria (16;17).	A I

ATQ-PG is considered a first-line treatment for acute, uncomplicated *P. falciparum* malaria from southeast Asia, South America and Africa with an efficacy of ~ 94% (16;19).	A I
There is insufficient evidence at this time to recommend ATQ-PG for the routine treatment of non-falciparum malaria (21;25–27).	C I

ABBREVIATIONS: ATQ-PG, atovaquone-proguanil; EBM, evidence-based medicine; *P*, *Plasmodium*.

NOTE: For a description of the categories and quality of evidence of the recommendations, see Appendix IV.

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. Chloroquine accumulates in the digestive vacuole of the *Plasmodium* parasite, where it binds haematin, leading to toxic metabolite formation within the digestive vacuole and damage to the plasmodial membranes.

INDICATIONS AND EFFICACY

Chloroquine–hydroxychloroquine, taken once weekly, is effective for malaria prevention in areas with chloroquine-sensitive malaria (16) and it remains the drug of choice for malaria chemoprophylaxis in areas with chloroquine-sensitive malaria. Chloroquine is the drug of choice for the treatment of chloroquine-sensitive falciparum malaria, chloroquine-sensitive *P. vivax,* as well as *P. ovale, P. malariae* and *P. knowlesi* infections (34).

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 8.11). 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 (Savarine®) is less efficacious than atovaquone-proguanil, doxycycline or mefloquine and is **not** routinely recommended for prevention of malaria for Canadian travellers going to sub-Saharan Africa because of the high risk of chloroquine-resistant *P. falciparum* malaria (17;35).

ADVERSE EFFECTS, CONTRAINDICATIONS AND PRECAUTIONS

Except for its bitter taste, chloroquine is usually well tolerated. Taking the drug with food may reduce other mild adverse effects, such as nausea and headache. Black-skinned people may experience generalized pruritus, which is not indicative of drug allergy. Lack of compliance due to pruritus may account for therapeutic failures associated with the use of chloroquine (36). Transient, minor visual blurring may occur initially but should not be a reason to discontinue chloroquine. Retinal toxicity is of concern when a cumulative dose of 100 g of chloroquine is reached. Anyone who has taken 300 mg of chloroquine weekly for more than five years and requires further prophylaxis should be screened twice-yearly for early retinal changes (16). Chloroquine may worsen psoriasis and, rarely, is associated with seizures and psychosis. It should not be used in individuals with a history of epilepsy or generalized psoriasis (6;16;37). Concurrent use of chloroquine interferes with antibody response to intradermal human diploid cell rabies vaccine.

TABLE 8.3: Chloroquine: evidence-based medicine recommendations

RECOMMENDATION	EBM RATING
Chloroquine–hydroxychloroquine, taken once weekly, is effective for malaria prevention in areas with chloroquine-sensitive malaria (16).	A I
Chloroquine is the drug of choice for the treatment of malaria caused by chloroquine-sensitive *P. falciparum* and *P. vivax,* and all *P. ovale, P. malariae* and *P. knowlesi* infections (16;34).	A I
Weekly prophylaxis with chloroquine plus daily proguanil (Savarine®) is less efficacious than ATQ-PG, doxycycline or mefloquine and is not recommended for travellers (17;35).	E I
Chloroquine should not be used in individuals with a history of epilepsy or generalized psoriasis (6;37).	C III

ABBREVIATIONS: ATQ-PG, atovaquone-proguanil; EBM, evidence-based medicine; *P*, *Plasmodium*.

NOTE: For a description of the categories and quality of evidence of the recommendations, see Appendix IV.

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.

TABLE 8.4: Clindamycin: evidence-based medicine recommendations

RECOMMENDATION	EBM RATING
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 (25) when artemisinin-derivatives (e.g. artesunate) are unavailable.	A I

ABBREVIATIONS: EBM, evidence-based medicine; *P*, *Plasmodium*.

NOTE: For a description of the categories and quality of evidence of the recommendations, see Appendix IV.

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 be as effective as atovaquone-proguanil and mefloquine for the prevention of chloroquine-resistant *P. falciparum (16).* Doxycycline is an efficacious chemoprophylactic agent against mefloquine-sensitive and mefloquine-resistant *P. falciparum* malaria (16) but must be taken daily for it to work, and for four weeks after leaving the malaria-endemic area. The major reason for doxycycline failures is noncompliance with this daily regimen.

Travellers taking minocycline for the treatment of acne or rheumatoid arthritis and for whom doxycycline was recommended for malaria chemoprophylaxis should switch to doxycycline 100 mg daily on arrival in the malaria-endemic area. Once they have completed their anti-malarial chemoprophylaxis (including the 4 weeks of doxycycline chemoprophylaxis after leaving the malaria-endemic area), they should resume their former dose of minocycline. Travellers should use an effective sunscreen, especially since the dose of doxycycline used for malaria chemoprophylaxis may be higher than the minocycline dose used in the treatment of acne. Note that the preponderance of literature on efficacy of tetracyclines as antimalarials has focused on doxycycline (38;39) and that insufficient data exist on the antimalarial prophylaxis efficacy of minocycline.

ADVERSE EFFECTS, CONTRAINDICATIONS AND PRECAUTIONS

Doxycycline can cause gastrointestinal upset and, rarely, esophageal ulceration or esophagitis (0.8%). These effects are less likely to occur if the drug is taken with food and large amounts of fluid. Absorption of doxycycline may be reduced if taken with dairy products. For this reason, pharmacies may advise taking doxycycline on an empty stomach. However, as noted above, this strategy is far more likely to cause gastrointestinal upset, which can be mitigated by ingesting the drug with fluids or small amounts of food. In randomized controlled trials of doxycycline at prophylactic doses, nausea and abdominal pain were the most commonly reported mild to moderate adverse events (38). Avoid taking doxycycline in the 30 minutes before lying down or with Pepto-Bismol® or antacids. Because doxycycline is photosensitizing, it may cause the skin to burn more easily; using a sunscreen that blocks ultraviolet A and B rays may reduce this problem (38). Doxycycline may also increase the risk of vaginal candidiasis, so 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, recent evidence fails to demonstrate any significant association (38;40). 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. There is a theoretical risk of reduced effectiveness of the oral typhoid vaccine (Ty21a) if given concurrently with doxycycline. Doxycycline should therefore not be used within 3 days of Ty21a vaccine administration (38).

Doxycycline is **contraindicated** during pregnancy, in breastfeeding women and in children aged less than 8 years. Doxycycline has been taken safely in prophylactic doses for at least 12 months, and tetracycline derivatives have been used at lower doses over many years for skin disorders such as acne.

TABLE 8.5: Doxycycline: evidence-based medicine recommendations

RECOMMENDATION	EBM RATING
Doxycycline has high level efficacy (93%–100%) for the prevention of chloroquine-resistant *P. falciparum and for mefloquine-resistant P. falciparum (38).*	A I
Travellers should be informed about the small doxycycline-associated risks of esophageal ulceration, vaginal candidiasis and photosensitivity (8;38) .	A I
Doxycycline is **contraindicated** during pregnancy, while breastfeeding and in children < 8 years of age (8;38).	A I
Concurrent use of doxycycline with barbiturates, carbamazapine or phenytoin may result in a 50% decrease in doxycycline serum concentration (8;38).	A I
People taking minocycline for the treatment of acne or rheumatoid arthritis should switch to doxycycline 100 mg daily for the duration of their stay in the malaria-endemic area plus for four weeks after leaving the area, then switch back to usual dose of minocycline.	C III

ABBREVIATIONS: EBM, evidence-based medicine; *P, Plasmodium*.

NOTE: For a description of the categories and quality of evidence of the recommendations, see Appendix IV.

MEFLOQUINE

Trade Name: Lariam®, Apo-Mefloquine

MECHANISM OF ACTION

Mefloquine is a quinoline-methanol. It is a lipophylic drug that acts on the intra-erythrocytic 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 chloroquine-resistant malaria (16). The chemoprophylactic efficacy of mefloquine is generally greater than 90%, except for small multidrug-resistant areas on the Thai-Cambodian, and Thai-Burma (Myanmar) borders.

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 (6). It is recommended, therefore, that the duration that mefloquine is used is not be arbitrarily restricted in individuals who tolerate this medication.

Consider giving travellers who will be at immediate high risk of drug-resistant falciparum a loading dose of mefloquine. If time permits, initiate mefloquine up to three 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 three 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 four days compared with seven to nine weeks with standard weekly dosing of mefloquine) (41). 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 tolerated when used for chemoprophylaxis. Approximately 25% to 50% of travellers will experience adverse effects from either mefloquine or chloroquine; most of these are mild and self-limiting (42;43). The most frequent adverse effects reported with mefloquine use are nausea, strange vivid dreams, dizziness, mood changes, insomnia, headache and diarrhea. Serious but rare adverse drug reactions include agranulocytosis, aplastic anemia, and hepatic impairment including hepatic failure (44). Approximately 1% to 6% of mefloquine users may have to discontinue prophylaxis because of adverse effects.

Controlled studies have shown a significant excess of neuropsychiatric events in mefloquine users versus comparators (28;45). Tens of millions of travellers have used mefloquine prophylaxis, and severe neuropsychiatric 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 adverse effects or only mild and temporary ones. Occasionally, a traveller (in particular, women (6;46) and people with low body weight (45) 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 another drug. This can sometimes be prevented by splitting the weekly dose of one tablet into two halves, taken twice a week for the same total weekly dose. Adverse reactions are generally reversible, but neuropsychological complaints occasionally persist 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 it is less well tolerated in treatment doses (25 mg base/kg). 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 (6).

CONTRAINDICATIONS

Contraindications 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 smaller than 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 (due to the risk of a potentially fatal prolongation of the QT interval, halofantrine and mefloquine should not be used concurrently, see section on halofantrine below); underlying cardiac conduction disturbances or arrhythmia; and first trimester of pregnancy.

Electrocardiographic investigations have shown that mefloquine alone does not alter ventricular repolarization. At the cellular level, most major antimalarial drugs inhibit potassium channels, which are regulated by the LQT1 and HERG genes responsible for the congenital long-QT syndrome, which may explain the synergistic prolongation of QT interval observed when mefloquine is co-administered with the HERG antagonist halofantrine (47). There have been concerns regarding the co-administration of mefloquine and agents known to alter cardiac conduction, including other related antimalarial compounds (quinine, quinidine, chloroquine), beta-blockers, calcium channel blockers, phenothiazines, nonsedating antihistamines and tricyclic antidepressants, because these drugs may contribute to a prolongation of the QT interval (44). At present, these concerns remain

theoretical, and the concurrent use of these agents is not contraindicated, but use should be monitored. 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.

Mefloquine is extensively metabolized in the liver by CYP3A4; caution should therefore be exercised when mefloquine is administered concomitantly with CYP3A4 inhibitors such as ketoconazole or macrolide antimicrobials because this can result in toxic levels of mefloquine (45). Co-administration with CYP3A4 inducers may result in subtherapeutic levels of mefloquine and mefloquine failures.

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, and discontinue the drug, substituting it with another medication.

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 less than 5 kg, it should be considered for children at high risk of acquiring chloroquine-resistant *P. falciparum* malaria (see Chapter 4; Chapter 5; Appendix I). There are no pharmacokinetic data upon which to recommend a correct dose for children weighing less than 15 kg. WHO has suggested a chemosuppressive dose of 5 mg base/kg weekly for children weighing more than 5 kg.

Vaccination with live, oral typhoid or cholera vaccines should be completed at least three days before the first dose of mefloquine (44).

TABLE 8.6: Mefloquine: evidence-based medicine recommendations

RECOMMENDATION	EBM RATING
If tolerated, mefloquine is one of the drugs of choice, along with atovaquone-proguanil or doxycycline, for the prevention of chloroquine-resistant malaria (16).	A I
Mefloquine is not recommended for prevention of malaria in border areas between Cambodia, Myanmar and Thailand, due to reports of treatment failures in excess of 50% in those areas (16).	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 (6).	B II
The most frequent adverse 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 (42).	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 (6).	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 (6).	C I–E I

ABBREVIATION: EBM, evidence-based medicine.

NOTE: For a description of the categories and quality of evidence of the recommendations, see Appendix IV.

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 not fully understood. However, primaquine is active 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

Primaquine is used in two major ways to prevent malaria: 1) as a primary chemoprophylactic agent, and 2) for prevention of relapse due to *P. vivax* or *P. ovale* infection (primaquine anti-relapse therapy [PART]).

1) Primary chemoprophylaxis: Primaquine is an effective chemoprophylactic agent for *P. falciparum* malaria (43). Recent studies have shown efficacy in semi-immune and nonimmune 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 (48). Primaquine is well tolerated in people who are not glucose-6-phosphate dehydrogenase (G6PD) deficient. Because of the causal effects of primaquine, it can be discontinued one 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.

