Review

Synthèse

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Malaria deaths in visitors to Canada and in Canadian travellers: a case series

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Abstract

Over the last decade there has been a marked increase in cases of drug-resistant and severe malaria in Canadian travellers. We report 7 deaths due to falciparum malaria that occurred in Canada or in Canadian travellers. Risks for malaria infection include inappropriate recommendations for malaria prevention by health care providers and lack of knowledge about or adherence to appropriate recommendations by the travelling public. Risks for death include delays in seeking medical attention, delays in diagnosis and inadequate care by Canadian physicians and hospitals, and lack of access to parenteral therapy for severe malaria. Malaria infections and deaths are preventable. Better education of health care providers and travellers about the risks of malaria and appropriate prevention and treatment measures may decrease this unnecessary burden on the Canadian health care system.

Preventable malaria-associated illness and death continue to occur in Canadian travellers. During the past 7 years, Canada has witnessed record numbers of cases of imported malaria,[1–3] with a peak of 1036 cases in Canadian travellers reported for 1997. This figure represents a 141% increase since 1994 and a per capita rate about 10 times that reported in the United States.[1–4] Furthermore, there has been a dramatic increase in the number of cases caused by drug-resistant parasites and an approximately 10-fold increase in the number of cases of severe malaria requiring admission to an intensive care unit[5,6] (unpublished data). Despite optimal management in an intensive care setting, severe malaria is associated with a case fatality rate that often exceeds 20%, even among young, previously healthy adults.[7,8] Severe malaria may be complicated by adult respiratory distress syndrome; in this situation, case fatality rates often exceed 80%.[9,10]

One of us (K.C.K.) contributed to a 1997 report of 2 fatal cases of falciparum malaria in Canadian travellers.[6] We now report an additional 7 deaths due to falciparum malaria that occurred in Canada or in Canadian travellers.

Case reports

Case 1

A 39-year-old Canadian man had been working in the oil fields of Zambia as a cook. His use of malaria chemoprophylaxis was unknown. Before his departure from Africa, he complained of fever and chills. In early May 1998, on his way home to Quebec, he stopped for a holiday in Cuba. A few days after arriving in Cuba, he was found unconscious in his hotel. Upon transfer to a local hospital, he was found to be jaundiced, dehydrated, severely acidotic and in renal failure. After intubation, ventilation and rehydration, he regained consciousness. A blood smear was reported as positive for *Plasmodium vivax* (5000/μL), and he was treated with oral chloroquine. Two days after his admission to hospital in Cuba, he was medevaced to Montreal. When he arrived at the Montreal General Hospital intensive care unit, he was in a coma. His serum potassium level was 7.8 mmol/L (normal level 3.2–5.0 mmol/L),

creatinine 655 µmol/L (normal level 60–110 µmol/L), pH 7.1 (normal level 7.35–7.45), hemoglobin 47 g/L (normal level 140–180 g/L) and glucose 0.7 mmol/L (normal level 2.5–4.2 mmol/L). He had 18% parasitemia with *Plasmodium falciparum*; no *P. vivax* parasites were identified. He suffered cardiac arrest and died 1.5 hours after arrival. Autopsy revealed features of severe, complicated malaria including adult respiratory distress syndrome and cerebral malaria.

Case 2

A 31-year-old woman, who had immigrated to Canada from Gabon, travelled back to Gabon for several weeks. She did not take malaria prophylaxis. In January 1997, 6 weeks after her return to Canada, she was admitted, in apparent good health, to a Montreal hospital for plastic surgery. The results of a preoperative medical examination 7 days before surgery, which included a complete blood count, were reported as normal. She had previously undergone plastic surgery with a general anesthetic. The day of her surgery she indicated that she was not feeling well, but her vital signs were normal. The 2-hour procedure was uneventful, and her stay in the recovery room was uncomplicated until 90 minutes after the surgery ended, when the nurse noticed a moderate amount of serosanguineous fluid oozing from the dressing. One hour later, the patient became unresponsive and experienced marked oxygen desaturation and cardiorespiratory arrest with ventricular fibrillation. She was resuscitated but remained unresponsive and obtunded. At the time of the postarrest resuscitation, her potassium level was 8.2 mmol/L (normal level 3.2–5.0 mmol/L) and hemoglobin 26 g/L (normal level 120–160 g/L), and she was noted to have 5.8% parasitemia with *P. falciparum*. Despite intravenous administration of quinidine and clindamycin, the patient died 48 hours after the surgery. Autopsy revealed pulmonary congestion, disseminated intravascular coagulation, massive intravascular hemolysis and acute bronchopneumonia with septicemia. Results of hemoglobin electrophoresis were normal, except for a Philadelphia trait, and her glucose 6-phosphate dehydrogenase level was normal.

