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Inside this issue: Mosquito-borne infections

Mosquitoes give more than bites: they transmit disease. This means that awareness and personal protection are more important than ever, both in Canada and when travelling. Read about five different mosquito-borne diseases in this issue: West Nile virus, malaria, chikungunya, dengue and Zika virus.

Commentary

Advisory committee recommendations

Infectious disease news briefs

Useful links

West Nile virus – protect yourself! Public Health Agency of Canada.
http://www.phac-aspc.gc.ca/wn-no/index-eng.php

Dengue fever: global update. Public Health Agency of Canada Travel Health Notice April 2014. http://www.phac-aspc.gc.ca/tmp-pmv/notices-avis/notices-avis-eng.php?id=44

Zika virus infection in Chile, French Polynesia, New Caledonia and the Cook Islands. Public Health Agency of Canada Travel Health Notice March 2014.
http://www.phac-aspc.gc.ca/tmp-pmv/notices-avis/notices-avis-eng.php?id=122

Upcoming events

Canadian Public Health Association Annual Conference. May 26-29, 2014, Toronto, ON
http://www.cpha.ca/en/conferences/conf2014.aspx

Webinar May 27, 1:00- 2:30 pm. EDT: Prevention and treatment of malaria: updated Canadian recommendations http://chnet-works.ca/index.php?option=com_rsevents&view=events&layout=show&cid=302%3Aprevention-and-treatment-of-malaria-updated-canadian-recommendations
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Canada

West Nile virus in Canada: ever-changing, but here to stay

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Summary

The incidence of West Nile virus (WNv) has waxed and waned in Canada over the past 12 years, but it is unlikely to disappear. Climate change models, which suggest warming temperatures and changing patterns of precipitation, predict an expansion of geographic range for WNv in some regions of Canada, such as the Prairie provinces. Such projected changes in WNv distribution might also be accompanied by genetic changes in the virus and/or the range of bird and insect host species it infects. To address this risk, emphasis should be placed on preventing exposure to infected mosquitoes, conducting high-quality surveillance of WNv and WNv disease, controlling mosquito vectors, and promoting public and professional education.

Introduction

West Nile virus a globally distributed member of the genus *Flavivirus*, infects a wide range of mammals, birds, reptiles and amphibians, as well as a variety of mosquito species, including members of the genus *Culex*. The virus is primarily maintained in bird populations through transmission by mosquitoes, and zoonotic transmission occurs when a mosquito that has fed on an infected bird subsequently bites a human host. WNv infection can also be transmitted from person to person through medical procedures, particularly blood transfusion and organ transplantation (1,2). Since 1999, when human WNv disease was first recognized in humans in North America, the virus has spread continent-wide in both Canada and the USA, with annual outbreaks of varying intensity and regional distribution.

The goal of this commentary is to suggest that, although the impact of WNv has waxed and waned over the past decade or more, the virus will continue to have significant individual and public health consequences for the foreseeable future, and concerted action is required to minimize these consequences. We will review the epidemiology of WNv and WNv disease, provide a brief overview of the WNv epidemic in North America and then close by highlighting the need for ongoing vigilance regarding this public health challenge.

Epidemiology

Although it remains unknown what proportion of individuals who are bitten by a mosquito carrying WNv become infected, serological surveys and studies of viremic blood donors suggest that 70%–80% of infections are asymptomatic and/or unrecognized (3,4). Symptomatic disease, which usually emerges 2–15 days after infection, ranges in severity from transient febrile illness with headache, chills, skin rash, nausea and muscle aches in the majority of cases to severe and sometimes fatal neurological disease in the form of meningitis, encephalitis or poliomyelitis/acute flaccid paralysis in approximately 1% of those infected (5). Most affected individuals recover fully from acute illness with presumably lifelong immunity to re-infection, but recovery can be prolonged, with sequelae of weakness, fatigue, neurologic and cognitive deficits, and psychiatric problems, some of which may be permanent. Individuals with underlying medical conditions and those over 70 years of age appear to be particularly susceptible to such effects (2,6). There are currently no approved WNv vaccines or specific treatments for WNv disease in humans.