2) Primaquine anti-relapse therapy (PART): *P. vivax* and *P. ovale* parasites can persist in the liver and cause relapses for as long as five 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 two 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) (49). None of the other currently recommended chemoprophylaxis regimens will prevent relapses due to *P. vivax* and *P. ovale*. PART should therefore be considered in travellers who have lived for 6 months or longer in a high-risk area or who have experienced intense exposure to *P. vivax*, in areas of the Omo River (Ethiopia) and Papua New Guinea (37).

Primaquine is also indicated as part of the treatment of confirmed bloodstream infection with *P. vivax* or *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 the acute febrile illness is over, but to overlap with the blood schizonticide (i.e. chloroquine or quinine). *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) (8). 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 southeast Asia (8).

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. Four classes of G6PD deficiency exist, and are classified based on the level of residual enzyme activity in red blood cells, with Class I being the most severe form, and Classes II to IV having diminishing degrees of deficiency. Most people with G6PD deficiency will have a moderate variant, with more than 10% residual G6PD red cell activity. As well, those receiving more than 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 people 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. Administering primaquine less frequently (e.g. weekly rather than daily) and for longer (e.g. eight weeks versus standard two weeks) enables effective PART with minimal risk of hemolysis in those with less severe forms of G6PD deficiency. When used at prophylactic doses (0.5 mg base/kg daily) in children and adults with normal G6PD activity, mean methemoglobin rates (5.8%) were below those associated with toxicity (> 10%). Advise travellers to stop their medication and report to a physician immediately if jaundice, gray skin or abnormally dark or brown urine is noted.

Primaquine is contraindicated in pregnancy. *P. vivax* or *P. ovale* infections occurring during pregnancy should be treated with standard doses of chloroquine (Table 8.3). Relapses can be prevented by weekly chemoprophylaxis with chloroquine 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.

TABLE 8.7: Primaquine: evidence-based medicine recommendations

RECOMMENDATION	EBM RATING
Primaquine (30 mg base daily) is an effective chemoprophylactic agent with a protective efficacy of 85%–93% against both *P. falciparum* and *P. vivax* infections; it is recommended when the first-line agents mefloquine, doxycycline and ATQ-PG cannot be used or in the prophylaxis of *P. vivax* or *P. ovale* malaria, when there is no G6PD deficiency (43;50).	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* (8;51).	A I

ABBREVIATIONS: ATQ-PG, atovaquone-proguanil; EBM, evidence-based medicine; G6PD, glucose-6-phosphate dehydrogenase; *P. Plasmodium*.

NOTE: For a description of the categories and quality of evidence of the recommendations, see Appendix IV.

QUININE AND QUINIDINE

MECHANISM OF ACTION

Quinine and quinidine are quinoline-containing antimalarials. They are alkaloid derivatives of Cinchona bark and 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 treatment for severe malaria (4). The CMN recommends reserving the use artesunate for those presenting with WHO-defined severe malaria and using parenteral quinine in those whose indication is vomiting or intolerance to oral therapy. Because of the significant cardiotoxic effects associated with parenteral quinidine it is to be considered only if the two first-line drugs are unavailable; 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, and 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 QT interval and therefore requires electrocardiographic monitoring.

TABLE 8.8: Quinine: evidence-based medicine recommendations

QUININE: EVIDENCE-BASED MEDICINE RECOMMENDATIONS	EBM RATING
Oral therapy with quinine (with a second agent—doxycycline or clindamycin) is indicated for the treatment of uncomplicated falciparum malaria and as step-down therapy after parenteral treatment of complicated malaria (16;25).	A I
Parenteral quinine is the alternative drug for the treatment of severe or complicated malaria when parenteral artesunate is not available (8).	A I

ABBREVIATION: EBM, evidence-based medicine.

NOTE: For a description of the categories and quality of evidence of the recommendations, see Appendix IV.

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, the number of effective medications available for treatment may be limited; indeed, some of the drugs used may be ineffective in nonimmune travellers or be associated with unacceptable adverse outcomes. In addition, drugs purchased locally may be counterfeit. As well, the level of health care available in some of these countries may put travellers at risk of other infectious diseases (52;53).

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 *not* to 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 (21;38;49;54). 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 bioavailability. 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 know of the danger of this drug. 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, Chinese scientists rediscovered piperaquine 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 therapy (ART) (55).

Proguanil should **not** be used as a single agent (e.g. Paludrine®), or in combination with chloroquine (Savarine®) for chemoprophylaxis (35;40;56–58). Further information is available for the combined product atovaquone-proguanil (Malarone®), above.

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 (59;60).

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 that has been used to treat *P. vivax* and *P. falciparum infections* for more than 20 years and has been shown to effectively treat falciparum malaria in children in Cameroon. It has more gastrointestinal adverse effects than chloroquine. Pyronaridine has been used in combination with the artemisinin derivatives in the treatment of falciparum malaria (61).

TABLE 8.9: Evidence-based medicine recommendations

RECOMMENDATIONS	EBM RATING
Azithromycin has been shown *not* to be very effective in the prevention of *P. falciparum* malaria (21;38;49;54).	E II
Amodiaquine is not recommended for malaria chemoprophylaxis because of its established risks of fatal hepatic or bone marrow toxicity (6;43;62).	D III
Halofantrine has been associated with cardiac toxicity and should **not** be used as an antimalarial (6;43). 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 ART (63).	B II
Pyrimethamine alone (Daraprim®) is not recommended for malaria chemoprophylaxis because of widespread antifolate drug resistance (59).	D III
Proguanil should **not** be used as a single agent for chemoprophylaxis because of widespread drug resistance (64).	D III
Pyrimethamine-sulfadoxine (Fansidar®) is not recommended for chemoprophylaxis because of the life-threatening complication of Stevens-Johnson syndrome and toxic epidermal necrolysis (6;64).	E III
Pyronaridine has received insufficient study to recommend its use for the treatment of malaria in nonimmune travellers.	D III
Proguanil alone or in combination with chloroquine (Savarine®) is less effective than mefloquine, doxycycline and ATQ-PG and is not recommended for malaria prophylaxis (35;57;60).	E II

ABBREVIATIONS: ART, artemisinin-based combination therapy; ATQ-PG, atovaquone-proguanil; EBM, evidence-based medicine; *P. Plasmodium*.

NOTE: For a description of the categories and quality of evidence of the recommendations, see Appendix IV.

TABLE 8.10: Base/salt equivalents of selected antimalarial drugs

DRUG	BASE (MG)	SALT (MG)
Chloroquine phosphate	155.0	250.0
Chloroquine sulphate[a]	100.0	136.0
Clindamycin hydrochloride	150.0	225.0
Mefloquine	250.0	274.0
Primaquine	15.0	26.3
Quinidine gluconate	5.0	8.0
	7.5	12.0
	10.0	16.0
	15.0	24.0
Quinidine sulphate[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 sulphate	250.0	300.0

[a] Not available in Canada.

[b] Intramuscular preparation should not be used intravenously.

TABLE 8.11: Drugs (generic and trade name) for the treatment and prevention of malaria
Please see the CATMAT website (www.phac-aspc.gc.ca/tmp-pmv/catmat-ccmtmv/index-eng.php) for updates to the information on drugs for the treatment and prevention of malaria.

INDICATION	ADULT DOSAGE	PEDIATRIC DOSAGE	ADVANTAGE	DISADVANTAGE	ADVERSE EFFECTS
ATOVAQUONE-PROGUANIL (ATQ-PG) (Malarone®) (Malarone® Pediatric)					
Prevention and treatment of *P. falciparum* and *P. vivax malaria*	**Adult tablet:** 250 mg atovaquone plus 100 mg proguanil hydrochloride **Prevention:** 1 tablet daily; start one day before entering malaria-endemic area and continue during exposure and for 7 days after leaving **Treatment:** 1,000 mg atovaquone AND 400 mg proguanil (4 tablets) once daily x 3 days	**Pediatric tablets:** 62.5 mg atovaquone plus 25 mg proguanil hydrochloride **Prevention:** 1 tablet daily; start 1 day before entering malarial area and continue during exposure and for 7 days after leaving; < 11 kg: see Chapter 5 (based on a pediatric tablet of 62.5 mg atovaquone/25 mg proguanil, the daily doses are ½ pediatric tablet for 5–8 kg, and ¾ pediatric tablet for > 8 to 10 kg) 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: (based on a pediatric tablet of 62.5 mg atovaquone/25 mg proguanil, the daily doses are 2 pediatric tablets for 5 to 8 kg, and 3 pediatric tablets 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

INDICATION	ADULT DOSAGE	PEDIATRIC DOSAGE	ADVANTAGE	DISADVANTAGE	ADVERSE EFFECTS
ARTESUNATE Vial 110 mg powder and vial buffered diluent					
Treatment of severe and complicated malaria	**Treatment:** 2.4 mg/kg intravenous bolus at hours 0, 12, 24 and 48 with possible doses daily for total of 7 days if concurrent doxycycline, ATQ-PG or clindamycin are not tolerated (see Chapter 7)	**Treatment:** 2.4 mg/kg at hours 0, 12, 24 and 48 with possible doses daily for total of 7 days if concurrent doxycycline, ATQ-PG or clindamycin are not tolerated (see Chapter 7)	Faster response than parenteral quinine; no cardiovascular or hypoglycemic effects	Requires concurrent therapy with second drug	**Frequent:** Dizziness, nausea, vomiting, anorexia, diarrhea, transient reticulocytopenia, metallic taste during infusion **Occasional:** Urticarial rash **Rare:** Severe allergic reactions (65)
CHLOROQUINE (Novo-Chloroquine) Tablet: 155 mg chloroquine base (250 mg chloroquine diphosphate)					
Prevention and treatment in chloroquine- sensitive *P. falciparum and P. vivax* areas Treatment of, *P. ovale*, *P. malariae* and *P. knowlesi* infections	**Prevention:** 310 mg base once weekly; start 1 week before entering malaria-endemic area and continue during exposure and for 4 weeks after leaving **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 malaria-endemic area and continue during exposure and for 4 weeks after leaving 15–20 kg: ½ tablet > 20–25 kg: ¾ tablet > 25–35 kg: 1 tablet > 35–50 kg: 1½ tablets > 50 kg: 2 tablets **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

INDICATION	ADULT DOSAGE	PEDIATRIC DOSAGE	ADVANTAGE	DISADVANTAGE	ADVERSE EFFECTS
CLINDAMYCIN (Dalacin C®, Apo-Clindamycin, Novo-Clindamycin, Clindamycine, Clindamycin Injection)					
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 (20 mg/kg/d orally divided TID-QID) is tolerated. **NOTE:** Should only use if the traveller 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 (20 mg/kg/d orally divided TID-QID) is tolerated. **NOTE:** Should only use if the traveller is unable to take doxycycline or ATQ-PG.	Safe in pregnancy and young children	Lower efficacy than ATQ-PG alone or combination of doxycycline plus quinine	**Frequent:** Diarrhea, rash **Occasional:** Pseudomembranous colitis **Rare:** Hepatotoxicity, blood dyscrasias
DOXYCYCLINE (Vibra-Tabs®, Apo-Doxy, Doxycin, Novo-Doxylin, Nu-Doxycycline, ratio-Doxycycline)					
Prevention of chloroquine-resistant *P. falciparum*; treatment of chloroquine-resistant *P. falciparum* when combined with a second drug	**Prevention:** 1 tablet (100 mg) once daily; start 1 day before entering malaria-endemic area and continue during exposure and for 4 weeks after leaving **Treatment:** 1 tablet (100 mg) or 100 mg IV twice daily for 7 days	**Prevention:** < 25 kg or < 8 yr: contraindicated Start 1 day before entering malaria-endemic area and continue during exposure and for 4 weeks after leaving 2 mg base/kg po once daily (max 100 mg daily) 25–35 kg: 50 mg daily > 35–50 kg: 75 mg daily > 50 kg: 100 mg daily **Treatment:** < 25 kg or < 8 yr: contraindicated 2 mg base/kg po or IV 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

INDICATION	ADULT DOSAGE	PEDIATRIC DOSAGE	ADVANTAGE	DISADVANTAGE	ADVERSE EFFECTS
HYDROXYCHLOROQUINE (Plaquenil, Apo-Hydroxyquine, Gen-Hydroxychloroquine) Tablet: 155 mg base					
Prevention and treatment in chloroquine- sensitive *P. falciparum* and *P. vivax* areas Treatment of *P. ovale*, *P. malariae* and *P. knowlesi* infections	**Prevention:** 310 mg base once weekly; start 1 week before entering malaria-endemic area and continue during exposure and for 4 weeks after leaving **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 malaria-endemic area and continue during exposure and for 4 weeks after leaving **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