Case 3

A 29-year-old Canadian man was employed for 2 months as a miner in rural Zambia. While in Zambia, his compliance with mefloquine prophylaxis was sporadic. He returned to Ontario on June 5, 1998, and later that day began to feel unwell. On June 6, fever, chills and cough developed, and he sought medical attention at the emergency department of the local hospital. He told the emergency room physician he was worried about malaria and that 2 of his coworkers had recently contracted the disease. His temperature was recorded as 40°C, and his platelet count was low (50×10^9/L). Thin smears for malaria were prepared and interpreted as negative by the on-call pathologist. The patient was diagnosed with bronchitis and discharged with prescriptions for clarithromycin and cough medicine. No repeat smears were requested. He was nursed at home by his wife, who was 8 months pregnant. On the morning of June 8, the patient became unresponsive, and he died several hours later. Review of the malaria smear from June 6 indicated the presence of *P. falciparum*. Autopsy revealed features of severe and cerebral malaria and sequestration of malaria parasites throughout the patient's body.

Case 4

A 22-year-old woman left Canada in April 1998 to do volunteer community work in rural Nigeria. She was 3 months pregnant at the time of departure. She sought pretravel advice while in Canada. No travel vaccinations were recommended, and antimalarial agents were not given. She later stated that she had been told that the drugs were contraindicated in pregnancy. While in Nigeria, she developed fever, but it was 10 days before she could reach medical assistance in Ibadan. Severe *P. falciparum* malaria requiring hemodialysis developed subsequently. On July 14, in the sixth month of her pregnancy, she spontaneously delivered a stillborn male infant. She was billed in excess of US$20 000 for her hospital care. At the time of writing, the woman was being assessed for other complications related to her infection and the medical care she received in Nigeria.

Case 5

A 68-year-old man, a long-term resident of Liberia, was visiting family in Canada during December 1998. On Dec. 25, 1998, he was found in an unresponsive state and was taken to the emergency department of a local hospital. He was not responsive to verbal commands, his respiratory rate was 24 breaths/min, and his pulse was 88 beats/min. He was afebrile and jaundiced. A complete blood count revealed normochromic, normocytic anemia (hemoglobin 92 g/L) and thrombocytopenia (platelets 57×10^9/L). A blood smear was positive for malaria parasites (2% to 3% parasitemia); no species identification was reported. The patient was given an intravenous loading dose of quinine and was transferred to the Toronto General Hospital on Dec. 26, 1998. After he was admitted to the intensive care unit, adult respiratory distress syndrome and renal and liver failure developed, and despite successful clearance of *P. falciparum* from the peripheral blood (as indicated by smear analysis) he suffered cardiorespiratory arrest and died on Jan. 5, 1999. Autopsy revealed microhemorrhages in the cerebral cortex consistent with cerebral malaria. There was no evidence of intracranial herniation. Malaria parasites or their pigment were identified in all sections of the brain.