West Nile virus in North America

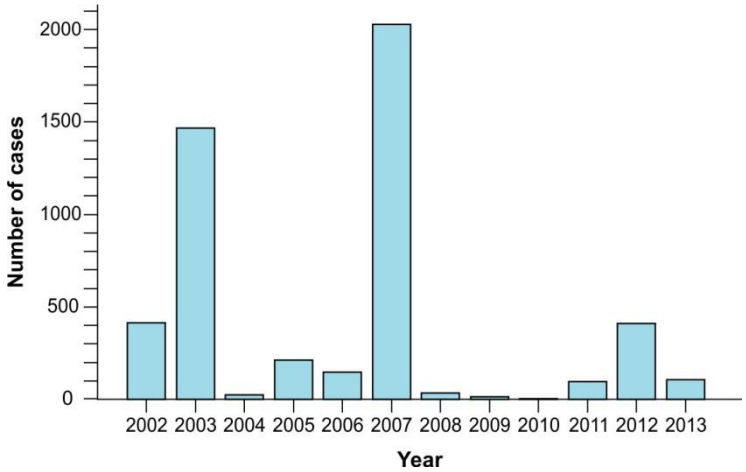
Historically, the first recorded case of WNv disease occurred in Uganda in 1937. Since then, local or regional WNvepidemics of relatively mild disease were reported intermittently from Africa and Israel until the 1990s, when outbreaks of severe disease emerged in western Russia as well as southern and eastern Europe (2). Such scattered epidemics continue to occur in Europe, possibly through repeated introductions by migratory birds (7). The first autochthonous North American cases of WNv disease were recorded in New York City in August 1999 (8). Strikingly, by 2001 WNv had spread to eastern Canada, the southeastern USA, Mexico and the Caribbean; by 2003 to the west coast of the USA; by 2005 to South America; and by 2008 to the west coast of Canada (9).The virus is now considered firmly established in the Americas.

WNv was first detected in Canada in 2001 in birds and mosquitoes collected from Ontario (10). Beginning with the first documented cases the following year, human WNv disease has now been reported from 10 Canadian provinces and territories (including travel-related cases in NB, NS, PE and YK). In total, 5,454 cases of WNv disease and asymptomatic infection were reported to the Public Health Agency of Canada between 2002 and 2013, including 1,072 cases of WNv neurological disease. Using the above rates it can therefore be estimated that in the range of 18,000–27,000 human WNv infections have occurred in Canada since 2002, possibly with a proportional rate of neurological disease higher than that reported from the USA. Several serosurveys have been conducted in Canada to estimate rates of human exposure to WNv, with resulting estimates typically of 3%–5%. However, in rural Saskatchewan following the 2003 WNv season, the seroprevalence was nearly 17% (11).

It should be noted that the reported annual national incidence of WNv disease has varied dramatically, from a total of 5 cases in 2010 and peaks of 1,495 and 2,401 cases in 2003 and 2007 respectively (Figure 1).

Regional variation has also been significant: for example, the majority of Canadian cases were reported from the Prairie provinces (AB, SK, MB) in 2003 and 2007, and from the Central provinces (ON, QC) in 2002 and 2012 (12). The long-term economic costs of acute care and persistent health effects in individuals affected by WNv disease can thus be assumed to be significant, although data that would support realistic estimates of these costs for Canada are lacking. A recent estimate of total cost to the US economy from 1999 through 2012 fell in the range of US $700M–1B (13).

Figure 1. Annual number of cases of human West Nile virus disease and asymptomatic infection reported to the Public Health Agency of Canada: 2002-2013



West Nile virus variation and change

During its evolutionary history WNv has undergone considerable genetic diversification, resulting in the presence of four major lineages, of which two (Lineages 1 and 2) are known to cause disease in humans. Lineage 2,

which has not yet been identified in North America, has recently caused human WNv disease in Europe (7). Within Lineage 1, the most widespread lineage globally, a number of sub-lineages have been identified, and certain genetic changes have been associated with North American colonization and the biological behavior of the virus, particularly in birds and mosquitoes (14). For example, the NY99 WNv sub-lineage that initially colonized the Eastern USA shares a specific genetic change with a 1998 Israeli bird-derived strain that appears to confer on the virus an ability to replicate to higher levels in birds (15). The NY99 sub-lineage was also itself rapidly displaced by a derivative sub-lineage (WN02), which appears capable of faster invasion of the salivary glands of *Culex* mosquitoes after feeding, especially at higher temperatures, in turn suggesting a capacity to spread more rapidly during warmer weather (16).

Thus, by enhancing the reproductive potential and virulence of WNv in mosquitoes and birds respectively, genetic change appears to have facilitated the establishment and spread of WNv in North America, as well as its capacity to cause disease outbreaks. These effects are expected in turn to be amplified by human-driven environmental modification and change. For example, one recent California-based study found associations between *per capita* income and related factors (e.g. density of poorly maintained swimming pools) and the prevalence of WNv infection in both mosquitoes and humans (17). Another research group found that bird species diversity, often affected by human activity, was negatively correlated with local WNv infection rates of *Culex* mosquitoes in a Chicago suburb (18).

On a broader scale, along with warming temperatures and changing patterns of precipitation, climate change models predict an expansion of geographic range for WNv in North America into regions with higher numbers of previously unexposed human and animal hosts (19). Some regions of Canada, such as the Prairie provinces, may be particularly subject to such effects (20). These changes in WNv distribution may also be accompanied by additional genetic changes in the virus and/or the range of bird and insect host species it infects. Combined with the known positive correlation between WNv prevalence and temperature, and the (somewhat unexpected) negative correlation with precipitation amounts, these considerations suggest that the public health risk of WNv disease may increase in North America in the coming decades (16,19).