INDICATION	ADULT DOSAGE	PEDIATRIC DOSAGE	ADVANTAGE	DISADVANTAGE	ADVERSE EFFECTS
MEFLOQUINE (Lariam®, Apo-Mefloquine)					
Prevention of *P. falciparum*	**Prevention:** Start at least 1 week (preferably 2–3 weeks) before departure and continue during exposure and for 4 weeks after leaving Loading dose—see text on page 76 (section on mefloquine) 250 mg once weekly **Treatment**: Not routinely recommended (see Chapter 7)	**Prevention:** Start at least 1 week (preferably 2–3 weeks) before departure and continue during exposure and for 4 weeks after leaving Loading dose—see text on page 76 (section on mefloquine) 5 mg/kg once weekly < 5 kg: no data (see Chapter 4 and Chapter 5) 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 Chapter 7)	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.	**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 (PART);* radical cure for *P. vivax* and *P. ovale* bloodstream infections	**Prevention:** Primary prophylaxis 30 mg base daily. Start 1 day before entering malarial area and continue during exposure and for 7 days after leaving **Terminal prophylaxis (PART) 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 during exposure and for 7 days after leaving **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 Chapter 4)	**Occasional:** GI upset, hemolysis in G6PD deficiency, methemoglobinemia

INDICATION	ADULT DOSAGE	PEDIATRIC DOSAGE	ADVANTAGE	DISADVANTAGE	ADVERSE EFFECTS
QUINIDINE GLUCONATE–SULPHATE					
	Prevention: no indication **Treatment:** see Chapter 7, Box 7.1	**Prevention:** no indication **Treatment:** see Chapter 7, Box 7.1 28 mg base/kg daily, divided q 8 hourly[a]		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 DIHYDROCHLORIDE					
	Prevention: no indication **Treatment:** see Chapter 7, Box 7.1	**Prevention:** no indication **Treatment:** see Chapter 7, Box 7.1			**Frequent:** Cinchonism (tinnitus, nausea, headache, blurred vision), hypoglycemia **Occasional:** Cardiac conduction disturbances, hypersensitivity **Rare:** Hemolysis
QUININE SULPHATE (Novo-Quinine®, Apo-Quinine, Quinine-Odan)					
	Prevention: no indication **Treatment oral:** 500 mg base 3 times daily for 3–7 days (7 days for SE Asia) IV: see Chapter 7, Box 7.1	**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 Chapter 7, Box 7.1			Similar to above

ABBREVIATIONS: ATQ-PG, atovaquone-proguanil; IV, intravenous; ART, artemisinin-based combination therapy; G6PD, glucose-6-phosphate dehydrogenase; GI, gastrointestinal; *P.*, *Plasmodium*; po, by mouth; q, every; QID, 4 times/day; SE, southeast; TID, 3 times/day.

[a] Where possible, refer the person to a compounding pharmacy, and dose at 5 mg/kg once weekly; tablet cannot be accurately subdivided into1/4 or 1/8 portions.

REFERENCE LIST

(1) Dondorp A, Nosten F, Yi P, Das D, Phyo AP, Tarning J, et al. Artemisinin resistance in *Plasmodium falciparum* malaria. N Engl J Med 2009;361:455–67.

(2) Davis TM, Karunajeewa HA, Ilett KF. Artemisinin-based combination therapies for uncomplicated malaria. Med J Aust 2005 Feb 21;182(4):181–5.

(3) Omari AA, Gamble C, Garner P. Artemether-lumefantrine (six-dose regimen) for treating uncomplicated falciparum malaria. Cochrane Database Syst Rev 2005;(4):CD005564.

(4) Sinclair D, Donegan S, Lalloo DG. Artesunate versus quinine for treating severe malaria. Cochrane Database Syst Rev 2011;3:CD005967.

(5) Dondorp AM, Fanello CI, Hendrikson EC, Gomes E, Seni A, Chhaganlal KD, et al. Artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): an open-label, randomized trial. Lancet 2010;376(9753):1647–57.

(6) Taylor WR, White NJ. Antimalarial drug toxicity: a review. Drug Saf 2004;27(1):25–61.

(7) Medhi B., Patyar S, Rao RS, Byrav P, Prakash A. Review: Pharmacokinetic and Toxicological Profile of Artemisinin Compounds: An Update. Pharmacology 2009;84:323–32.

(8) World Health Organization. Guidelines for the treatment of malaria, Second edition. 2010.

(9) Li Q, Hickman M. Toxicokinetic and toxicodynamic (TK/TD) evaluation to determine and predict the neurotoxicity of artemisinins. Toxicology 2011;279(1–3):1–9.

(10) Toovey S, Jamieson A. Audiometric changes associated with the treatment of uncomplicated falciparum malaria with co-artemether. Trans R Soc Trop Med Hyg 2004 May;98(5):261–7.

(11) Dellicour S, Hall S, Chandramohan D, Greenwood B. The safety of artemisinins during pregnancy: a pressing question. Malar J 2007;6:15.

(12) Newton P, Proux S, Green M, Smithuis F, Rozendaal J, Prakongpan S, et al. Fake artesunate in southeast Asia. Lancet 2001 Jun 16;357(9272):1948–50.

(13) Malarone Product Monograph 2005. Mississauga: GlaxoSmithKline; 2005.

(14) Slinger R, Giulivi A, Bodie-Collins M, Hindieh F, John RS, Sher G, et al. Transfusion-transmitted malaria in Canada. CMAJ 2001 Feb 6;164(3):377–9.

(15) Overbosch D, Schilthuis H, Bienzle U, Behrens RH, Kain KC, Clarke PD, et al. Atovaquone-proguanil versus mefloquine for malaria prophylaxis in nonimmune travelers: results from a randomized, double-blind study. Clin Infect Dis 2001 Oct 1;33(7):1015–21.

(16) World Health Organization. International travel and health. 2012.

(17) Petersen E. Malaria chemoprophylaxis:when should we use it and what are the options? Expert Rev Anti Infect Ther 2004 Feb 1;2(1):119–32.

(18) Krudsood S, Patel SN, Tangpukdee N, Thanachartwet W, Leowattana W, Pornpininworakij K, et al. Efficacy of atovaquone-proguanil for treatment of acute multidrug-resistant Plasmodium falciparum malaria in Thailand. Am J Trop Med Hyg 2007 Apr;76(4):655–8.

(19) Patel SN, Kain KC. Atovaquone/proguanil for the prophylaxis and treatment of malaria. Expert Rev Anti Infect Ther 2005 Dec;3(6):849–61.

(20) Osei-Akoto A, Orton L, Owusu-Ofori SP. Atovaquone-proguanil for treating uncomplicated malaria. Cochrane Database Syst Rev 2005;(4):CD004529.

(21) Boggild AK, Parise ME, Lewis LS, Kain KC. Atovaquone-proguanil: report from the CDC expert meeting on malaria chemoprophylaxis (II). Am J Trop Med Hyg 2007 Feb;76(2):208–23.

(22) Schwartz E, Bujanover S, Kain KC. Genetic confirmation of atovaquone-proguanil-resistant Plasmodium falciparum malaria acquired by a nonimmune traveler to East Africa. Clin Infect Dis 2003 Aug 1;37(3):450–1.

(23) Kuhn S, Gill MJ, Kain KC. Emergence of atovaquone-proguanil resistance during treatment of Plasmodium falciparum malaria acquired by a non-immune north American traveller to west Africa. Am J Trop Med Hyg 2005 Apr;72(4):407–9.

(24) Farnert A, Lindberg J, Gil P, Swedberg G, Berqvist Y, Thapar MM, et al. Evidence of Plasmodium falciparum malaria resistant to atovaquone and proguanil hydrochloride: case reports. BMJ 2003 Mar 22;326(7390):628–9.

(25) Griffith KS, Lewis LS, Mali S, Pairse ME. Treatment of malaria in the United States. JAMA 2007 May 23;297(20):2264–77.

(26) Looareesuwan S, Wilairatana P, Glanarongran R, Indravijit KA, Supeeranontha L, Chinnapha S, et al. Atovaquone and proguanil hydrochloride followed by primaquine for treatment of Plasmodium vivax malaria in Thailand. Trans R Soc Trop Med Hyg 1999 Nov;93(6):637–40.

(27) Lacy MD, Maguire JD, Barcus MJ, Ling J, Bangs MJ, Gramzinski R, et al. Atovaquone/proguanil therapy for plasmodium falciparum and plasmodium vivax malaria in Indonesians who lack clinical immunity. Clin Infect Dis 2002 Nov 1;35(9):e92–5.

(28) Jacquerioz FA, Croft AM. Drugs for preventing malaria in travellers. Cochrane Database Syst Rev 2009;(4):CD006491.

(29) Armstrong G, Bed MF, Scahill S. Warfarin potentiated by proguanil. BMJ 1991;303:789.

(30) Pasternak B, Hviid A. Atovaquone-proguanil use in early pregnancy and the risk of birth defects. Arch Intern Med 2011 Feb 14;171(3):259–60.

(31) McGready R, Ashley EA, Moo E, Cho T, Barends M, Hutagalung R, et al. A randomized comparison of artesunate-atovaquone-proguanil versus quinine in treatment for uncomplicated falciparum malaria during pregnancy. J Infect Dis 2005 Sep 1;192(5):846–53.

(32) McGready R, Stepniewska K, Edstein MD, Cho T, Gilveray G, Looareesuwan S, et al. The pharmacokinetics of atovaquone and proguanil in pregnant women with acute falciparum malaria. Eur J Clin Pharmacol 2003 Oct;59(7):545–52.

(33) McGready R, Keo NK, Villegas L, White NJ, Looareesuwan S, Nosten F. Artesunate-atovaquone-proguanil rescue treatment of multidrug-resistant Plasmodium falciparum malaria in pregnancy: a preliminary report. Trans R Soc Trop Med Hyg 2003 Sep;97(5):592–4.

(34) Centers for Disease Control and Prevention. Guidelines for Treatment of Malaria in the United States. 2009.

(35) Lobel HO, Miani M, Eng T, Bernard KW, Hightower AW, Campbell CC. Long-term malaria prophylaxis with weekly mefloquine. Lancet 1993 Apr 3;341(8849):848–51.

(36) Aghahowa SE, Obianwu HO, Isah AOAIM. Chloroquine-induced Pruritus. Indian J Pharm Sci 2010;72(3):283–9.

(37) Baird JK. Chloroquine resistance in Plasmodium vivax. Antimicrob Agents Chemother 2004 Nov;48(11):4075–83.

(38) Tan KR, Magill AJ, Parise ME, Arguin PM. Doxycycline for Malaria Chemoprophylaxis and Treatment: Report from the CDC Expert Meeting on Malaria Chemoprophylaxis. Am J Trop Med Hyg 2011 Apr;84(4):517–31.

(39) Bacaner N, Stauffer B, Boulware DR, Walker PF, Keystone JS. Travel medicine considerations for North American immigrants visiting friends and relatives. JAMA 2004 Jun 16;291(23):2856–64.

(40) Neely JL, Abate M, Swinker M, D'Angio R. The effect of doxycycline on serum levels of ethinyl estradiol, norethindrone, and endogenous progesterone. Obstet, Bynecol 1991 Mar;77(3):416–20.

(41) Schlagenhauf P. Mefloquine for malaria chemoprophylaxis 1992–1998: a review. J Travel Med 1999 Jun;6(2):122–33.

(42) Kain KC, Shanks GD, Keystone JS. Malaria chemoprophylaxis in the age of drug resistance. I. Currently recommended drug regimens. Clin Infect Dis 2001;33(2):226–34.

(43) Shanks GD, Kain KC, Keystone JS. Malaria chemoprophylaxis in the age of drug resistance. II. Drugs that may be available in the future. Clin Infect Dis 2001 Aug 1;33(3):381–5.

(44) Hoffman-La Roche Limited. Product Monograph: Lariam (mefloquine). 2011. Ref Type: Catalog

(45) Schlagenhauf P, Adamcova M, Regep L, Schaerer MT, Rhein HG. The position of mefloquine as a 21st century malaria chemoprophylaxis. Malar J 2010;9(357):1–15.

(46) Schlagenhauf P, Tschopp A, Johnson R, Nothdurft HD, Beck B, Schwartz E, et al. Tolerability of malaria chemoprophylaxis in non-immune travellers to sub-Saharan Africa: multicentre, randomised, double blind, four arm study. BMJ 2003 Nov 8;327(7423):1078.

(47) Kang J, Chen XL, Wang L, Rampe D. Interactions of the antimalarial drug mefloquine with the human cardiac potassium channels KvLQT1/minK and HERG. J Pharmacol Exp Ther 2001;299(1):290–6.

(48) Baird JK, Fryauff DJ, Hoffman SL. Primaquine for prevention of malaria in travelers. Clin Infect Dis 2003 Dec 15;37(12):1659–67.

(49) Hill DR, Baire JK, Parise ME, Lewis LS, Ryan ET, Magill AJ. Primaquine: report from CDC expert meeting on malaria chemoprophylaxis I. Am J Trop Med Hyg 2006;75(3):402–15.

(50) Chen LH, Keystone JS. New strategies for the prevention of malaria in travelers. Infect Dis Clin North Am 2005 Mar;19(1):185–210.

(51) Galappaththy GN, Omari AA, Tharyan P. Primaquine for preventing relapses in people with Plasmodium vivax malaria. Cochrane Database Syst Rev 2007;(1):CD004389.

(52) Svenson JE, MacLean JD, Gyorkos TW, Keystone J. Imported malaria. Clinical presentation and examination of symptomatic travelers. Arch Intern Med 1995 Apr 24;155(8):861–8.