Case 6

A 51-year-old Canadian man and his 52-year-old wife

were working as long-term missionaries in Malawi. Before departure from Canada they had been given prescriptions for mefloquine for malaria chemoprophylaxis. While in Africa they discontinued the mefloquine and started taking dapsone–pyrimethamine weekly for malaria chemosuppression. In April 1999 the husband experienced headache and a flu-like illness. He self-medicated with three sulfadoxine–pyrimethamine tablets but continued to feel unwell, with shaking chills and intermittent episodes of diarrhea. Two days after the self-treatment he presented to a local laboratory in Malawi. Blood smear results led to a diagnosis of *P. falciparum* malaria (2% parasitemia). He was told by local physicians that other medications could not be given so soon after the sulfadoxine–pyrimethamine, that malaria was not a serious disease and that it would take time for the disease to respond to the medication he had already taken. Over the next 2 days his condition continued to deteriorate, and at his wife's insistence he began to take oral quinine. However, he completed only 2 doses before his condition deteriorated further and he was admitted to hospital. Intravenous administration of quinine was started, and his condition initially improved, but he then became increasingly disoriented. Coma and jaundice developed, and he died the day after admission. His wife also experienced flu-like symptoms and fever during the course of her husband's illness. The day before he died, she requested malaria smears, which were positive for *P. falciparum* (0.5% parasitemia). She was treated with parenteral quinine for 1.5 days and then oral quinine for another 1.5 days. She was concurrently treated with doxycycline 100 mg bid for 7 days. She recovered gradually while returning to Canada with her husband's body.

Case 7

A 55-year-old citizen of the United Kingdom was visiting family in Canada during July 1999. He had been a long-term resident of Mombasa on the coast of Kenya. He had experienced 3 previous episodes of malaria, the most recent occurring 3 months before his travel to Canada. He arrived in Canada on July 14, 1999, and experienced fever approximately 2 days later. When the fever and confusion increased, he presented to the emergency department of a hospital in the Niagara region on July 18, 1999. A malaria smear was reported as positive at that time, but the species was not identified. The smear was later confirmed as positive for *P. falciparum* (2.2% parasitemia). Chloroquine was prescribed, and the patient was discharged. His condition continued to deteriorate despite the chloroquine therapy, and he re-presented at the hospital on July 20, 1999. At that time, he exhibited evidence of renal failure and decreased level of consciousness. He was transferred to the Toronto General Hospital on July 21, 1999. A blood smear at that time revealed *P. falciparum* (15% parasitemia). He was given a parenteral loading dose of quinine and underwent exchange transfusion. Although subsequent peripheral smears became negative for the parasite, coma, acute renal failure, hypotension and adult respiratory distress syndrome developed, and the patient died on July 23, 1999.

Comments

The prevalence of drug-resistant malaria is escalating worldwide. The mortality rate associated with drug-resistant falciparum malaria has increased as much as 8-fold over the last decade in some regions of sub-Saharan Africa,[11,12] despite the fact that deaths due to this form of malaria are preventable. The 7 cases presented here illustrate how inadequate measures to prevent infection, delays in recognition and incorrect treatment can result in unnecessary illness and death. Each case also provides important insights into the changing epidemiology of imported malaria in Canada.

All 7 people acquired the infection in Africa, where falciparum malaria is now largely resistant to chloroquine, pyrimethamine and proguanil and is becoming increasingly resistant to combination drugs such as sulfadoxine–pyrimethamine and dapsone–pyrimethamine.[2,11,12] However, the chemoprophylactic drugs currently recommended by Health Canada (through the Committee to Advise on Tropical Medicine and Travel),[13] the US Centers for Disease Control and Prevention,[14] and the World Health Organization,[15] such as mefloquine and doxycycline, remain extremely effective in preventing malaria in high-risk travellers to sub-Saharan Africa. For people who cannot take or tolerate mefloquine or doxycycline, primaquine or newer agents such as the combination of atovaquone and proguanil may be useful alternatives.[2,16] Despite the availability of these highly active drugs in all of the cases reported here, the patients were receiving either no, inappropriate or irregular malaria prophylaxis. Tragically, in at least 2 of the cases (cases 4 and 6) the patients had been advised, inappropriately, not to take chemoprophylaxis or to change to an alternative agent. Travellers are often instructed by local physicians and residents to discontinue their current prophylactic regimen, even though it is well tolerated, and to switch to other regimens, which are usually less effective and often more toxic. For example, the couple described in case 6 switched to dapsone–pyrimethamine, which is less effective than mefloquine and which, at doses sufficient to prevent malaria, is associated with a 1 in 2000 risk of agranulocytosis.[17]