The need for prevention

As discussed above, complex interactions occur among WNv, its numerous insect, bird and mammal hosts, and the environment, and for these reasons it has not yet proven possible to anticipate the occurrence of WNv or WNV disease at a level of spatial detail that would permit highly targeted local public health intervention. It is therefore clear that to minimize the impacts of WNv disease on the health of Canadians emphasis should be placed on primary prevention of human exposure to mosquitoes that may be carrying the virus, with the support of high-quality surveillance of WNv and WNv disease, control of mosquito vectors, and public and professional education. In Canada, a number of these preventive approaches are in place. For example, WNv disease is nationally notifiable and reportable, by statute, in all provinces and territories in Canada, and integrated national surveillance has been carried out through federal/provincial/territorial (F/P/T) partnership since 2002 (10,12). The national surveillance effort is based on weekly sharing of surveillance data on humans, horses, birds and mosquitoes with the Public Health Agency of Canada by diverse partners, including provincial/territorial ministries of health, Canadian Blood Services and Héma-Québec, the Canadian Food Inspection Agency and the Canadian Cooperative Wildlife Health Centre. This information is then assembled into weekly national reports (12) during the peak risk season, as determined by an F/P/T working group at the beginning of each summer. The weekly reports are supplemented with information regarding WNv activity in the USA and in Europe.

Municipalities often undertake targeted control of mosquito populations, based on information about mosquito activity, infection rates and the occurrence of human and/or animal WNv disease in the area. Other important, national, public health measures are routine testing of blood donations by Canadian Blood Services and Héma-Québec to prevent blood-borne WNv transmission and often to provide the earliest indication of WNv activity in a given season, and delivery of expert scientific, epidemiological and laboratory diagnostic support (federally, through the National Microbiology Laboratory and the Centre for Food-borne, Environmental and Zoonotic Infectious Diseases). There is also, of course, much that Canadians can do to protect themselves and their families from exposure to mosquitoes that could carry WNv. Such measures include minimizing standing water

to reduce local mosquito abundance, using insect repellents containing the active ingredient *N*,*N*-diethyl-*m*-toluamide (DEET), reducing outdoor activity when mosquitoes are most active and wearing protective clothing (21).

Conclusions

West Nile virus and the health problems it causes are likely to remain significant concerns for Canada in the foreseeable future. Surveillance, medical diagnosis and screening, mosquito control and public education programs have all been instituted in Canada. However, the dynamic nature of the pathogen, the complexity of its ecological interactions and the unpredictability of its detailed behaviour in time and space all indicate that additional efforts are required to maintain and improve the efficacy of primary prevention. Surveillance, research, logistic support and intervention measures undertaken by federal, provincial and territorial governments will continue to play key roles in these efforts. However, the issue of WNv is of importance to all Canadians, and access to up-to-date, scientifically based knowledge will continue to have a major positive impact.

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Summary of recommendations on malaria issues in special hosts

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.

Objective: To provide guidelines on malaria issues related to special hosts.

Methods: CATMAT reviewed all major sources of information on malaria prevention, 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: All people visiting malaria endemic regions should use effective personal protective measures (PPM; topical repellants, bed nets, behavioural choices) and the prescribed chemoprophylaxis. Chemoprophylaxis for pregnant and breastfeeding women and for children requires careful consideration in the context of the pregnancy trimester, the age or size of the infant/child as well as their glucose-6-phosphate dehydrogenase (G6PD) status. Recommendations for long-term travellers, expatriates and people visiting friends and relatives (VFRs) do not differ markedly from those for short-term travellers. Some underlying medical conditions may make individuals more vulnerable to malaria. In addition, some conditions or their treatment may preclude the use of one or more antimalarial medications.

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).

The Committee to Advise on Tropical Medicine and Travel (CATMAT) provides the Public Health Agency of Canada with ongoing and timely medical, scientific and public health advice relating to tropical disease and health risks associated with international travel. This is a summary of one section 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 (2). These guidelines include a full description of the recommendations on risk assessment, prevention and treatment of malaria, a disease that is still uncommon in Canada. Two additional summaries of the guidelines are available focusing on prevention and treatment of malaria (3,4).

Special groups of travellers have different risks of acquiring malaria infection compared with the average traveller. If unable to defer travel to areas with high risk of malaria, pregnant and breastfeeding women and small children should receive tailored antimalarial chemoprophylaxis, since some of the drugs are contraindicated in these groups. Long-term travellers, expatriates and travellers visiting friends and relatives (VFRs) may perceive malaria risk differently and may adhere differently to chemoprophylaxis. They require additional information about self-diagnosis and treatment. The issue of counterfeit drugs is addressed specifically for long-term travellers

Methods

The Malaria Subcommittee, a working group of CATMAT, developed the guidelines. The process undertaken to develop them has been described previously (3). 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 various malaria issues pertaining to special hosts were developed with associated rating scales for the strength and quality of the evidence.

