

## Summary of recommendations for the diagnosis and treatment of malaria by the Committee to Advise on Tropical Medicine and Travel (CATMAT)

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### Abstract

**Background:** On behalf of the Public Health Agency of Canada, the Committee to Advise on Tropical Medicine and Travel (CATMAT) developed the *Canadian Recommendations for the Prevention and Treatment of Malaria Among International Travellers* for Canadian health care providers who are preparing patients for travel to malaria-endemic areas and treating travellers who have returned ill. These recommendations aim to achieve appropriate diagnosis and management of malaria, a disease that is still uncommon in Canada.

**Objective:** To provide recommendations on the appropriate diagnosis and treatment of malaria.

**Methods:** CATMAT reviewed all major sources of information on malaria diagnosis and treatment, as well as recent research and national and international epidemiological data, to tailor guidelines to the Canadian context. The evidence-based medicine recommendations were developed with associated rating scales for the strength and quality of the evidence.

**Recommendations:** Malarial management depends on rapid identification of the disease, as well as identification of the malaria species and level of parasitemia. Microscopic identification of blood samples is both rapid and accurate but can be done only by trained laboratory technicians. Rapid diagnostic tests are widely available, are simple to use and do not require specialized laboratory equipment or training; however, they do not provide the level of parasitemia and do require verification. Polymerase chain reaction (PCR), although still limited in availability, is emerging as the gold standard for high sensitivity and specificity in identifying the species.

Severe or complicated malaria requires admission to hospital for regular monitoring of respiratory rate and pattern, coma score, and glucose and urine output, especially if the patient is unconscious. In high levels of parasitemia, exchange transfusion may be beneficial to remove infected red blood cells and toxic mediators from the circulation, and reduce the parasite load. Because of the elevated risk of severe or complicated malaria, those with a diagnosis of *Plasmodium falciparum* malaria should also be admitted to hospital or receive initial treatment in an observation unit.

Uncomplicated malaria is treated to cure the infection and prevent progression to severe disease. When treatment regimens are being chosen, drug tolerability, the adverse effects of drugs and the speed of therapeutic response should be considered.

## Introduction

Malaria is a 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. Infections caused by *P. falciparum* have the highest fatality rates. The overall case-fatality rate of falciparum malaria varies from about 1% to 5% and increases to 20% for those with severe malaria (1-2).

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 of which about 40% were in India, Nigeria and the Democratic Republic of Congo (3). Malaria is still diagnosed in Canada following travel in endemic countries. The Canadian Notifiable Diseases Surveillance System, which monitors nationally notifiable infectious diseases, received reports of 4,254 cases of malaria from 2001 to 2011 (D.Taylor, Public Health Agency of Canada, unpublished data, 2013).

From August 2001 to August 2012, the Canadian Malaria Network, which facilitates rapid access to parenteral treatment of severe malaria, received reports of 195 cases of severe or complicated malaria (personal communication, A. McCarthy and J. Geduld, Committee to Advise on Tropical Medicine and Travel, 2012).

The most important factors determining patient survival are early diagnosis and appropriate therapy. The majority of malaria deaths are preventable and are frequently the result of delays in diagnosis and treatment. Among the cases reported to the Canadian Malaria Network, only 20% presented to medical care within 24 hours of onset of symptoms, and 44% waited more than three days (personal communication, A. McCarthy and J. Geduld, K. Cullen and P. Arguin, US Centers for Disease Control and Prevention, 2012). Diagnosis by health care provider was delayed more than 24 hours in 34% of the cases (personal communication, A. McCarthy and J. Geduld, 2012).

This is a summary of the CATMAT [Canadian Recommendations for the Prevention and Treatment of Malaria Among International Travellers](#), developed for Canadian health care providers who are preparing patients for travel to malaria-endemic areas and treating travellers who have returned ill (4). These guidelines include a full description of recommendations on diagnosis and treatment of malaria.

## Methods

The Malaria Subcommittee, a working group of CATMAT, developed the guidelines. The process undertaken to develop them has been described previously (5). It included a review of recent research and national and international epidemiological data, and the consideration of other factors, such as malaria epidemiology, and the anticipated values and preferences of travellers and health care providers. The evidence-based medicine recommendations for the diagnosis and treatment of malaria were developed with associated rating scales for the strength and quality of the evidence.