(53) Svenson JE, Gyorkos TW, MacLean JD. Diagnosis of malaria in the febrile traveler. Am J Trop Med Hyg 1995;53(5):518–21.

(54) Taylor WR, Richie TL, Tryauff DJ, Picarima H, Ohrt C, Tang D, et al. Malaria prophylaxis using azithromycin: a double-blind, placebo-controlled trial in Irian Jaya, Indonesia. Clin Infect Dis 1999;28:74–81.

(55) Marx A, Pewsner D, Egger M, Nuesch R, Bucher HC, Genton B, et al. Meta-analysis: accuracy of rapid tests for malaria in travelers returning from endemic areas. Ann Intern Med 2005 May 17;142(10):836–46.

(56) Kofoed K, Petersen E. The efficacy of chemoprophylaxis against malaria with chloroquine plus proguanil, mefloquine, and atovaquone plus proguanil in travelers from Denmark. J Travel Med 2003 May;10(3):150–4.

(57) Sutherland CJ, Haustein T, Gadalla N, Armstrong M, Doherty JF, Chiodini PL. Chloroquine-resistant plasmodium falciparum infections among UK travellers returning with malaria after chloroquine prophylaxis. J Antimicrob Chemother 2007 Jun;59(6):1197–9.

(58) Shanks GD, Oloo AJ, Aleman GM, Ohrt C, Klotz FW, Braitman D, et al. A new primaquine analogue, tafenoquine (WR 238605), for prophylaxis against Plasmodium falciparum malaria. Clin Infect Dis 2001 Dec 15;33(12):1968–74.

(59) Shanks GD. Treatment of falciparum malaria in the age of drug resistance. J Postgrad Med 2006;52(4):277–80.

(60) Fontanet AL, Houze S, Keundjian A, Schiemann R, Ralaimazava P, Durand R, et al. Efficacy of antimalarial chemoprophylaxis among French residents travelling to Africa. Trans R Soc Trop Med Hyg 2005 Feb;99(2):91–100.

(61) Ramharter M, Kurth F, Schreier AC, Nemeth J, Glasenapp I, Bélard S, et al. Fixed-Dose Pyronaridine-Artesunate Comination for Treatment of Uncomplicated Falciparum Malaria in Pediatric Patients in Gabon. J Infect Dis 2008;198(6):911–9.

(62) Croft AM. Malaria: prevention in travellers. Clin Evid 2003 Dec;10:911–30.

(63) Davis TM, Hung TY, Sim IK, Karunajeewa HA, Ilett KF. Piperaquine: a resurgent antimalarial drug. Drugs 2005;65(1):75–87.

(64) World Health Organization. Susceptibility of plasmodium falciparum to antimalarial drugs: Report on global monitoring: 1996–2004. Geneva, Switzerland: WHO; 2005.

(65) Hess KM, Goad JA, Arguin PM. Intravenous artesunate for the treatment of severe malaria. Ann Pharmacother 2010 Jul;44(7–8):1250–8.

APPENDIX I: MALARIA RISK AND RECOMMENDED CHEMOPROPHYLAXIS BY GEOGRAPHIC AREA*

*Geographic Areas as per WHO International Travel and Health

While relatively accurate in the shorter term, the risk areas, elevations, and seasonality data shown in the tables in Appendix I can change from year to year and season to season. For those countries where risk for malaria is present year-round in all areas, there is little variation that would affect malaria chemoprophylaxis recommendations from year to year. In other areas, however, risk may vary. Informative websites to keep travel health practitioners abreast of changes include the Public Health Agency of Canada's Travel Health website (www.travelhealth.gc.ca), the World Health Organization's *International Travel and Health* report (www.who.int/ith/en) and the Centers for Disease Control and Prevention *Yellow Book* (1).

For certain countries, CATMAT now includes a duration-of-exposure component in its recommendations, expressed in the format: "Chloroquine for stays > 2 weeks; Chloroquine or PPM [personal protective measures] alone for stays of ≤ 2 weeks." The intent is to allow the travel health practitioner to be more flexible for those countries where malaria risk is particularly low. That is to say, practitioners may consider recommending PPM alone for stays equal to or shorter than the identified time period, but CATMAT continues to recommend chemoprophylaxis along with PPM for all longer stays. When no chemoprophylaxis has been used, urgent medical consultation should be sought in the event of a fever. The rationale for this decision is outlined in Chapter 2.

TABLE I.1: Malaria risk and recommended chemoprophylaxis by geographic area
Please see the CATMAT website (www.phac-aspc.gc.ca/tmp-pmv/catmat-ccmtmv/index-eng.php) for updates to the information on malaria risk and recommended chemoprophylaxis by geographic area.

COUNTRY	MALARIA TRANSMISSION AREAS (2–4)	CHEMOPROPHYLAXIS RECOMMENDED BY CATMAT* (2–9)	SEASON (3;4)	*PLASMODIUM FALCIPARUM* (2–4) %
A				
Afghanistan	All areas at elevations < 2000 m.	Atovaquone-proguanil, doxycycline or mefloquine.	May–Nov	10–20
Albania	No malaria transmission.	None.	n/a	n/a
Algeria	No malaria transmission.	None.	n/a	n/a
American Samoa	No malaria transmission.	None.	n/a	n/a
Andorra	No malaria transmission.	None.	n/a	n/a
Angola	All areas.	Atovaquone-proguanil, doxycycline or mefloquine.	Year-round	90
Anguilla (UK)	No malaria transmission.	None.	n/a	n/a
Antigua and Barbuda	No malaria transmission.	None.	n/a	n/a
Argentina	No malaria transmission in urban areas, Iguassu Falls, or provinces not listed below.	None.	n/a	n/a
	Rare in Misiones province along the border with Paraguay.	None; use PPM.	Oct–May	0
	Rural areas of northern Jujuy and Salta Province (along Bolivian border).	Chloroquine for stays > 2 weeks; *chloroquine or PPM alone for stays* of ≤ 2 weeks.		
Armenia	No malaria transmission.	None.	n/a	n/a
Aruba (NL)	No malaria transmission.	None.	n/a	n/a
Australia	No malaria transmission.	None.	n/a	n/a
Austria	No malaria transmission.	None.	n/a	n/a
Azerbaijan	Areas at elevations < 1500 m in the rural lowlands between the Kura and Arax rivers.	Use PPM.	Jun–Oct	0
B				
Bahamas	No malaria transmission.	None.	n/a	n/a
Bahrain	No malaria transmission.	None.	n/a	n/a

COUNTRY	MALARIA TRANSMISSION AREAS (2–4)	CHEMOPROPHYLAXIS RECOMMENDED BY CATMAT* (2–9)	SEASON (3;4)	*PLASMODIUM FALCIPARUM* (2–4) %
Bangladesh	No malaria transmission in the city of Dhaka.	None.	n/a	n/a
	Little or no risk in areas of the country not described below. Transmission occurs only in rural areas in 13 of 64 districts. The risk is high in Chittagong Hill Tract districts (Bandarban, Rangamati and Khagrachari), Chittagong district and Cox Bazaar district. Low risk exists in the districts of Hobigonj, Kurigram, Moulvibazar, Mymensingh, Netrakona, Sherpur, Sunamgonj and Sylhet. Most parts of the country, including Daka City, have no malaria.	PPM Atovaquone-proguanil, doxycycline or mefloquine.	Year-round	> 50
Barbados	No malaria transmission.	None.	n/a	n/a
Belarus	No malaria transmission.	None.	n/a	n/a
Belgium	No malaria transmission.	None.	n/a	n/a
Belize	No malaria transmission in Belize City and islands frequented by tourists.	None.	n/a	n/a
	Low risk in Belize, Corozal, and Orange Walk Districts.	None; use PPM.	Year-round	0–5
	Moderate risk in Cayo, Stann Creek, and Toledo Districts.	Chloroquine.		
Benin	All areas.	Atovaquone-proguanil, doxycycline or mefloquine.	Year-round	85
Bermuda (UK)	No malaria transmission.	None.	n/a	n/a
Bhutan	Areas at elevations < 1700 m in the southern districts along the border with India: Geylegphug, Samdrup Jongkhar, Samtse (Samchi), Sarpang, Tsirang (Chirang), and Zhemgang (Shemgang).	Atovaquone-proguanil, doxycycline or mefloquine.	Year-round	60

COUNTRY	MALARIA TRANSMISSION AREAS (2–4)	CHEMOPROPHYLAXIS RECOMMENDED BY CATMAT* (2–9)	SEASON (3;4)	*PLASMODIUM FALCIPARUM* (2–4) %
Bolivia (Plurinational State of)	No malaria transmission in areas at elevations > 2500m, including the city of La Paz.	None.	n/a	n/a
	All areas at elevations < 2500 m. The risk is predominantly due to *P. vivax*, with exceptions listed below.	Atovaquone-proguanil, chloroquine, doxycycline or mefloquine.	Year-round	7
	Transmission of *P. falciparum* malaria occurs in the northern departments of Beni and Pando (especially in the localities—of Guayaramerín and Riberalta-, and in Santa Cruz.	Atovaquone-proguanil,doxycycline or mefloquine.		
Bosnia and Herzegovina	No malaria transmission.	None.	n/a	n/a
Botswana	No malaria transmission in the cities of Francistown or Gaborone or in other areas not listed below.	None.	n/a	n/a
	Northern parts of the country: Bobirwa, Boteti, Chobe, Ngamiland, Okavango, Tutume districts/sub-districts. None in North East district.	Atovaquone-proguanil, doxycycline or mefloquine.	Predominantly Nov–Jun	90
Brazil	Little to no malaria transmission at Iguazu Falls; in the Pantanal region; in the cities of Brasília, Recife, Rio de Janeiro, São Paulo, and Salvador; or in other areas not listed below.	None; use PPM.	Year-round	15
	Areas at elevations < 900 m in most forested areas of the states of Acre, Amapá, Amazonas, Rondônia, Roraima and Tocantins (western part) and parts of states of Maranhão (western part), Mato Grosso (northern part), Pará (except Belém City) and Tocantins (western part). Transmission also occurs in some peripheral urban areas of - Boa Vista, Cruziero do Sul, Macapá, Manaus, Maraba, Pôrto Velho, Rio Branco, and Santarém.	Atovaquone-proguanil, doxycycline or mefloquine.		
British Virgin Islands (UK)	No malaria transmission.	None.	n/a	n/a

COUNTRY	MALARIA TRANSMISSION AREAS (2–4)	CHEMOPROPHYLAXIS RECOMMENDED BY CATMAT* (2–9)	SEASON (3;4)	*PLASMODIUM FALCIPARUM* (2–4) %
Brunei Darussalam	Human infection with *P. knowlesi* reported.	None; use PPM.	n/a	n/a
Bulgaria	No malaria transmission.	None.	n/a	n/a
Burkina Faso	All areas.	Atovaquone-proguanil, doxycycline or mefloquine.	Year-round	80
Burma (Myanmar)	No malaria transmission at elevations > 1000 m or in the cities of Rangoon (Yangon) and Mandalay.	None.	n/a	n/a
	Areas at elevations < 1000 m, except Rangoon (Yangoon) and Mandalay. Risk of transmission is highest in remote forested areas.	Atovaquone-proguanil, doxycycline or mefloquine.	Year-round	90
	Resistance to mefloquine reported in the provinces of Bago, Kachin, Kayah, Kayin, Shan and Tanintharyi.	Atovaquone-proguanil or doxycycline.		
Burundi	All areas.	Atovaquone-proguanil, doxycycline or mefloquine.	Year-round	86
C				
Cambodia	No malaria transmission in the city of Phnom Penh and the area around Lake Tonlé Sap (Siem Reap). Negligible transmission in the tourist area of Angkor Wat and Siem Reap.	None; use PPM.	Year-round	86
	Mefloquine resistance is reported in the western provinces of Banteay Meanchey, Battambang, Koh Kong, Odder Meanchey, Pailin, Kampot, PreahVihear, Pursat, and Siemreap bordering Thailand.	Doxycycline or atovaquone-proguanil.		
	All other areas.	Atovaquone-proguanil, doxycycline or mefloquine.		
Cameroon	All areas.	Atovaquone-proguanil, doxycycline or mefloquine.	Year-round	85
Canada	No malaria transmission.	None.	n/a	n/a
Cape Verde	Limited cases in São Tiago (Santiago) Island.	None; use PPM.	Aug–Nov	Primarily *P. falciparum*
Cayman Islands (UK)	No malaria transmission.	None.	n/a	n/a