Recommendations

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

Children

Malaria disproportionately affects children and can have nonspecific symptoms that mimic other common childhood illnesses, 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 (5).

Young children should avoid travel to areas with significant malaria transmission, particularly of chloroquine-resistant malaria (6). When travel to malaria-endemic areas is unavoidable consider the following:

- All children should use effective personal protective measures (PPM: topical repellants, bed nets, behavioural choices) (7) and appropriate malaria chemoprophylaxis (1,8).
- For chloroquine-resistant areas, mefloquine, doxycycline (for those ≥ 8 years) and atovaquone-proguanil (≥ 5 kg) are most appropriate (9-12)
- Primaquine may be suitable for children who are unable to take the first-line prophylactic agents, once adequate G6PD (glucose-6-phosphate dehydrogenase) levels have been confirmed (13).
- Prescribe antimalarial drugs for breastfeeding infants even if their mother is taking antimalarials (6,14).
- Specific instructions related to dosing:

    - Prescribe sufficient tablets to allow a few doses to be vomited or spat out. Give clear instructions when to repeat doses that were not successfully ingested;
    - Have tablets pre-cut or crushed and inserted into capsules to increase the accuracy and ease of dosing;
    - Describe how to adjust the dose of medications to allow for an increase in children's weight.

- Explain that because there are few pediatric formulations, malaria tablets may be crushed and mixed with something sweet to disguise their unpleasant taste.

Pregnant and breastfeeding women

Pregnant women should defer travel to malaria-endemic areas and particularly to regions with drug-resistant falciparum malaria (15). Malaria increases the risk of maternal and neonatal death, miscarriage and stillbirth. Low birth-weight infants are more commonly born to women taking ineffective prophylaxis (15).

If travel is unavoidable,

- Pregnant and breastfeeding women should use PPM (topical repellents, insecticide-treated bed nets, and behavioural choices) (16).
- Prescribe chemoprophylaxis based on destination:

    - Chloroquine in chloroquine-sensitive areas;
    - Mefloquine where exposure to chloroquine-resistant falciparum malaria is unavoidable (17-19);
    - Discuss the benefits and risks of atovaquone-proguanil after the first trimester in women who cannot avoid travel to mefloquine-resistant areas or who cannot take mefloquine (20,21);
    - Although safe in pregnancy, the combination of chloroquine and proguanil is inadequate as an antimalarial and cannot be recommended for chloroquine-resistant areas (22);
    - Doxycycline is contraindicated during pregnancy.

Nursing women should continue to breastfeed if using chemoprophylaxis that is safe in infancy (chloroquine, mefloquine, atovaquone-proguanil in infants weighing $\geq$ 5 kg). Doxycycline absorption through breast milk is probably negligible, and breastfeeding is not an absolute contraindication to maternal use (23).

Migrants

Although in most cases disease will develop within three months of last exposure, malaria could be the reason for any fever that develops within 12 months of leaving a malaria-endemic region (24). The risk of malaria exists for migrants after their arrival in Canada:

- For at least 12 months after migrants arrive in Canada, test for malaria in cases of unexplained fever.
- Consider malaria screening in asymptomatic new migrants from highly endemic areas, and treat those with parasitemia (apart from the presence of gametocytes only) in blood smears.
- Ask migrants from malaria-endemic countries about future travel plans to provide anticipatory guidance about malaria (25).

Long-term travellers, expatriates and visiting friends and relatives

Recommendations for preventing malaria in long-term travellers (travel for longer than one month), expatriates or visiting friends and relatives are very similar to the standard recommendations for the short-term traveller (26): use prescribed malaria chemoprohylaxis and PPM consistently, including insecticide-treated bed nets and topical repellents containing 20%–30% DEET or 20% icaridin.

Some of the topics to cover when counselling expatriates and long-term travellers about malaria prevention include the following:

- Possible concern about safety with prolonged use of chemoprophylaxis medication.
- Use of PPM over the long term.
- Cost of medication over the long term.

- Use of locally procured and possibly counterfeit drugs.
- Conflicting counsel about chemoprophylaxis and self-treatment.
- Need for ongoing adherence to chemoprophylaxis.

Since overall nonadherence rates for chemoprophylaxis are as high as 61% (27), pre-travel advice should focus on these aspects:

- Malaria symptoms and risk, emphasizing the need for early diagnosis and treatment.
- Development of a plan for accessing competent medical care in case of illness.
- Standby emergency therapy (self-treatment).
- The affordability of chemoprophylaxis.
- The likelihood that local malaria drugs are counterfeit (28).
- The loss of partial immunity among visiting friends and relatives because of residence in a country without malaria (25).

The risk of malaria among visiting friends and relatives is almost the same as for local residents, but the risk of *severe* disease is higher because of loss of partial immunity after having lived in a non-endemic area (25).