## Recommendations

The evidence-based CATMAT recommendations for malaria diagnosis and treatment are summarized in **Table 1**. A discussion of some of the key recommendations follows.

**Table 1: Evidence-based medicine recommendations for the diagnosis and treatment of malaria**

Recommendation	EBM <sup>1</sup> rating
1. Parenteral artesunate is recommended as first-line treatment for severe <i>P. falciparum</i> malaria, with parenteral quinine as an alternative (3).	A I
2. To prevent relapses of <i>P. vivax</i> and <i>P. ovale</i> malaria, primaquine phosphate (30 mg base daily for 2 weeks) should follow chloroquine treatment (6).	B I
3. The treatments of choice for uncomplicated <i>P. falciparum</i> malaria are as follows: <ul style="list-style-type: none"> <li>• Oral chloroquine (ONLY if from chloroquine-sensitive areas);</li> <li>• Oral atovaquone-proguanil (7);</li> <li>• Oral quinine combined with oral doxycycline or clindamycin;</li> <li>• Combination therapy with an artemisinin derivative (not yet available in Canada) (7).</li> </ul>	B III
4. Exchange transfusion may have benefits for treating hyperparasitemic cases of <i>P. falciparum</i> (8).	C III
5. Individuals in chloroquine-sensitive regions should self-treat with chloroquine and then resume or start chloroquine prophylaxis (9-11).	C III
6. In chloroquine- and/or chloroquine- and mefloquine-resistant <i>P. falciparum</i> regions, self-treatment should consist of a drug different to that used for prophylaxis, chosen from one of the following: <ul style="list-style-type: none"> <li>a. atovaquone-proguanil (Malarone<sup>®</sup>) or</li> <li>b. oral quinine and doxycycline or</li> <li>c. artemether-lumefantrine (Coartem<sup>®</sup>), 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 (10-13).</li> </ul>	C III
7. The use of steroids to treat severe or cerebral malaria has been associated with worse outcomes and should be <b>avoided</b> (14).	E I
8. A number of antimalarials are contraindicated in the treatment of malaria (self-treatment or otherwise): <ul style="list-style-type: none"> <li>a) mefloquine (15)</li> <li>b) pyrimethamine-sulfadoxine (Fansidar) (16)</li> <li>c) mefloquine-Fansidar (17)</li> <li>d) halofantrine (7)</li> <li>e) chloroquine-Fansidar (18).</li> </ul>	E II

<sup>1</sup> EBM = Evidence based medicine. The EBM ratings are as follows:

**Strength of 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

**Quality of evidence:**

- I = Evidence from at least one properly randomized, controlled trial
- II = Evidence from at least one well-designed clinical trial without randomization; from cohort or case-controlled analytic studies, preferably from more than one centre; from multiple time series; or from dramatic results in uncontrolled experiments
- III = Evidence from opinions of respected authorities on the basis of clinical experience, descriptive studies, or reports of expert committees

## Malaria Diagnosis

Malaria could be the reason for any etiologically unidentified fever that develops while a traveller is in a malaria-endemic area or up to one year after leaving, irrespective of chemoprophylaxis use (19). If a fever occurs during this time, the traveller should seek medical attention immediately and tell the health care provider about his/her travel history. Particular attention should be paid to fevers that develop in the three months following travel, as more than 90% of falciparum malaria presents during this period.

Since the disease can progress from asymptomatic infection to severe and complicated malaria and even death within 36 to 48 hours, survival of patients particularly with *P. falciparum* malaria (20) is affected by early diagnosis and correct speciation to determine the required life-saving treatment. Quantitating parasitemia is also important to determine the need for parenteral treatment, for exchange transfusion or for admission to an intensive care unit (ICU). In addition, it is important for monitoring response to treatment.

Microscopy, which involves examining thick and thin blood smears, is both rapid and accurate. A Canadian laboratory should be able to confirm the presence of a parasite and, in most cases, identify the species within one to two hours of receiving a blood specimen (21-24). However, accurate examination of a blood smear requires considerable training and experience (23,25).