COUNTRY	MALARIA TRANSMISSION AREAS (2–4)	CHEMOPROPHYLAXIS RECOMMENDED BY CATMAT* (2–9)	SEASON (3;4)	*PLASMODIUM FALCIPARUM* (2–4) %
Central African Republic	All areas.	Atovaquone-proguanil, doxycycline or mefloquine.	Year-round	85
Chad	All areas.	Atovaquone-proguanil, doxycycline or mefloquine.	Year-round	85
Chile	No malaria transmission.	None.	n/a	n/a
China	No malaria transmission in urban areas or northern China.	None.	n/a	n/a
	Limited transmission of *P. vivax* malaria occurs in the southern provinces and some central provinces, including Anhui, Ghuizhou, Henan, Hubei, and Jiangsu. The risk of contracting malaria in central China is small.	For travellers visiting major cities and making daytime excursions into the countryside or on Yangtze river cruises: none; use PPM. For those travelling extensively in or through rural southern China: chloroquine.	Year-round	9
	Transmission of *P.falciparum* malaria occurs in the province of Yunnan and, to a lesser extent, in the province of Hainan. *P. falciparum* resistance to chloroquine and sulfadoxine-pyrimethamine reported.	Atovaquone-proguanil, doxycycline or mefloquine.		
	P. falciparum resistance to mefloquine reported in the province of Yunnan in the areas bordering Burma (Myanmar).	Atovaquone-proguanil or doxycycline.		
Colombia	No malaria transmission in urban areas, including Bogotá and vicinity and Cartagena; at elevations > 1600 m; or on the islands of San Andrés and Providencia in the Caribbean Sea.	None.	n/a	n/a
	Rural or jungle areas at elevations < 1600m.	Atovaquone-proguanil, doxycycline or mefloquine.	Year-round	35–40
Comoros	All areas.	Atovaquone-proguanil, doxycycline or mefloquine.	Year-round	Primarily *P. falciparum*
Congo	All areas.	Atovaquone-proguanil, doxycycline or mefloquine.	Year-round	90

COUNTRY	MALARIA TRANSMISSION AREAS (2–4)	CHEMOPROPHYLAXIS RECOMMENDED BY CATMAT* (2–9)	SEASON (3;4)	*PLASMODIUM FALCIPARUM* (2–4) %
Congo, Democratic Republic of the (formerly Zaïre)	All areas.	Atovaquone-proguanil, doxycycline or mefloquine.	Year-round	90
Cook Islands (NZ)	No malaria transmission.	None.	n/a	n/a
Costa Rica	Little to no risk of malaria transmission in most of the country, with exception noted below. No malaria transmission in the city of Limón (Puerto Limón).	None; use PPM.	Year-round	Predominantly *P vivax*
	Limón province (except the city of Limón), mostly in the canton of Matina.	Chloroquine.		
Côte D'Ivoire (Ivory Coast)	All areas.	Atovaquone-proguanil, doxycycline or mefloquine.	Year-round	85
Croatia	No malaria transmission.	None.	n/a	n/a
Cuba	No malaria transmission.	None.	n/a	n/a
Curaçao (NL)	No malaria transmission.	None.	n/a	n/a
Cyprus	No malaria transmission.	None.	n/a	n/a
CzechRepublic	No malaria transmission.	None.	n/a	n/a
D				
Denmark	No malaria transmission.	None.	n/a	n/a
Djibouti	All areas.	Atovaquone-proguanil, doxycycline or mefloquine.	Year-round	90
Dominica	No malaria transmission.	None.	n/a	n/a
Dominican Republic	Little to no malaria transmission in the resort areas of Romana and Samaná and the cities of Santo Domingo, Santiago, and Puerto Plata.	None; use PPM.	Year-round	100
	Some transmission has previously occurred in La Altagracia province, including resort areas such as Punta Cana.	In the absence of any further outbreaks in La Altagracia, PPM alone for resorts in that province. Seek medical attention if a fever develops.		
	Rural areas, with the highest risk in the provinces of Dajabón, Elias Piña, and San Juan bordering Haiti.	Chloroquine.		
E				

COUNTRY	MALARIA TRANSMISSION AREAS (2–4)	CHEMOPROPHYLAXIS RECOMMENDED BY CATMAT* (2–9)	SEASON (3;4)	*PLASMODIUM FALCIPARUM* (2–4) %
Ecuador	No malaria transmission at elevations > 1500 m, including Cuenca, Quito, and other cities and villages in the Andean highlands; in the city of Guayaquil or on the Galápagos Islands.	None.	n/a	n/a
	All other areas at elevations < 1500 m. Higher risk along the coast, in the north.	Atovaquone-proguanil, doxycycline or mefloquine.	Year-round	10
Egypt	No malaria transmission.	None.	n/a	n/a
El Salvador	Rare cases along the Guatemalan border.	None; use PPM.	Year-round	< 1
Equatorial Guinea	All areas.	Atovaquone-proguanil, doxycycline or mefloquine.	Year-round	85
Eritrea	No malaria transmission at elevations > 2200 m, including the city of Asmara.	None.	n/a	n/a
	All areas at elevations < 2200 m.	Atovaquone-proguanil, doxycycline or mefloquine.	Year-round	85
Estonia	No malaria transmission.	None.	n/a	n/a
Ethiopia	No malaria transmission at elevations > 2200 m, including Addis Ababa.	None.	n/a	n/a
	All areas at elevations < 2200 m, including Axum (2139 m),Dire Dawa (1262 m), Harar (1848 m), and Nazret (1725 m).	Atovaquone-proguanil, doxycycline or mefloquine.	Year-round	60–70
F				
Fiji	No malaria transmission.	None.	n/a	n/a
Finland	No malaria transmission.	None.	n/a	n/a
France	No malaria transmission.	None.	n/a	n/a
French Guiana	No malaria transmission in the city of Cayenne or on Devil's Island (*Île du Diable*).	None.	n/a	n/a
	All other areas. Risk along the coast is low but increases towards the interior. High risk of transmission in municipalities bordering Brazil and Suriname.	PPM can be considered for coastal states. Atovaquone-proguanil, doxycycline or mefloquine.	Year-round	< 50
French Polynesia	No malaria transmission.	None.	n/a	n/a
G				

COUNTRY	MALARIA TRANSMISSION AREAS (2–4)	CHEMOPROPHYLAXIS RECOMMENDED BY CATMAT* (2–9)	SEASON (3;4)	*PLASMODIUM FALCIPARUM* (2–4) %
Gabon	All areas.	Atovaquone-proguanil, doxycycline or mefloquine.	Year-round	90
Gambia	All areas.	Atovaquone-proguanil, doxycycline or mefloquine.	Year-round	> 85
Georgia	Limited risk in the eastern areas bordering Azerbaijan. The city of Tbilisi is risk-free.	None; use PPM.	June–Oct	0
Germany	No malaria transmission.	None.	n/a	n/a
Ghana	All areas.	Atovaquone-proguanil, doxycycline or mefloquine.	Year-round	> 90
Gibraltar (UK)	No malaria transmission.	None.	n/a	n/a
Greece	No malaria transmission.	None.	n/a	n/a
Greenland (Denmark)	No malaria transmission.	None.	n/a	n/a
Grenada	No malaria transmission.	None.	n/a	n/a
Guadeloupe (FR)	No malaria transmission.	None.	n/a	n/a
Guam (US)	No malaria transmission.	None.	n/a	n/a
Guatemala	No malaria transmission in urban areas or areas at elevations > 1500 m none in Guatemala City, Antigua, and Lake Atitlán.	None.	n/a	n/a
	Rural areas at elevations < 1500 m.	Chloroquine.	Year-round	3
Guinea	All areas.	Atovaquone-proguanil, doxycycline or mefloquine.	Year-round	85
Guinea-Bissau	All areas.	Atovaquone-proguanil, doxycycline or mefloquine.	Year-round	85
Guyana	All areas at elevations < 900 m. Risk is high in all parts of the interior. Sporadic cases have been reported from the densely populated coastal belt. Rare cases in the cities of Amsterdam and Georgetown.	Georgetown and New Amsterdam: PPM. Coastal areas between Vreed en Hoop and New Amsterdam: PPM may be considered. Atovaquone-proguanil, doxycycline or mefloquine.	Year-round	50
H				
Haiti	All areas.	Chloroquine.	Year-round	99
Holy See (Vatican City)	No malaria transmission.	None.	n/a	n/a

COUNTRY	MALARIA TRANSMISSION AREAS (2–4)	CHEMOPROPHYLAXIS RECOMMENDED BY CATMAT* (2–9)	SEASON (3;4)	*PLASMODIUM FALCIPARUM* (2–4) %
Honduras	No malaria transmission—in the cities of Tegucigalpa and San Pedro Sula. Risk is low in higher mountainous areas in the west where PPM can be considered.	None.	n/a	n/a
	Risk is high in departments of Gracias a Dios and Islas de la Bahia (Bay Islands), and moderate in Atlantida, Colon, Olancho, and Yoro.	Chloroquine.	Year-round	7
Hong Kong (China)	No malaria transmission.	None.	n/a	n/a
Hungary	No malaria transmission.	None.	n/a	n/a
I				
Iceland	No malaria transmission.	None.	n/a	n/a
India	No malaria transmission at elevations > 2000 m in parts of the states of Himachal Pradesh, Jammu and Kashmir, and Sikkim.	None.	n/a	n/a
	All other areas - including most urban areas such as Bombay (Mumbai) and Delhi. Risk is lower in most of the southernmost regions of India. Risk is low in central urban areas of Agra and Bangalore.	Atovaquone-proguanil, doxycycline or mefloquine. PPM alone can be considered for stays of <1 week in central urban areas of Delhi, Agra and Bangalore.	Year-round	> 40

COUNTRY	MALARIA TRANSMISSION AREAS (2–4)	CHEMOPROPHYLAXIS RECOMMENDED BY CATMAT* (2–9)	SEASON (3;4)	*PLASMODIUM FALCIPARUM* (2–4) %
Indonesia	No malaria transmission in Jakarta Municipality, major metropolitan areas including Ubud, or major tourist resorts in Bali and Java.	None.	n/a	n/a
	In general, risk is higher in more easterly regions of Indonesia: in particular, the provinces of East Nusa Tenggara, Maluku, North Maluku, Papua (Irian Jaya) and West Papua. There is also risk on LombokIsland and the rural areas of KalimantanIsland (Borneo). There is a low risk of transmission in rural Java and Bali and sporadic cases reported among travellers to rural areas of Bali. In the other parts of the country, there is malaria risk in some districts.	Atovaquone-proguanil, doxycycline or mefloquine.	Year-round	66
Iran, Islamic Republic of	Rural areas in the provinces of Hormozgan, Kerman (tropical part only), and Sistan-Baluchestan (southern part only).	Atovaquone-proguanil, doxycycline, or mefloquine.	Mar–Nov	12
	All other areas.	None.	n/a	n/a
Iraq	No locally acquired cases reported since 2009.	None.	n/a	n/a
Ireland	No malaria transmission.	None.	n/a	n/a
Israel	No malaria transmission.	None.	n/a	n/a
Italy	No malaria transmission.	None.	n/a	n/a
J				
Jamaica	No malaria transmission.	None.	n/a	n/a
Japan	No malaria transmission.	None.	n/a	n/a
Jordan	No malaria transmission.	None.	n/a	n/a

COUNTRY	MALARIA TRANSMISSION AREAS (2–4)	CHEMOPROPHYLAXIS RECOMMENDED BY CATMAT* (2–9)	SEASON (3;4)	*PLASMODIUM FALCIPARUM* (2–4) %
K				
Kazakhstan	No malaria transmission.	None.	n/a	n/a
Kenya	Little to no malaria transmission at elevations > 2500 m or in the city of Nairobi.	None; use PPM.	Year-round	85
	All areas at elevations < 2500 m, except the city of Nairobi.	Atovaquone-proguanil, doxycycline or mefloquine.		
Kiribati	No malaria transmission.	None.	n/a	n/a
Korea, Democratic People's Republic of (North Korea)	Limited risk in some southern areas.	None; use PPM.	Presumed to be March to Dec	Presumed 0
Korea, Republic of (South Korea)	Limited risk in the demilitarized zone (DMZ); rural areas in the northern parts of the provinces of Gyeonggi-do (Kyonggi) and Gangwon-do (Kangwon-do); and the northern part of the city of Incheon.	None; use PPM.	Mar–Dec	0
Kosovo	No malaria transmission.	None.	n/a	n/a
Kuwait	No malaria transmission.	None.	n/a	n/a
Kyrgyzstan	No risk of transmission.	None.	Jun–Oct	n/a
L				
Lao People's Democratic Republic (Laos)	No malaria transmission in the city of Vientiane.	None.	n/a	n/a
	Mefloquine resistance has been reported along the Loas-Burma (Myanmar) border in the provinces of Bokeo and Louang Namtha and along the Laos-Thailand boarder in the provinces of Champasak and Saravan.	Atovaquone-proguanil or doxycycline.	Year-round	95
	All other areas.	Atovaquone-proguanil, doxycycline or mefloquine.		
Latvia	No malaria transmission.	None.	n/a	n/a
Lebanon	No malaria transmission.	None.	n/a	n/a
Lesotho	No malaria transmission.	None.	n/a	n/a