VFRs tend to show certain characteristics:

- Be less likely to seek out or comply with preventive travel health advice (29-31), possibly because of
    - Financial or time restrictions (25);
    - Misconceptions about risk of disease and immunity; or
    - Reliance on advice from family members or local providers at their destination (25,27,28,32,33).
- Stay in rural locations (with higher rates of malaria transmission than urban centres) and for longer visits (25).
- Stay with local family members rather than in air-conditioned and well-screened hotels (25).
- Travel with their Canadian-born children (25).
- Make last-minute emergency travel plans (25).

Table 1: Evidence-based medicine recommendations for malaria prevention and treatment in special hosts

Recommendation		EBM rating*
Children		
1.	Young children should avoid travel to areas with significant malaria transmission, particularly of chloroquine-resistant malaria (6).	C III
2.	All children who travel to malaria-endemic areas should use PPM (7).	A I
3.	In chloroquine-resistant areas, mefloquine, doxycycline (≥ 8 years) and atovaquone-proguanil (≥ 5 kg) are the drugs of choice for chemoprophylaxis (9-12).	A I
4.	Primaquine chemoprophylaxis may be suitable for children who cannot take any of the first-line prophylactic agents, after confirmation of G6PD status (13).	B II
Pregnant women		
5.	Pregnant women should avoid travel to areas with significant malaria transmission (15).	C III
6.	Pregnant women who travel to malaria-endemic areas should use PPM, including appropriate topical repellents and insecticide-treated bed nets (16).	A I
7.	In chloroquine-sensitive areas, pregnant women should use chloroquine as chemoprophylaxis.	A I
8.	Where exposure to chloroquine-resistant falciparum malaria is unavoidable, pregnant women should use mefloquine from conception through the first trimester (A II) and during the second and third trimesters (A I) (17-19).	A II, A I

Recommendation		EBM rating*
9.	There are no currently approved antimalarials for pregnant women travelling to mefloquine-resistant regions. Atovaquone-proguanil after the first trimester may be considered after careful discussion of the benefits and risks (20,21).	B II
10.	Although safe in pregnancy, the combination of chloroquine and proguanil is inadequate as an antimalarial and cannot be recommended for chloroquine-resistant areas (22).	E I
Breastfeeding women		
11.	Infants should receive their own appropriate chemoprophylaxis even if breastfed (23).	A III
12.	Women breastfeeding a child < 5 kg should avoid atovaquone-proguanil (23).	C II
13.	Limited data suggest that doxycycline absorption through breast milk is negligible and that breastfeeding is not an absolute contraindication to maternal use (23).	C III
Migrants		
14.	For at least 12 months after migrants arrive in Canada, test for malaria in cases of unexplained fever.	C III
15.	Consider malaria screening in asymptomatic new arrivals from highly endemic areas, and treat those who have parasitemia (apart from the presence of gametocytes only) in blood smears.	C III
16.	Ask migrants from malaria-endemic countries about future travel plans. Doing so may provide the opportunity for anticipatory guidance about malaria (25).	C III
Long-term travellers or expatriates		
17.	Guidelines for preventing malaria in long-term travellers or expatriates should not deviate considerably from the recommendations for short-term travellers (26).	B III
18.	Training long-term travellers in the use of rapid diagnostic tests is reasonable (26,34).	C III
19.	For long-term travellers who are more likely to buy drugs in countries without quality controls, provide education about counterfeit antimalarial medications (35-37).	C II
20.	Consider primaquine for terminal prophylaxis for military personnel, long-term travellers or expatriates returned from regions with *P. vivax* transmission (26,38,39).	A I
Visiting friends and family (VFRs)		
21.	Inform Canadian VFRs travelling to malaria-endemic countries about the risk of malaria, including the loss of partial immunity from living in Canada and the increased risk of severe disease in children and pregnant women (25).	C III
22.	Counsel Canadian VFRs travelling to malaria-endemic countries about PPM (repellents, bed nets, behavioural choices) and chemoprophylaxis (25).	C III
23.	Discuss the affordability of chemoprophylaxis with Canadian VFRs travelling to malaria-endemic countries, taking cost into account in deciding about choices (25).	C III
Travellers with co-morbidities		
24.	Individuals who are immunosuppressed or have co-morbidities should consult with a travel medicine or infectious disease expert (40).	B III
25.	Potential drug interactions and overlapping toxicities warrant careful review before antimalarial drugs are prescribed for people with chronic medical conditions, including HIV infection (41).	A I
26.	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.	B III
27.	Provide standby antimalarial therapy for travellers with asplenia who may experience delays in accessing appropriate care for febrile illness.	A II
28.	A pre-travel trial with INR (international normalized ratio) testing should be done if mefloquine, doxycycline or proguanil (including atovaquone-proguanil) are to be used by people taking warfarin	A II

Recommendation		EBM rating*
	(42-45).	
29.	Avoid chloroquine and mefloquine in the presence of a chronic seizure disorder.	E II
30.	Avoid chloroquine and mefloquine for travellers with myasthenia gravis.	E III
31.	Carefully review mental health history before prescribing mefloquine to ensure that psychotic, depressive or anxiety disorders are absent (46).	A I
32.	Chloroquine may exacerbate psoriasis. Mefloquine, doxycycline and atovaquone-proguanil are preferable to chloroquine in patients with underlying psoriasis.	B III
33.	Primaquine should not be used as chemoprophylaxis in the presence of G6PD deficiency.	E II
34.	Atovaquone-proguanil may be the preferred choice for malaria prophylaxis in the presence of porphyria.	B III

*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.