Rapid diagnostic tests are simple to use and do not require any specialized laboratory equipment or skills. They are essential diagnostic tools if malaria microscopy results are not available within two hours (26). However, both positive and negative results must be verified by expert microscopy or PCR to determine the level of parasitemia and to identify the species. Note that the use of rapid diagnostic tests by travellers to self-diagnose is unreliable.

Although still limited in its availability, PCR is emerging as the gold standard for high sensitivity and specificity in speciation. It is being increasingly used for quality control (27-29).

## General principles of malaria management

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. *P. falciparum* can cause life-threatening disease in a nonimmune host and is a medical emergency. Consider hospital admission for all nonimmune cases and for all children to ensure that antimalarial drugs are tolerated and to detect complications or early treatment failure.

### 2) Is this severe or complicated malaria?

In a case of *P. falciparum* and no other obvious cause of symptoms, having one or more of the following clinical or laboratory features indicates severe or complicated 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) (1)
Pulmonary edema (radiological)	Hyperlactatemia
Abnormal bleeding	Hyperparasitemia (≥ 2%)
Jaundice	—
Hemoglobinuria	—

Adapted from *Guidelines for the Treatment of Malaria*, World Health Organization, 2010 (7).

Severe malaria is usually due to *P. falciparum* infection, although it can also occur with *P. knowlesi*, and *P. vivax* can occasionally lead to severe disease.

### 3) Where was the infection acquired?

Appendix I of the *Canadian Recommendations for the Prevention and Treatment of Malaria Among International Travellers* shows a country-by-country and regional characterization of malaria transmission areas (4). Malarial parasites in most of the world are drug resistant. When in doubt, treat all *P. falciparum* malaria as drug resistant.

### Managing severe or complicated malaria

Severe or complicated malaria, or the inability to tolerate oral therapy, requires urgent, parenteral therapy and intensive medical management (especially in the case of children), ideally in an ICU. If possible, consult with an infectious or tropical disease expert when managing a patient with severe falciparum malaria.

The primary objective of treatment is to prevent death. Prevention of neurological deficits is also an important objective for cerebral malaria. There are several treatments:

- Parenteral artesunate is the WHO-recommended first-line treatment for severe *P. falciparum* malaria.
- Parenteral quinine can be used to treat severe or complicated malaria when parenteral artesunate is not available and is the preferred drug if the only indication for parenteral therapy is intolerance to oral therapy.
- Parenteral artesunate and quinine are available 24 hours per day through the Canadian Malaria Network (30).
- Follow parenteral administration of artesunate or quinine with oral therapy using one of the following medications:
  - Atovaquone-proguanil (unless used as malaria chemoprophylaxis);
  - doxycycline (unless used as malaria chemoprophylaxis; contraindications: pregnancy, breastfeeding, age < 8 years) (7);
  - clindamycin (only if the patient is unable to take doxycycline or atovaquone-proguanil).

**Table 2** identifies the common antimalarial drugs and their indications.

**Table 2: Recommendations for common antimalarial drugs**

	Indication	Additional notes
<b>Intravenous artesunate</b>	First-line treatment of severe falciparum malaria (3,7,31) or if intravenous quinine is not tolerated.	Follow parenteral artesunate with a full course of atovaquone-proguanil (Malarone <sup>®</sup> ) or doxycycline (clindamycin in pregnant women or children < 8 years) or artemisinin-based combination therapy.  Patients treated with IV artesunate should have weekly CBC x 4 done. As well they should be counselled to report signs of hemolysis such as dark urine, yellowing of the skin or whites of the eyes, fever, abdominal pain, pallor, fatigue, shortness of breath and/or chest pain.
<b>Oral artemisinin combination therapy</b> (not yet available in Canada)	Uncomplicated falciparum malaria or when the causative species has not been identified.	