At present, mefloquine remains the antimalarial drug of choice for most high-risk travellers to sub-Saharan Africa (Table 1, Fig. 1). Overall, this drug is as well tolerated as other chemoprophylactic regimens.[19] However, real and perceived intolerances to mefloquine have received substantial and occasionally irresponsible coverage in the Canadian media. As a result, many Canadian travellers refuse to take mefloquine, even when it is clearly the most appropriate choice. Yet the deaths reported here would have been unlikely had the patients been using mefloquine

or an agent with similar efficacy. Similar negative media campaigns against mefloquine in the United Kingdom resulted in a decrease in use of the drug by travellers. A 10-fold increase in imported falciparum malaria, an increase in severe malaria and several deaths were associated with this decrease in use of mefloquine by travellers.[20]

Even in travellers who are not taking antimalarial drugs and who do acquire infection, early recognition and appropriate treatment will almost always yield a good outcome. However, delays in recognizing and treating malaria are clearly linked to increases in illness and death.[2,6,8,21–23] A delay of as little as 24 hours in diagnosis and initiation of treatment can increase the case fatality rate by as much as 5 times. The cases presented here illustrate a number of ways in which these delays occur. The diagnosis may be missed when the patient first presents for medical attention. In a recent prospective study in Toronto,[5] the diagnosis of malaria was missed in 59% of patients when they first presented to a physician. Alternatively, laboratories may fail to correctly prepare and interpret thick and thin blood smears, which results in false-negative results or incorrect species identification, which in turn leads to delays in initiating therapy or to incorrect therapy (because the particular treatment depends on the species involved).[5,6] Laboratory diagnostic errors occurred in at least 4 of the cases presented here: missed recognition of *P. falciparum* in case 3, incorrect identification of the parasite species (*P. vivax* mistaken for *P. falciparum*) in case 1 and failure to identify the species in cases 5 and 7. Lack of recognition of malaria by physicians and laboratory errors increase the risk of severe malaria, a form of the disease that is associated with a high fatality rate even in young, previously healthy adults. Once severe malaria ensues, especially that associated with adult respiratory distress syndrome, as in cases 1, 5 and 7, even optimal management in an intensive care setting may have little impact on the outcome. Case fatality rates for falciparum malaria with adult respiratory distress syndrome often exceed 80%.[9,10]

Cases 1, 4 and 6 illustrate a common but underreported problem. Travellers, especially those living and working abroad, often discontinue malaria chemoprophylaxis or switch to a less effective regimen and rely on local medical care if they experience a "malaria-like" fever. The patients in cases 1 (in Cuba), 4 (in Nigeria) and 6 (in Malawi) depended on such help. The delays and problems associated with seeking help in a country with different diagnostic services, health care practices and language from those in the traveller's country of origin can have a negative impact on outcome. Travellers to Africa may encounter problems in gaining access to accurate information about malaria, competent malaria diagnosis and appropriate antimalarial drugs.[7] Access to parenteral therapy for severe malaria can also be a problem in Canada. Lack of availability of parenteral quinine to treat severe malaria was a contributing factor in case 7 reported here, as well as in another fatal case in Ontario.[6] A phone survey several years ago indicated that fewer than half of tertiary care teaching hospitals in Canada stocked therapeutic agents for severe malaria.[6]

Case 2 was unusual. Six weeks after returning from a trip to Gabon and 1 week after being declared fit for surgery in a

Table 1: Antimalarial chemoprophylactic regimens for at-risk individuals* according to type of drug resistance present in malarial area†