Long-term safety of chemoprophylaxis and PPM

Long-term use of chemoprophylaxis recommended for short-stay travellers does not result in additional risk of severe adverse events although data on the effectiveness and tolerance of recommended regimens are limited. **Table 2** summarizes the safety of chemoprophylaxis with long-term use.

Table 2: Safety of chemoprophylaxis with long-term use

Chemoprophylactic drug	Effects of long-term use
Chloroquine	Requires an ophthalmologic examination at least every 2 years (30). However, chloroquine is seldom indicated because of extensive drug resistance.
Mefloquine	Well tolerated (47-50). Mefloquine tolerance improves over time, possibly because any adverse events become apparent relatively early (47). Consequently, there does not appear to be increased risk with long-term use (28).
Atovaquone-proguanil	Although data on prolonged use of atovaquone-proguanil are limited, the individual components have been used for extended periods (30).
Doxycycline	Although data are limited, the drug and the related minocycline have been used for extended periods for other indications (31).

Currently, no long-lasting, insecticide-treated nets are registered for use in Canada. Insecticide-treated bed nets can be obtained from some Canadian travel health clinics and other domestic and international suppliers (8):

- The insecticide in most bed nets starts to lose its effect after six months (8).
- Liquid permethrin used to treat bed nets is not available in Canada.
- Travellers should renew the insecticide treatment of their bed nets at the start of rainy seasons.

Counterfeit drugs

Many expatriates and long-term travellers may have the opportunity to buy their antimalarial chemoprophylaxis and antimalarial drugs over the counter at local pharmacies where they are staying and cannot evaluate the authenticity of these drugs. Encourage all travellers and expatriates to buy a supply of medication in countries with strict quality control measures (35-37).

If travellers are buying outside of Canada bear in mind the following:

- Coartem® (artemether-lumefantrine) is not yet licensed for distribution in Canada but is recommended by the World Health Organization as first-line treatment for *P. falciparum* malaria. Travellers should buy it in Europe, the USA or other countries where counterfeiting is unlikely (39).
- Atovaquone-proguanil prophylaxis may be too expensive for most long-term use. Long-term travellers and expatriates may choose to purchase enough for one or two self-treatment courses (51).

Rapid diagnostic tests

Rapid diagnostic tests are essential diagnostic tools when malaria microscopy results are not available within two hours (26). Rapid diagnostic tests are simple to use, require no equipment or specialized laboratory skills and can be valuable adjuncts in diagnosing malaria (52). However, many travellers are unable to complete the procedures or interpret the results correctly (26,53,54). Without adequate training of laboratory staff, the usefulness of Rapid diagnostic tests may be no better among expatriates (34,55). Nevertheless, key members of a reasonably stable expatriate community could be trained in their use and in administration of appropriate self-treatment (26,34).

Standby emergency self-treatment

Self-treatment is a temporary, life-saving measure for 24 hours while medical attention is sought. Travellers to high-risk regions should never rely exclusively on self-treatment (40,56-58). Self-treatment regimens by region are summarized in **Table 3**.

Reasons for self-treatment include travelling/staying in these areas:

- Sub-Saharan Africa, where 90% of global malaria morbidity and mortality occurs.
- Remote regions where access to health care is a problem.
- Regions where malaria risk is small and self-treatment is preferable to long-term prophylaxis (26,28,56,59).

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.

Table 3: Self-treatment regimens

Region	Self-treatment regimens
Chloroquine-sensitive regions	Self-treat with chloroquine and then resume or start chloroquine prophylaxis (54,56,60).
Chloroquine-resistant and/or chloroquine- and mefloquine-resistant *P. falciparum* regions	Self-treat with a drug different from that used for prophylaxis: a. Atovaquone-proguanil (Malarone®) or b. oral quinine and doxycycline or c. artemether-lumefantrine (Coartem®), purchased from a country with high standards of quality control to minimize the likelihood of being sold counterfeit products (36,37,54,60).

Some antimalarials are contraindicated for the treatment of malaria (self-treatment or otherwise):

- mefloquine (61,62)

- pyrimethamine-sulfadoxine (Fansidar) (63)
- mefloquine-Fansidar (62)
- halofantrine (39)
- chloroquine-Fansidar (59).