	Indication	Additional notes
<b>Atovaquone-proguanil</b> <b>Trade Name:</b> Malarone®	First-line treatment of acute, uncomplicated <i>P. falciparum malaria</i> and <i>P. vivax malaria</i>  Uncomplicated malaria in adults and in children $\geq 11$ kg.	
<b>Chloroquine (or hydroxychloroquine)</b> <b>Trade Name:</b> Novo-Chloroquine (or Plaquenil®), Apo-Hydroxyquine, Gen-Hydroxychloroquine)	Chloroquine-sensitive <i>P. falciparum</i> , <i>P. vivax</i> , <i>P. ovale</i> , <i>P. malariae</i> and <i>P. knowlesi</i> infections.	Suitable for all ages and in pregnancy.
<b>Clindamycin</b> <b>Trade Name:</b> (Dalacin C®), Apo-Clindamycin, Novo-Clindamycin	Clindamycin is combined with quinine to treat chloroquine- or mefloquine-resistant <i>P. falciparum</i> malaria in pregnant women, children (< 8 years) and tetracycline-intolerant adults when artemisinin-derivatives are unavailable.	Less effective than doxycycline or atovaquone-proguanil.
<b>Doxycycline</b> <b>Trade Name:</b> Vibra-Tabs™, Apo-Doxy, Doxycin, Novo-Doxylin, Nu-Doxycycline, ratio-Doxycycline	To prevent and treat chloroquine-resistant <i>P. falciparum</i> l.	<b>Contraindicated</b> in pregnancy, while breastfeeding and in children aged < 8 years of age.
<b>Quinine and quinidine</b>	Parenteral quinine is used to treat severe or complicated malaria when parenteral artesunate is unavailable and is the first-line drug for those who cannot take oral therapy and do not meet any criteria for severe disease.  Oral treatment using quinine with doxycycline or clindamycin is indicated for uncomplicated falciparum malaria and as step-down therapy after parenteral treatment of complicated malaria.	The Canadian Malaria Network recommends reserving artesunate for those with severe malaria (as defined by the WHO) and using parenteral quinine in those who do not tolerate oral therapy or are vomiting.  Parenteral quinidine should only be used if the two first-line drugs are unavailable; cardiac monitoring is required.
<b>Primaquine</b> <b>Trade Name:</b> Primaquine (primaquine phosphate)	Used to prevent relapse due to <i>P. vivax</i> or <i>P. ovale</i> infection.  Used as a “radical cure” to reduce the risk of relapse after the treatment of symptomatic <i>P. vivax</i> or <i>P. ovale</i> infection.	Contraindicated in people with severe G6PD deficiencies, in pregnancy and in nursing mothers if the infant is G6PD deficient.

If parenteral artesunate or quinine is indicated but is not available for more than an hour, start quinine orally (after a dose of gravol) or by nasogastric tube until the parenteral drug is available. Patients should have at least 24 hours of parenteral therapy before switching to oral therapy.

Frequent clinical observations should monitor vital signs and assess respiratory rate and pattern, coma score and urine output. Use rapid stick tests to monitor blood glucose at least every four hours. Treat seizures promptly with benzodiazepines (7). Clinically assess all patients daily until fever ends and whenever symptoms recur; for *P. falciparum* cases, repeat malaria smears daily until these are negative.

In cases with high parasitemia ( $\geq 10\%$ ), exchange transfusion to remove infected red blood cells and toxic mediators from the circulation and reduce the parasite load may be beneficial (8,32).

### Managing uncomplicated falciparum malaria

Uncomplicated falciparum malaria refers to symptomatic malaria with no evidence of severe disease or of vital organ dysfunction. Uncomplicated malaria is treated to cure the infection and prevent progression to severe disease. When choosing treatment regimens, consider drug tolerability, adverse effects of drugs and the speed of the therapeutic response.

The treatments of choice for uncomplicated *P. falciparum* malaria are as follows:

- Oral chloroquine (ONLY for those with travel to exclusively chloroquine-sensitive areas);
- Oral atovaquone-proguanil (7);
- Oral quinine combined with oral doxycycline simultaneously or sequentially, starting with quinine; if doxycycline is contraindicated, administer oral quinine and clindamycin, simultaneously or sequentially (33-34);
- Combination therapy with an artemisinin derivative (not yet available in Canada) (7).

### Managing non-falciparum malaria

Conduct a clinical assessment daily until fever ends and whenever symptoms recur. For *P. vivax* infections, recurrence of asexual parasitemia less than 30 days after treatment suggests chloroquine-resistant *P. vivax*; recurrence after 30 days suggests primaquine-resistant *P. vivax*.