COUNTRY	MALARIA TRANSMISSION AREAS (2–4)	CHEMOPROPHYLAXIS RECOMMENDED BY CATMAT* (2–9)	SEASON (3;4)	*PLASMODIUM FALCIPARUM* (2–4) %
Liberia	All areas.	Atovaquone-proguanil, doxycycline or mefloquine.	Year-round	85
Libyan Arab Jamahiriya (Libya)	No malaria transmission.	None.	n/a	n/a
Liechtenstein	No malaria transmission.	None.	n/a	n/a
Lithuania	No malaria transmission.	None.	n/a	n/a
Luxembourg	No malaria transmission.	None.	n/a	n/a
M				
Macao (China)	No malaria transmission.	None.	n/a	n/a
Macedonia	No malaria transmission.	None.	n/a	n/a
Madagascar	All areas. Risk is highest in coastal areas.	Atovaquone-proguanil, doxycycline or mefloquine.	Year-round	85
Malawi	All areas.	Atovaquone-proguanil, doxycycline or mefloquine.	Year-round	90
Malaysia	No malaria transmission in urban and coastal areas.	None.	n/a	n/a
	Transmission in Peninsular Malaysiais limited to areas in the rural interior. Risk in east Malaysian Borneo limited to deep hinterland in the states of Sabah and Sarawak. *P. knowlesi* present in both Malaysian Borneo and peninsular Malaysia and reported to cause 28% of cases in Sarawak.	Atovaquone-proguanil, doxycycline or mefloquine.	Year-round	40
Maldives	No malaria transmission.	None.	n/a	n/a
Mali	All areas.	Atovaquone-proguanil, doxycycline or mefloquine.	Year-round	85
Malta	No malaria transmission.	None.	n/a	n/a
Marshall Islands	No malaria transmission.	None.	n/a	n/a
Martinique (FR)	No malaria transmission.	None.	n/a	n/a

COUNTRY	MALARIA TRANSMISSION AREAS (2–4)	CHEMOPROPHYLAXIS RECOMMENDED BY CATMAT* (2–9)	SEASON (3;4)	*PLASMODIUM FALCIPARUM* (2–4) %
Mauritania	No malaria transmission in the northern provinces of Dakhlet-Nouadhibou, and Tiris-Zemmour.	None.	n/a	n/a
	Present in southern provinces including Nouakchott.	Atovaquone-proguanil, doxycycline or mefloquine.	Year-round, except July–Oct in Adrar and Inchiri	85
Mauritius	No malaria transmission.	None.	n/a	n/a
Mayotte (FR)	All areas.	Atovaquone-proguanil, doxycycline or mefloquine.	Year-round	40–50
Mexico	Minimal or no malaria transmission in major resort areas on the coasts, including the city of Acapulco or along the Mayan Riviera, including the cities of Cancún, Cozumel, and Playa del Carmen. None along the border with the United States. Little malaria transmission in the states of Jalisco, Quintana Roo, Sonora and Tabasco.	None. Use PPM.	Year-round	0
	Moderate risk in parts of the states of Chiapas and Oaxaca.	Chloroquine.		
	Low risk in rural areas of the states of Nayarit, Sinaloa, Chihuahua, and Durango.	Chloroquine for stays > 1 week; chloroquine or PPM alone for stays of ≤ 1 week.		
Micronesia, Federated States of	No malaria transmission.	None.	n/a	n/a
Moldova, Republic of	No malaria transmission.	None.	n/a	n/a
Monaco	No malaria transmission.	None.	n/a	n/a
Mongolia	No malaria transmission.	None.	n/a	n/a
Montenegro	No malaria transmission.	None.	n/a	n/a
Montserrat (UK)	No malaria transmission.	None.	n/a	n/a

COUNTRY	MALARIA TRANSMISSION AREAS (2–4)	CHEMOPROPHYLAXIS RECOMMENDED BY CATMAT* (2–9)	SEASON (3;4)	*PLASMODIUM FALCIPARUM* (2–4) %
Morocco	No malaria transmission.	None.	n/a	n/a
Mozambique	All areas.	Atovaquone-proguanil, doxycycline or mefloquine.	Year-round	90
N				
Namibia	No malaria transmission in southern two-thirds of the country, including the city of Windhoek.	None.	n/a	n/a
	The regions of Caprivi; Kunene, including areas along the Kunene River and Etosha National Park; and Kavango.	Atovaquone-proguanil, doxycycline or mefloquine.	Year-round	90
	The regions of Ohangwena, Omaheke, Omusati, Oshana, Oshikoto, and Otjozondjupa.		Nov–June	
Nauru	No malaria transmission.	None.	n/a	n/a
Nepal	No malaria transmission at elevations > 1200 m, including the city of Kathmandu.	None.	n/a	n/a
	All areas at elevations < 1200 m. A malaria transmission area commonly visited by tourists is the Terai region in southern Nepal, which includes Chitwan National Park.	Atovaquone-proguanil, doxycycline or mefloquine.	Year-round	15
Netherlands	No malaria transmission.	None.	n/a	n/a
New Caledonia (FR)	No malaria transmission.	None.	n/a	n/a
New Zealand	No malaria transmission.	None.	n/a	n/a
Nicaragua	Little to no malaria transmission in departments not listed below.	None; use PPM.	Year-round	10
	Departments of Chinandega, Léon, Managua, and Matagalpa and the autonomous regions of Atlántico Norte (RAAN) and Atlántico Sur (RAAS).	Chloroquine.		
Niger	All areas.	Atovaquone-proguanil, doxycycline or mefloquine.	Year-round	85

COUNTRY	MALARIA TRANSMISSION AREAS (2–4)	CHEMOPROPHYLAXIS RECOMMENDED BY CATMAT* (2–9)	SEASON (3;4)	*PLASMODIUM FALCIPARUM* (2–4) %
Nigeria	All areas.	Atovaquone-proguanil, doxycycline or mefloquine.	Year-round	85
Niue (NZ)	No malaria transmission.	None.	n/a	n/a
Northern Mariana Islands (US)	No malaria transmission.	None.	n/a	n/a
Norway	No malaria transmission.	None.	n/a	n/a
O				
Oman	No malaria transmission.	None.	n/a	n/a
P				
Pakistan	All areas at elevations < 2000 m. Risk is due to both *P. vivax* and *P. falciparum*. Risk lower in the north, including Islamabad, especially during winter months because of cool temperatures.	Atovaquone-proguanil, doxycycline or mefloquine.	Year-round	30
Palau	No malaria transmission.	None.	n/a	n/a
Panama	Little to no malaria transmission in Panama City, the Canal zone, or regions not listed below.	None; use PPM.	Year-round	1
	Provinces and indigenous territories (comarcas) along the Caribbean coast and the borders with Costa Rica and Colombia: Bocas del Toro, Chiriquí, Colón, Ngöbe-Buglé, Panamá, and Veraguas.	Chloroquine for stays > 1 week; *chloroquine or PPM alone for stays of <1 week.*		
	Most transmission in provinces east of the Panama Canal toward the border with Colombia.*P. falciparum* resistance to chloroquine has been reported in Darién and Kuna Yala (San Blas).	Atovaquone-proguanil, doxycycline or mefloquine.		
Papua New Guinea	All areas at elevations < 1800 m.	Atovaquone-proguanil, doxycycline or mefloquine.	Year-round	65—80
Paraguay	Little to no malaria transmission in departments not listed below.	None; use PPM.	Oct–May	5
	Departments of Alto Paraná and Caaguazú.	Chloroquine for stays > 2 weeks; *chloroquine or PPM alone for stays* of ≤2 weeks.		

COUNTRY	MALARIA TRANSMISSION AREAS (2–4)	CHEMOPROPHYLAXIS RECOMMENDED BY CATMAT* (2–9)	SEASON (3;4)	*PLASMODIUM FALCIPARUM* (2–4) %
Peru	No malaria risk at elevations > 2000 m, including the highland tourist areas (Machu Picchu, Lake Titicaca, and the cities of Arequipa, Cuzco, Puno) or in the cities of Limaand south of Lima including Moquegua, Nazca, and Tacna.	None.	n/a	n/a
	All areas < 2000 m (except cities listed above). This includes the cities of Puerto Maldonado and Iquitos. Most *P.falciparum* cases occur in the region of Loreto.	Atovaquone-proguanil, doxycycline or mefloquine.	Year-round	15
Philippines	Little to no malaria transmission in urban areas or on islands not listed below.	None; use PPM.	Year-round	70–80
	Rural areas at elevations < 600 m on islands of Basilu, Luzon, Mindanao, Mindoro, Palawan, Sulu (Jolo) and Tawi-Tawi.	Atovaquone-proguanil, doxycycline or mefloquine.		
PitcairnIslands (UK)	No malaria transmission.	None.	n/a	n/a
Poland	No malaria transmission.	None.	n/a	n/a
Portugal	No malaria transmission.	None.	n/a	n/a
Puerto Rico (US)	No malaria transmission.	None.	n/a	n/a
Q				
Qatar	No malaria transmission.	None.	n/a	n/a
R				
Réunion (FR)	No malaria transmission.	None.	n/a	n/a
Romania	No malaria transmission.	None.	n/a	n/a
Russian Federation (Russia)	No malaria transmission.	None.	n/a	n/a
Rwanda	All areas.	Atovaquone-proguanil, doxycycline or mefloquine.	Year-round	90
S				
Saint-Barthélemy (FR)	No malaria transmission.	None.	n/a	n/a
Saint Helena (UK)	No malaria transmission.	None.	n/a	n/a
Saint Kitts and Nevis	No malaria transmission.	None.	n/a	n/a

COUNTRY	MALARIA TRANSMISSION AREAS (2–4)	CHEMOPROPHYLAXIS RECOMMENDED BY CATMAT* (2–9)	SEASON (3;4)	*PLASMODIUM FALCIPARUM* (2–4) %
Saint Lucia	No malaria transmission.	None.	n/a	n/a
Saint Martin (FR)	No malaria transmission.	None.	n/a	n/a
Saint Pierre and Miquelon (FR)	No malaria transmission.	None.	n/a	n/a
Saint Vincent and the Grenadines	No malaria transmission.	None.	n/a	n/a
Samoa	No malaria transmission.	None.	n/a	n/a
San Marino	No malaria transmission.	None.	n/a	n/a
São Tomé and Príncipe	All areas.	Atovaquone-proguanil, doxycycline or mefloquine.	Year-round	85
Saudi Arabia	No malaria transmission in northern parts of the country; in the cities of Mecca, Medina, Jeddah, Riyadh, or Ta'if; or in the high altitude areas of Asir province.	None.	n/a	n/a
	Along the southern border with Yemen, except high altitude areas of Asir province.	Atovaquone-proguanil, doxycycline or mefloquine.	Year-round (but mainly Sep–Jan)	Predominantly *P. falciparum*
Senegal	All areas.	Atovaquone-proguanil, doxycycline or mefloquine.	Year-round	> 85
Serbia	No malaria transmission.	None.	n/a	n/a
Seychelles	No malaria transmission.	None.	n/a	n/a
Sierra Leone	All areas.	Atovaquone-proguanil, doxycycline or mefloquine.	Year-round	85
Singapore	No malaria transmission.	None.	n/a	n/a
Saint Maarten (NL)	No malaria transmission.	None.	n/a	n/a
Slovakia	No malaria transmission.	None.	n/a	n/a
Slovenia	No malaria transmission.	None.	n/a	n/a
Solomon Islands	No malaria transmission on a few of the outlying islets in the east and south.	None.	n/a	n/a
	All other areas.	Atovaquone-proguanil, doxycycline or mefloquine.	Year-round	60
Somalia	All areas. Risk of malaria transmission is lower and follows a seasonal pattern in the north.	Atovaquone-proguanil, doxycycline or mefloquine.	Year-round	90

COUNTRY	MALARIA TRANSMISSION AREAS (2–4)	CHEMOPROPHYLAXIS RECOMMENDED BY CATMAT* (2–9)	SEASON (3;4)	*PLASMODIUM FALCIPARUM* (2–4) %
South Africa	No malaria transmission in most of the country including the Garden Route and major cities.	None.	n/a	n/a
	Low-altitude areas in the provinces of Mpumalanga (including the Kruger National Park), Limpopo (formerly Northern), and north-eastern Kwa Zulu-Natal as far south as the Tugela River.	Atovaquone-proguanil, doxycycline or mefloquine.	Year-round (risk is highest from Oct–May)	90
South Sudan	All areas.	Atovaquone-proguanil, doxycycline or mefloquine.	Year-round	90
Spain	No malaria transmission.	None.	n/a	n/a
Sri Lanka	No malaria transmission in the districts of Colombo, Galle, Gampaha, Kalutara, Matara, and Nuwara Eliya.	None.	n/a	n/a
	All other areas.	Atovaquone-proguanil, doxycycline or mefloquine for stays > 1 week; Atovaquone-proguanil, doxycycline, or mefloquine *or PPM alone for stays of ≤ 1 week.*	Year-round	15
Sudan, Republic of	All areas. Risk of malaria transmission is highest in the southern parts of the country. Risk is lower and follows a seasonal pattern in the north. Risk along the Red Sea coast is very limited.	Atovaquone-proguanil, doxycycline or mefloquine.	Year-round (predominantly during wetter season in the north)	90
Suriname	Little to no malaria transmission in the seven districts along the Atlantic Coast, including in the city of Paramaribo.	None; use PPM.	Year-round	70
	Areas in the interior of the country. Risk of malaria transmission is highest along the eastern border with French Guiana and in gold mining areas.	Atovaquone-proguanil, doxycycline or mefloquine.		
Swaziland	Areas in the east of the country, including all of Lubombo district and the eastern halves of Hhohho, Manzini, and Shiselweni districts. Mbabane is risk-free.	Atovaquone-proguanil, doxycycline or mefloquine.	Year–round	90