Terminal prophylaxis

P. vivax and *P. ovale* parasites can persist in the liver and cause relapses for as long as five years after the person has left a malaria-endemic area. Primaquine anti-relapse therapy (PART) decreases the risk of relapses by acting against the liver stages of *P. vivax* and *P. ovale*. PART is usually administered during or after the last two weeks of chemoprophylaxis to those who have been in malaria-endemic regions (most malarial areas of the world except Haiti and the Dominican Republic) (26,38,39,64). Primaquine is contraindicated for use as PART in people with G6PD deficiencies, in pregnancy and in nursing mothers if the infant is G6PD deficient.

Travellers with co-morbidities

Interactions between malaria and other underlying medical conditions may result in increased susceptibility to and severity of malaria or complications of the underlying conditions. Some underlying health conditions may be exacerbated by or preclude using one or more antimalarial medications.

Routinely undertake a drug interaction check to avoid any potential adverse drug interactions unless the traveller's medications are known to be safely used with the proposed antimalarial agent.

Immunocompromised hosts

Immunocompromised travellers should carefully adhere to both PPM and chemoprophylaxis.

HIV/AIDS

There is a significant and complex interaction between human immunodeficiency virus (HIV) and *P. falciparum*. Assess for drug interactions, and consider the risk of overlapping adverse effect profiles (65). CATMAT recommends consulting with a travel/tropical medicine/infectious disease expert and the traveller's HIV specialist (40).

Asplenia

Asplenia increases the risk, magnitude and duration of parasitemia, even among partially immune individuals in malaria-endemic countries (41), and enhances the risk of severe and fatal malaria in travellers with this condition (66). Recommend standby self-treatment *in addition* to prophylactic measures if the traveller is heading to remote regions and/or access to care is limited. Since fever may be due to malaria or bacterial infection, provide antibacterial standby treatment (67).

Other conditions

A list of other conditions and their effects on the choice of malaria chemoprophylaxis are summarized in Table 4.

Table 4: Other conditions that affect choice of malaria chemoprophylaxis

Condition	Impact on choice of malaria chemoprophylaxis
Abnormal coagulation	Mefloquine, doxycycline and proguanil may potentiate warfarin (42-45,68). Conduct a medication trial several weeks in advance of travel and International Normalized Ratio (INR) serial testing to allow adjustment of the anticoagulant dose both before and after travel.
Seizure disorders	Chloroquine and mefloquine may exacerbate seizures, so prescribe alternative agents. 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 the half-life of doxycycline, and may require dosage adjustment (45).

Myasthenia gravis	Malaria infections may exacerbate myasthenia gravis. Optimal prevention through adherence to chemoprophylaxis and PPMs should be reinforced. Avoid chloroquine, mefloquine and doxycycline as they have been associated with worsening of myasthenic symptoms. Doxycycline may be considered in stable patients, particularly for those with only ophthalmologic symptoms, though CATMAT recommends a pre-travel therapy trial. A pre-travel trial of atovaquone-proguanil therapy is recommended, since proguanil monotherapy has been reported to worsen myasthenic symptoms (69). Primaquine has not been associated with myasthenic symptoms and may be an option for *P. falciparum* prophylaxis (after ruling out G6PD deficiency) in myasthenic travellers who are unable to tolerate doxycycline and atovaquone-proguanil.
Psychiatric disorders	Assess for history of depression, generalized anxiety disorder or psychosis before prescribing mefloquine (46,70). Dose-related neuropsychiatric adverse effects are well recognized with mefloquine and to a lesser extent with chloroquine (71,72).
Hepatic or renal dysfunction	Moderate to severe hepatic or renal dysfunction may alter antimalarial medication levels.* If necessary, consult with a travel/tropical medicine expert. Severe renal insufficiency (creatinine clearance < 30 mL/min) is a contraindication to atovaquone-proguanil use.
Psoriasis	Avoid chloroquine as it may trigger acute flares of psoriasis (73,74).
Glucose-6-phosphate dehydrogenase (G6PD) deficiency	Primaquine is associated with a potentially life-threatening risk of hemolysis. Although G-6PD deficiency is raised as a concern by the manufacturers of chloroquine, experts do not consider this a contraindication, since significant hemolysis is unlikely at prophylactic doses.
Porphyria	Apart from atovaquone-proguanil (75), all the first-line malaria chemoprophylactic agents may be porphyrinogenic. Use with caution.

* See Canadian Recommendations for the Prevention and Treatment of Malaria Among International Travellers, Table 5.4.3: Antimalarial drug considerations for people with renal or hepatic disease.

Conclusion

Special groups of travellers require additional information for prevention and management of malaria. In addition, they should recognize the importance of adherence to recommendations for chemoprophylaxis and PPM. Treatment varies according to the species of *Plasmodium*, the severity of disease and the region where the malaria was acquired, as well as potential interactions between chronic medications and recommended antimalarial therapy.

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Conflict of interest

There are no conflicts of interest to declare.