The treatment of choice for non-falciparum malaria outside of chloroquine-resistant regions continues to be chloroquine. The optimal chemoprophylaxis or treatment of *P. vivax* acquired in chloroquine-resistant regions is unknown, although a seven-day course of quinine is often required to cure *P. vivax* infection.

### Managing undefined malaria

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 two hours, start a therapeutic antimalarial that is effective for the area of travel/acquisition.

### Managing relapses

*P. vivax* and *P. ovale* have a persistent liver phase (hypnozoites) that is responsible for relapses for months or even years after exposure, even in the absence of primary symptomatic malaria infection. None of the currently recommended chemoprophylaxis regimens will prevent relapses due to *P. vivax* or *P. ovale*.

To reduce the risk of relapse after the treatment of symptomatic *P. vivax* or *P. ovale* infection, primaquine is indicated to provide a “radical cure”. Initiate the primaquine radical cure after the acute febrile illness is over, but so that it overlaps with the blood schizonticide (i.e. chloroquine or quinine) (7).

Primaquine is **contraindicated** in people with severe G6PD deficiencies and in pregnancy. Prevent relapses in pregnancy with weekly doses of chloroquine until after delivery, when primaquine can be safely used for mothers with normal G6PD levels unless they are breastfeeding. Nursing mothers should only use primaquine if the infant has been tested and is not G6PD deficient.

*P. knowlesi*, a threat in southeast Asia, can be confused microscopically as *P. malariae* except that it has higher (> 1%) parasitemia. Systemic symptoms and complications can mimic *P. falciparum* malaria. Treatment with chloroquine is reportedly effective, but systemic symptoms and complications similar to those of hyperparasitemic *P. falciparum* infections require very close monitoring and careful management (25, 35), and, potentially, parenteral therapy with artesunate.

### Self-treatment of presumptive malaria

Self-treatment may be a life-saving measure for 24 hours while medical attention is sought. Travellers to high-risk regions (e.g. sub-Saharan Africa, where 90% of global malaria morbidity and mortality occurs) should never rely

exclusively on self-treatment (9,21,23,25). The signs and symptoms of malaria are nonspecific, and malaria cannot be definitively diagnosed without a laboratory test (10,37,38).

Travellers at risk of malaria and unable to access medical care within 24 hours for adequate malaria treatment drugs should carry effective medication for self-treatment of presumptive malaria.

- In chloroquine-sensitive regions, self-treat with chloroquine and then resume or start chloroquine prophylaxis (9-11).
- In chloroquine- and/or chloroquine- and mefloquine-resistant *P. falciparum* regions, self-treatment requires a different drug if the traveller is taking a chemoprophylactic agent. Ideally, this should have been brought from a country with high standards of quality control to minimize the likelihood of counterfeit products:
  - Atovaquone-proguanil
  - oral quinine and doxycycline (10-11,13)
  - artemether-lumefantrine

### Contraindicated malaria drugs

A number of antimalarials are *contraindicated* for the treatment of malaria (self-treatment or otherwise):

- mefloquine
- pyrimethamine-sulfadoxine (Fansidar)
- mefloquine-Fansidar
- halofantrine
- chloroquine-Fansidar

## Summary

A summary of the key changes made to the 2014 Guidelines are noted in **Table 3**.

**Table 3: Summary of key additions and changes to the 2014 Guidelines pertaining to the diagnosis and treatment of malaria (4)**

Additions
1. The management of severe malaria has been updated to include new information on the use of exchange transfusion (see Chapter 7).
2. 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.
Changes
1. Chapter 8, “Drugs for the Prevention and Treatment of Malaria,” includes up-to-date information on pediatric dosing of atovaquone/proguanil; 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 and quinine/quinidine.
2. Change in parasitemia level to define hyperparasitemia with severe malaria: now $\geq 2\%$ from 5% in non-immune travellers.

## Conclusions

Malarial management depends on rapid identification of the disease, as well as identification of the malaria species and level of parasitemia. Severe or complicated malaria requires admission to hospital. Uncomplicated malaria is treated to cure the infection and prevent progression to severe disease. Treatment varies according to the species of malaria, severity and where the malaria was acquired.

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## Conflict of interest

There are no conflicts of interest to declare.

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