COUNTRY	MALARIA TRANSMISSION AREAS (2–4)	CHEMOPROPHYLAXIS RECOMMENDED BY CATMAT* (2–9)	SEASON (3;4)	*PLASMODIUM FALCIPARUM* (2–4) %
Sweden	No malaria transmission.	None.	n/a	n/a
Switzerland	No malaria transmission.	None.	n/a	n/a
Syrian Arab Republic (Syria)	No malaria transmission.	None.	n/a	n/a
T				
Tajikistan	All areas at elevations < 2000 m, particularly in the provinces of Gorno-Badakhshan and Khatlon; the Dushanbe districts; and Ghafurov (formerly Leninabad) District.	Atovaquone-proguanil, doxycycline or mefloquine for stays > 1 week; Atovaquone-proguanil, doxycycline or mefloquine *or PPM alone for stays of ≤ 1 week.*	Jun–Oct	10
Tanzania, United Republic of	All areas at elevations < 1800 m.	Atovaquone-proguanil, doxycycline or mefloquine.	Year-round	> 85
Thailand	No malaria transmission in cities, including Bangkok, Chiang Mai, Chiang Rai, Pattaya, Koh Samui, Phang Nga, Town of Phuket and Koh Phangan, or in major tourist resorts.	None.	n/a	n/a
	Rural forested areas near the borders with Cambodia, Burma (Myanmar) and Laos. Rural forested areas in districts of Phang Nga and Phuket. Some islands have malaria risk. Mefloquine resistance reported.	Atovaquone-proguanil or doxycycline.	Year-round	50–75
Timor-Leste (East Timor)	All areas.	Atovaquone-proguanil, doxycycline or mefloquine.	Year-round	50
Togo	All areas.	Atovaquone-proguanil, doxycycline or mefloquine.	Year-round	85
Tokelau (NZ)	No malaria transmission.	None.	n/a	n/a
Tonga	No malaria transmission.	None.	n/a	n/a
Trinidad and Tobago	No malaria transmission.	None.	n/a	n/a
Tunisia	No malaria transmission.	None.	n/a	n/a

COUNTRY	MALARIA TRANSMISSION AREAS (2–4)	CHEMOPROPHYLAXIS RECOMMENDED BY CATMAT* (2–9)	SEASON (3;4)	*PLASMODIUM FALCIPARUM* (2–4) %
Turkey	No malaria transmission in western and northeastern parts of the country, including the common tourist destinations of the cities of Izmir and Istanbul and the Cappadocia region.	None.	n/a	n/a
	Limited malaria transmission in the southeastern part of the country.	Chloroquine for stays > 2 weeks; *chloroquine or PPM* alone for stays of ≤2 weeks.	May–Oct	Sporadically
Turkmenistan	No malaria transmission.	None.	n/a	n/a
Turks and Caicos Islands (UK)	No malaria transmission.	None.	n/a	n/a
Tuvalu	No malaria transmission.	None.	n/a	n/a
U				
Uganda	All areas.	Atovaquone-proguanil, doxycycline or mefloquine.	Year-round	> 85
Ukraine	No malaria transmission.	None.	n/a	n/a
United Arab Emirates	No malaria transmission.	None.	n/a	n/a
United Kingdom	No malaria transmission.	None.	n/a	n/a
United States	No malaria transmission.	None.	n/a	n/a
US Virgin Islands	No malaria transmission.	None.	n/a	n/a
Uruguay	No malaria transmission.	None.	n/a	n/a
Uzbekistan	No malaria transmission.	None.	June–Oct	n/a

COUNTRY	MALARIA TRANSMISSION AREAS (2–4)	CHEMOPROPHYLAXIS RECOMMENDED BY CATMAT* (2–9)	SEASON (3;4)	*PLASMODIUM FALCIPARUM* (2–4) %
V				
Vanuatu	All areas.	Atovaquone-proguanil, doxycycline or mefloquine.	Year-round	60
Venezuela, Bolivarian Republic of	No malaria transmission in most urban areas or on Margarita Island.	None.	n/a	n/a
	Predominantly *P. vivax* malaria transmission occurs in rural areas in the states of Anzoátegui, Apure, Delta Amacuro, Monagas, Sucre, and Zulia.	Atovaquone-proguanil,chloroquine, doxycycline or mefloquine.	Year-round	17
	Transmission of *P. falciparum* malaria mainly occurs in the states of Amazonas and Bolívar (including Angel Falls).	Atovaquone-proguanil, doxycycline or mefloquine.		
Vietnam	None in urban areas, Red River Delta and coastal plain of central Vietnam. Rare cases in Mekong Delta. The common coastal itinerary between Ho Chi Minh City and Hanoi with overnights mainly in urban areas does not typically require chemoprophylaxis.	Use PPM.	Year-round	50–90
	Rural areas, excluding those listed above. Risk in the town of Sapa in the hills to the northwest of Hanoi is lower; PPM can be considered for stays <1 week, particularly in the winter months.	Atovaquone-proguanil, doxycycline or mefloquine.		
	Mefloquine resistance reported in the southern part of the country in the provinces of Dac Lac, Gia Lai, Khanh Hoa (western part), Kon Tum, Lam Dong, Ninh Thuan (western part), Song Be, and Tay Ninh.	Atovaquone-proguanil or doxycycline.		
W				
West Bank and Gaza Strip	No malaria transmission.	None.	n/a	n/a
Western Sahara	Malaria transmission very rare.	None; use PPM.	Unknown	Unknown

COUNTRY	MALARIA TRANSMISSION AREAS (2–4)	CHEMOPROPHYLAXIS RECOMMENDED BY CATMAT* (2–9)	SEASON (3;4)	*PLASMODIUM FALCIPARUM* (2–4) %
Y				
Yemen	No malaria transmission at elevations > 2000 m, including in the city of Sana'a.	None.	n/a	n/a
	Very limited transmission on Socotra Island.	None; use PPM.	Year-round but main risk Sept–Feb	95
	All areas at elevations < 2000 m.	Atovaquone-proguanil, doxycycline or mefloquine.		
Z				
Zambia	All areas.	Atovaquone-proguanil, doxycycline or mefloquine.	Year-round	> 90
Zimbabwe	Negligible malaria transmission in Harare and Bulawayo.	None; use PPM.	Nov–Jun	> 90
	All other areas < 1200 m.	Atovaquone-proguanil, doxycycline or mefloquine.		
	Malaria transmission occurs year-round in the Zambezi Valley, including at Victoria Falls.		Year-round	

ABBREVIATIONS: FR, France; n/a, not applicable; NL, Netherlands; NZ, New Zealand; PPM, personal protective measures; UK, United Kingdom; US, United States.

NOTE: PPM are outlined in Chapter 3: "Malaria Education for Travellers" and the *CATMAT Statement on Personal Protective Measures to Prevent Arthropod Bites*.

* Chemoprophylaxis is recommended only in the risk areas identified during the transmission season identified. Chemoprophylaxis should always be used in conjunction with PPM.

REFERENCE LIST

(1) Centers for Disease Control and Prevention. CDC health information for international travel 2012. Atlanta: US Department of Health and Human Services, Public Health Service; 2012.

(2) Centers for Disease Control and Prevention. Yellow Fever & Malaria Information, by Country. Yellow Book 2012: CDC Health Information for International Travel. Available from: http://wwwnc.cdc.gov/travel/page/yellowbook-2012-home.htm. 2011.

(3) World Malaria Risk Chart. International Association for Medical Assistance to Travellers 2011

(4) World Health Organization. ITH 2011 Country List. International travel and health. Available from: www.who.int/ith/chapters/en. 2011.

(5) Deutsche Gesellschaft für Tropenmedizin und Internationale Gesundheit. Empfehlungen zur Malariavorbeugung. 2011. [Cited 2011 June 12]. Available from: www.dtg.org/uploads/media/Malaria_2011.pdf.

(6) Division maladies transmissibles. Paludisme (malaria)—mise à jour 2010. 2010. [Cited 2010 November 18]. Available from: www.bag.admin.ch/themen/medizin/00682/00685/03062/index.html?lang=fr, Office fédéral de la santé publique, Confédération suisse. Bulletin OFSP.

(7) Haut Conseil de la santé publique. Recommandations sanitaires pour les voyageurs 2011 (à l'attention des professionnels de santé). 2011. [Cited 2011 June 01]. Available from: http://opac.invs.sante.fr/doc_num.php?explnum_id=7068, Institut de veille sanitaire.

(8) Institut de médecine sociale et préventive de l'Université de Zurich. Santé-voyages: Vaccinations et mesures antipaludiques. 2010. [Cited 2010 November 18]. Available from: www.bag.admin.ch/themen/medizin/00682/00685/03062/index.html?lang=fr, Office fédéral de la santé publique, Confédération suisse. Bulletin OFSP.

(9) Smittskyddsinstitutet. Malariaprofylax 2010: Rekommendationer för malariaprofylax 2010. 2010. [Cited 2010 Nov 24]. Available from: www.smittskyddsinstitutet.se/upload/Publikationer/malariaprofylax-2010.pdf.

APPENDIX II: PRE-TRAVEL CHECKLIST FOR ADVISING TRAVELLERS TO MALARIAL AREAS

The following checklist highlights points to consider when advising travellers who are planning to travel to regions with a risk of malaria transmission.

ASSESS THE RISK OF MALARIA (SEE CHAPTER 2 AND APPENDIX I)

DISTRIBUTION AND TRANSMISSION INTENSITY OF MALARIA IN DESTINATION COUNTRY(IES).

Seasonal variation in malaria transmission?

Species of malaria present/predominant in destination country(ies)?

Drug resistance documented/prevalent?

SELECT APPROPRIATE CHEMOPROPHYLAXIS RECOMMENDATIONS (CHAPTER 4)

Does the traveller have any drug allergies?

Does the traveller have any contraindications to the recommended (first-line) antimalarial agents?

If yes, select an alternative.

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?

Are there drug/drug interactions to consider?

EDUCATION ABOUT MALARIA CHEMOPROPHYLAXIS (CHAPTER 3)

Start chemoprophylaxis before travel, as directed.

Use chemoprophylaxis continuously while in malaria-endemic areas and for four weeks after leaving such areas (except for atovaquone-proguanil and primaquine, which are taken for one week after leaving such areas).

All antimalarial drugs can cause adverse effects; most minor side effects abate even with continued use of a drug. Seek medical advice if adverse effects persist but continue with the chemoprophylaxis.

If *serious* adverse effects occur, seek medical advice promptly and discontinue using the drug. Switch to another effective drug immediately.

You can still get malaria despite using chemoprophylaxis.

Colleagues, websites and even health care providers in destination countries may offer conflicting opinions about antimalarial drugs. These sources are often inaccurate and/or based on approaches elaborated for other populations, e.g. residents of malaria-endemic areas. Continue using the chemoprophylactic medications that were prescribed.

Some popular antimalarial measures (e.g. papaya tea) promoted in endemic areas have not been proven effective and should *not* be substituted for chemoprophylactic agents with documented efficacy.

EDUCATE ABOUT PERSONAL PROTECTIVE (ANTI-MOSQUITO) MEASURES (CHAPTER 3)

Use insecticide-impregnated bed nets, especially if mosquitoes cannot be otherwise excluded, (e.g. by screening on windows).

20%–30% DEET or 20% icaridin (a repellent recently registered in Canada) are recommended to protect adults against mosquito bites.

Icaridin at a concentration of 20% is recommended to protect children (aged 6 months–12 years) against mosquito bites.

For infants aged less than 6 months, there are no repellents approved for use in Canada. However, if mosquito bites cannot be otherwise prevented, for example by using netting over cribs, strollers, etc., use up to 10% DEET or 20% icaridin.

Follow label instructions on how and where to apply insect repellent. Reapply insect repellent if you see mosquitoes biting before the recommended reapplication interval noted on the product label.

p-menthane-3,8-diol is recommended as a second choice after DEET or icaridin.

Other repellents are not recommended (e.g. citronella, soybean oil) for protection against the bites of malaria vectors.

Other interventions such as insecticide vaporizers, mosquito coils, electronic devices, etc., are not recommended for protection against the bites of malaria vectors.

Refer to CATMAT Statement on Personal Protective Measures to Prevent Arthropod Bites for more detailed information.

EDUCATE ABOUT MALARIA ILLNESS (SEE CHAPTER 3)

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.

Symptoms of malaria may be mild and nonspecific, and malaria should be considered in any unexplained fever or "flu-like" illness during or after travel to endemic areas. Any such illness during or after travel should prompt the traveller to seek medical help as soon as is possible.