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Infectious disease news briefs

This feature is back by popular demand – offering short summaries of recently published infectious disease articles.

Chikungunya fever in Canada: fever and polyarthritis in a returned traveller

A previously healthy, 28-year-old woman from Canada experienced extensive mosquito bites while visiting Mumbai, India, in September 2010. Twelve days into her trip, an acute onset of fever, chills and severe joint pain developed, primarily affecting her wrists, neck and ankles. While in India, she received treatment for presumptive malaria and was given parenteral analgesia. After three days, her fever resolved. In addition to fever and joint pain, she reported skin hyperpigmentation on the bridge of the nose. During her convalescence, there was no recurrence of fever, but she remained unable to extend and rotate her wrists, dorsiflex, plantar flex, or internally or externally rotate her ankles without substantial pain.

Chikungunya is an emerging arboviral infection among travellers and one that Canadian physicians are increasingly likely to encounter. Chikungunya fever is caused by the chikungunya virus, which is spread by the *Aedes aegypti* mosquito and less commonly by *A. albopictus*.

Schwartz KL, Giga A, Boggild AK. Chikungunya fever in Canada: fever and polyarthritis in a returned traveller. CMAJ 2014 Feb 24. http://www.cmaj.ca/content/early/2014/02/24/cmaj.130680.long

Preventing dengue through mobile phones: evidence from the field

Dengue is the most rapidly spreading mosquito-borne viral disease in the world (WHO, 2009). During the last two decades, the dramatic rise in the number of dengue infections has been particularly evident in Latin American and the Caribbean countries. This paper examines the experimental evidence of the effectiveness of mobile phone technology in improving households' health preventive behaviour in dengue-endemic areas. The main results suggest that repeated exposure to health information encourages households' uptake of preventive measures against dengue.

Dammert AC, Galdo JC, Galdo V. Preventing dengue through mobile phones: evidence from a field experiment in Peru. J Health Econ 2014 Mar 5;35C:147-161. doi: 10.1016/j.jhealeco.2014.02.002.

Zika virus infection in French Polynesia: implications for blood transfusion

French Polynesia, in the South Pacific, has reported the largest outbreak of ZIKAV infection, which began in October 2013 and had involved an estimated 28,000 cases in February 2014 (about 11% of the population), concomitantly with the circulation of dengue virus serotypes 1 and 3. To the best of our knowledge, the occurrence of ZIKAV infection resulting from transfusion of infected blood has not been investigated. Since other arboviruses have been reported to be transmitted by blood transfusion, several prevention procedures, including nucleic acid testing of blood donors, have been implemented to date to prevent transmission of ZIKAV through transfusion in French Polynesia. We report here the detection of ZIKAV in 42 of 1,505 blood donors, who were asymptomatic at the time of blood donation.

Zika virus (ZIKAV), an arthropod-borne virus (arbovirus) belonging to the family *Flaviviridae* and genus *Flavivirus*, was first isolated in 1947 from a monkey in the Zika forest, Uganda. Sporadic human Zika fever cases have been reported since the 1960s. The first documented outbreak outside Africa and Asia occurred in 2007 in the Yap State, Micronesia, in the North Pacific, where Zika fever was characterized by rash, conjunctivitis and arthralgia. ZIKAV has been isolated from several *Aedes* mosquito species, notably *Ae. aegypti* and *Ae. albopictus*. *Ae. aegypti* is widespread in the tropical and subtropical regions of the world, and *Ae. albopictus* is now established in many parts of Europe, especially Mediterranean countries. Recent reports of imported cases of ZIKAV infection from south-east Asia or the Pacific to Europe or Japan highlight the risk of ZIKAV emergence in parts of the world where the vector is present.

Musso D, Nhan T, Robin E, Roche C, Bierlaire D, Zisou K, Shan Yan A, Cao-Lormeau VM, Broult J. Potential for Zika virus transmission through blood transfusion demonstrated during an outbreak in French Polynesia, November 2013 to February 2014 . Euro Surveill 2014;19(14):pii=20761. http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20761

WHO statement on international spread of wild poliovirus

In the context of the global polio eradication initiative, the (International Health Regulations Emergency) Committee advised that the international spread of polio…constitutes an 'extraordinary event'…for which a coordinated international response is essential. If unchecked, this situation could result in failure to eradicate globally one of the world's most serious vaccine preventable diseases…

Pakistan, Cameroon, and the Syrian Arab Republic pose the greatest risk of further wild poliovirus exportations in 2014… Afghanistan, Equatorial Guinea, Ethiopia, Iraq, Israel, Somalia and particularly Nigeria …. pose an ongoing risk for new wild poliovirus exportations in 2014. (All of) These States should encourage residents and long-term visitors to receive a dose of OPV or IPV 4 weeks to 12 months prior to international travel.

WHO statement 5 May 2014 http://www.who.int/mediacentre/news/statements/2014/polio-20140505/en/