Advise health care providers of travel to malaria-endemic areas.

Accurate diagnosis of malaria requires laboratory testing (Chapter 6: microscopic examination of blood smears, polymerase chain reaction or rapid diagnostic tests). Diagnosis based on symptoms alone is relatively inaccurate. Nevertheless, if a malaria diagnosis has been made in an endemic area—even if reliable testing has not been done—it is prudent to treat for malaria. This is because malaria can rapidly progress to life-threatening disease if treatment is delayed.

If malaria is suspected, laboratory testing (microscopic examination of blood smears, polymerase chain reaction or rapid diagnostic tests) should be done on one or more occasions to verify the diagnosis. Self-treatment (if prescribed) should only be taken if medical care is not readily available. Medical advice should still be sought as soon as is possible after self-treatment.

Chemoprophylaxis should be continued even if malaria has been diagnosed.

SPECIAL TRAVELLERS (SEE CHAPTERS 5)

Certain populations are at increased risk of malaria.

Pregnant women (or women who may become pregnant while travelling or living in endemic areas) should be advised that pregnancy is a time of heightened risk of severe malaria and adverse consequences to both mother and fetus. In addition, certain drugs are contraindicated during prenancy, (e.g. doxycycline).

Young children can be at increased risk of malaria and also require special consideration with respect to appropriate chemoprophylactic and personal protection options.

People with comorbidities can be at increased risk of malaria, and also might require special attention because of drug contraindications and/or interactions.

People who originate from malaria-endemic areas are often are at higher risk of malaria, for example because they (and their families) visit areas where transmission is intense and/or do not take all appropriate precautions. These travellers should receive specific counselling to address misperceptions about malaria immunity (i.e. they do not have it) and the need for personal protective measures (i.e. they should use them).

Long-term travellers may choose to discontinue malaria chemoprophylaxis because of concerns about long-term drug use and/or a misguided attempt to build up immunity. Advise these travellers 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 tolerate the medication.

(Adapted from *International Travel and Health*, World Health Organization, Geneva, 2011).

APPENDIX III: FREQUENTLY ASKED QUESTIONS ABOUT MALARIA

* *This document may be freely copied and distributed.*

IS MALARIA A RISK FOR CANADIAN TRAVELLERS?
Yes. Malaria is a major killer worldwide and is the principal life-threatening infectious disease for Canadians travelling to malaria-endemic areas. Between 400 and 1,000 cases of malaria are reported among Canadian travellers annually, resulting in one to two deaths per year.

WHERE IS MALARIA A RISK?
Most malaria cases and deaths occur in sub-Saharan Africa. Transmission occurs in:

- Most of sub-Saharan Africa and limited areas in Northern Africa;
- Large areas of Southern Asia, Southeast Asia, and some parts of East Asia;
- Areas in Central America including the Dominican Republic, Haiti, parts of Mexico and much of South America;
- Papua New Guinea and other small islands in the South Pacific / Oceania region and in limited areas in the Middle East and Eastern Europe.

Please consult Appendix I: Malaria Risk and Recommended Chemoprophylaxis by Geographic Area for information about specific areas with risk of transmission.

WHAT ARE THE SIGNS AND SYMPTOMS OF MALARIA INFECTION?
Any individual who has travelled to a malaria-endemic area and subsequently developed fever should urgently seek medical advice and request testing to rule out malaria, even if the fever appears many months after returning to Canada. Early symptoms also 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. As a result, it is easy to overlook malaria.

DOES PREVIOUS EXPOSURE TO MALARIA OFFER ANY PROTECTION TO TRAVELLERS?
No. Canadian travellers who were born, grew up or used to live in malaria-endemic areas are *not* protected from malaria. They remain at risk regardless of past exposures or episodes of illness.

DO ALL TRAVELLERS TO THE TROPICS NEED MALARIA CHEMOPROPHYLAXIS?
No. Some destinations in the tropics are free of malaria or have such a low risk that malaria chemoprophylaxis might not be indicated. In some countries, malaria chemoprophylaxis may only be required in particular regions (usually rural areas), during particular seasons or for longer stays. The boundaries of malaria-free zones within malaria-endemic countries can change rapidly, and all individuals (adults and children) travelling to areas with any risk of malaria should use personal protective measures, such as treated mosquito nets and insect repellents, to avoid mosquito bites. These also protect against other insect-borne disease like dengue.

CAN TRAVELLERS STOP TAKING ANTIMALARIAL MEDICATIONS OR USING PERSONAL PROTECTIVE MEASURES IF THEY DO NOT SEE ANY MOSQUITOES AT THEIR DESTINATION?

No. Even if travellers do not notice any mosquitoes, they should continue taking antimalarial medications. Malaria mosquitoes are different from the mosquitoes typically in Canada—they tend to bite when we sleep, and often are less aggressive.

SHOULD PREGNANT WOMEN, BABIES AND CHILDREN TRAVELLING TO MALARIA-ENDEMIC AREAS RECEIVE MALARIA CHEMOPROPHYLAXIS?

Yes. Pregnant women, babies and small children are at particular risk of acquiring malaria and of suffering severe complications from malaria. If they must go to high-risk areas, they should use the best available antimalarial medications (see Chapter 5), along with personal protective measures. Antimalarial medication taken by breastfeeding mothers will not provide protection for the breastfed child.

DO MOST PEOPLE WHO TAKE MALARIA CHEMOPROPHYLAXIS HAVE SERIOUS SIDE EFFECTS?

No. The majority of people taking antimalarial medications (95% to 99%) have either no side effects or only mild, temporary ones. In most studies, only 1% to 6% of people change to an alternative medication because of side effects. Reactions to antimalarial medications are almost always reversible.

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 chemoprophylaxis.

The final choice of which antimalarial medication to use should be based on an individual risk assessment performed by a knowledgeable travel health practitioner. The risk assessment should take into account the medication'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 medications.

If side effects are significant, then an alternative antimalarial medication should be chosen. Travellers who are concerned about their ability to tolerate medications may wish to consult a travel health practitioner well before travelling and consider a trial of antimalarial medication before leaving.

ARE THERE SAFER AND/OR MORE EFFECTIVE ANTIMALARIAL MEDICATIONS AVAILABLE?

For high-risk regions of the world with chloroquine-resistant malaria, three equally effective medications are currently licensed in Canada: atovaquone-proguanil (Malarone®), doxycycline and mefloquine (Lariam®). Each has advantages and disadvantages. Cheaper medications available locally in destination countries may be ineffective, counterfeit, more toxic or inappropriate for high-risk individuals. These include chloroquine, proguanil (Paludrine®), amodiaquine (Camoquine®), pyrimethamine (Daraprim®), pyrimethamine plus sulfadoxine (Fansidar®) and pyrimethamine plus dapsone (Maloprim®).

WHY DO TRAVELLERS NEED TO CONTINUE TAKING MEDICATIONS AFTER THEY LEAVE THE MALARIA-ENDEMIC AREA?

Most antimalarial medications do not actually prevent the initial stages of malaria infection when the parasites are in the liver. Rather, they work 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 present within the first three months after leaving the malaria-endemic area. Most antimalarial medications (chloroquine, mefloquine, doxycycline) must be continued for four weeks after leaving a malaria-endemic area

to prevent disease caused by the parasites that emerge from the liver. Some antimalarial medications (atovaquone-proguanil, primaquine) are effective against the liver stages of infection, and these medications may be discontinued several days to one week after leaving the malaria-endemic area.

WHAT IS THE MAXIMUM LENGTH OF TIME A TRAVELLER CAN SAFELY USE MALARIA CHEMOPROPHYLAXIS?

There is no absolute time limit on how long one can take antimalarial medication. The few individuals who experience significant side effects from antimalarial medications usually do so within the first few weeks of use. Many mild side effects tend to diminish over time, even with continued use of the medication. Long-term travellers should not discontinue a well-tolerated and effective antimalarial medication simply because they have been taking it for a long period of time.

FOR TRAVELLERS USING MALARIA CHEMOPROPHYLAXIS, WHAT IS THE RISK OF DEVELOPING MALARIA?

Proper use of an effective antimalarial medication provides a high degree of protection and can reduce the risk of malaria illness by more than 90%, but no antimalarial medication is 100% effective. Therefore, even if travellers have taken chemoprophylaxis, malaria should be considered in febrile patients during or after travel to malaria-endemic areas.

DOES THE USE OF MALARIA CHEMOPROPHYLAXIS MAKE IT MORE DIFFICULT TO DIAGNOSE MALARIA?

The use of malaria chemoprophylaxis may reduce the severity of symptoms and the number of parasites in the blood and could therefore rarely result in a minor delay in definitive diagnosis. However, properly used antimalarial medications will prevent the vast majority of malaria episodes and 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 balanced with the significant benefit of preventing disease and reducing the risk of severe disease.

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.

ONCE YOU ARE INFECTED WITH MALARIA, ARE YOU ARE INFECTED FOR LIFE?

No. Appropriate treatment and follow-up can cure malaria.

Further information on travel-related health issues is available on the Public Health Agency of Canada's Travel Health website: www.travelhealth.gc.ca.

APPENDIX IV: STRENGTH AND QUALITY OF EVIDENCE SUMMARY

STRENGTH AND QUALITY OF EVIDENCE SUMMARY TABLE:

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

SOURCE: Committee to Advise on Tropical Medicine and Travel. *Evidence-based medicine.* CCDR 1994;20:145–47

APPENDIX V: CANADIAN MALARIA NETWORK—ACCESSING PARENTERAL ARTESUNATE OR QUININE

The Canadian Malaria Network (CMN), in collaboration with Health Canada's Special Access Programme and the Public Health Agency of Canada, keeps supplies of intravenous artesunate and quinine at major medical centres across the country for rapid access to effective treatment for severe malaria. These life-saving drugs are available 24 hours per day by contacting the pharmacies listed on the CMN webpage. These drugs are not licenced in Canada and are only available through the CMN, and require treating physicians to report on the use of these drugs (see below).

Severe malaria is not common in Canada, with 195 cases treated through the CMN between August 2001 and August 2012. The number of cases per year has increased from 7 cases in 2002 to 30 in 2010 and cases have been spread across the country. This means that these scarce drugs must be strategically distributed across the country (see Chapter 7 for information on management of malaria).

Each of the participating CMN centres has on-site a designated physician with experience in treating malaria. For after-hours assistance, please contact the infectious disease consultant on call at the closest centre.

Each treatment dose comes with dispensing information and two surveillance forms (Form A and Form B). The attending physician fills out Form A at the time of access to / request for intravenous artesunate or quinine and Form B at discharge / end of malaria therapy. This information is vital to inform policy for distribution of these drugs. In addition, the organizations that supply these drugs need to be notified of any drug-related adverse events.

TABLE V.1: Criteria for severe falciparum malaria*

CLINICAL MANIFESTATION	LABORATORY TEST
Prostration/impaired consciousness	Severe anemia (hematocrit < 15%; Hb ≤ 50 g/L)
Respiratory distress	Hypoglycemia (blood glucose < 2.2 mmol/L)
Multiple convulsions	Acidosis (arterial pH < 7.25 or bicarbonate < 15 mmol/L)
Circulatory collapse	Renal impairment (creatinine > 265 µmol/L)
Pulmonary edema (radiological)	Hyperlactatemia
Abnormal bleeding	Hyperparasitemia (≥ 2%)
Jaundice	—
Hemoglobinuria	—

Adapted from: *Guidelines for tâhe treatment of malaria*, World Health Organization, 2010.

* In patients with *Plasmodium falciparum* asexual parasitemia and no other obvious cause of symptoms, the presence of one or more of the clinical manifestations or laboratory features shown in Table V.1 classifies the patient as having severe malaria. Please note for those individuals who do NOT meet criteria for severe malaria, but require parenteral therapy, due to inability to tolerate oral treatment, IV quinine should be used. Artesunate is in short supply and should be reserved for those with severe malaria.

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

APPENDIX VI: MALARIA CARD

To be given to travellers with information about their chemoprophylaxis and an important reminder to seek medical attention in the event of fever illness after travel.

Malaria is serious and potentially life-threatening. Always protect yourself against mosquito bites with appropriate clothing, bed nets, and effective insect repellent.

http://travel.gc.ca/travelling/health-safety/diseases/malaria

Your doctor's name/phone number:

_____

_____

Antimalarial drug prescribed:

_____

_____

Remember to continue medication for the correct period after leaving the malarial area. If you miss a dose, take it as soon as possible.

If you develop a fever, particularly if accompanied by other flu-like symptoms (muscle aches, headache, vomiting, abdominal pain and/or diarrhea), while travelling or up to 1 year later, you should seek medical attention immediately.

Untreated malaria can progress rapidly to severe and fatal infection.

Information for health care professionals

2014 Malaria Recommendations:

www.phac-aspc.gc.ca/tmp-pmv/catmat-ccmtmv/index-eng.php

The Canadian Malaria Network provides access to life-saving medication and advice for physicians:

www.phac-aspc.gc.ca/tmp-pmv/quinine/index.html