Drug resistance in malarial area	Drug(s) of choice (and adult dose)	Alternative drugs (and adult dose)
No chloroquine resistance	Chloroquine (300 mg [base] weekly)‡	Doxycycline (100 mg daily)§
Chloroquine resistance¶	Mefloquine (one 250-mg [base] tablet weekly)‡	First choice: doxycycline (100 mg daily)§
		Second choice: primaquine (30 mg [base] daily)**††
		Third choice:‡‡ chloroquine (300 mg base] weekly)‡ plus proguanil (200 mg daily)§
Chloroquine and mefloquine resistance¶	Doxycycline (100 mg daily)§	

*Protection from mosquito bites (by means of insecticide-treated bed nets, DEET-based [*N,N*-diethyl-meta-toluamide] insect repellents and similar measures) is the first line of defence against malaria for *all* travellers. In the Americas and Southeast Asia, chemoprophylaxis is recommended *only* for travellers who will be exposed outdoors during evening or at night in rural areas.

†See also Fig. 1. More detailed information is available from Health Canada,[13] the Centers for Disease Control and Prevention[14] and the World Health Organization.[15]

‡Chloroquine and mefloquine are to be taken for 1 week before entering a malarial area, for the duration of the stay in the malarial area and for 4 weeks after leaving the malarial area.

§Doxycycline and proguanil may be started 1 day before entering a malarial area; they must be taken for the duration of the stay in the malarial area and continued for 4 weeks after departure from the malarial area. Doxycycline is contraindicated in pregnant women and in children less than 8 years old.

¶Evidence indicates that a fixed-dose tablet of atovaquone–proguanil also offers excellent protection against drug-resistant falciparum malaria. However, it is not currently licensed in Canada for this indication.[18]

**Primaquine is started 1 day before entering a malarial area; it must be taken for the duration of the stay in the malarial area and may be discontinued 7 days after leaving the malarial area.

††Contraindicated in people with deficiency of glucose-6-phosphate dehydrogenase (G6PD) and in pregnant women. G6PD level must be measured before this drug is prescribed. This drug is *not* currently licensed in Canada for use as an malaria chemoprophylactic.

‡‡Chloroquine plus proguanil is less effective than mefloquine or doxycycline in areas where chloroqine-resistant malaria occurs.

preoperative medical examination that included a complete blood count, the patient experienced severe hemolysis-induced hyperkalemia and died; later examination of the peripheral thin smear prepared in association with the preoperative blood count was negative for malarial parasites. The interaction of surgery or anesthesia (or both) with *P. falciparum* infection is poorly understood. It may be prudent to prepare both thick and thin malaria blood smears as part of the preoperative work-up for anyone who has been in the malarial tropics within the previous 4 months.

Case 4 illustrates the severe consequences of malaria in pregnancy. Malaria parasitemia is higher in pregnancy, and the consequences for mother and child are particularly serious. For this reason, malaria control programs worldwide make chemoprophylactic malaria prevention in pregnancy a principal focus. Yet too often, travellers are poorly informed about the risk. If a woman is pregnant or plans to become pregnant and cannot defer travel to a high-risk area, then appropriate chemoprophylaxis and measures to prevent mosquito bites are essential. Doxycycline and primaquine are contraindicated during pregnancy. Mefloquine may be considered for use during pregnancy when exposure to chloroquine-resistant *P. falciparum* is unavoidable.[13–15,19] The combination of chloroquine plus proguanil is safe during pregnancy but its efficacy is considerably less than that of mefloquine.

Canada has a high rate of imported malaria. The increasing incidence of drug-resistant malaria in Canadians is a result of increased international travel, an increase in the number of new Canadians returning to visit friends and relatives in their malarious homelands, and inadequate education regarding malaria risk and effective prevention measures.[1,2,24,25] Delays in the recognition and diagnosis of malaria and errors in treatment by health care providers are contributing to an increase in the occurrence of severe malaria and the number of deaths, as reported here. This situation represents a considerable yet avoidable burden on the Canadian health care system.

There is an urgent need for better education of Canadian travellers and health care providers about malaria risk, prevention, diagnosis and management. An effective strategy to decrease malaria in Canadians should include a targeted public health program to educate high-risk travellers such as new Canadians, travellers whose trips last longer than 1 month and the physicians who care for them.[1] This task could be facilitated by support from the travel industry

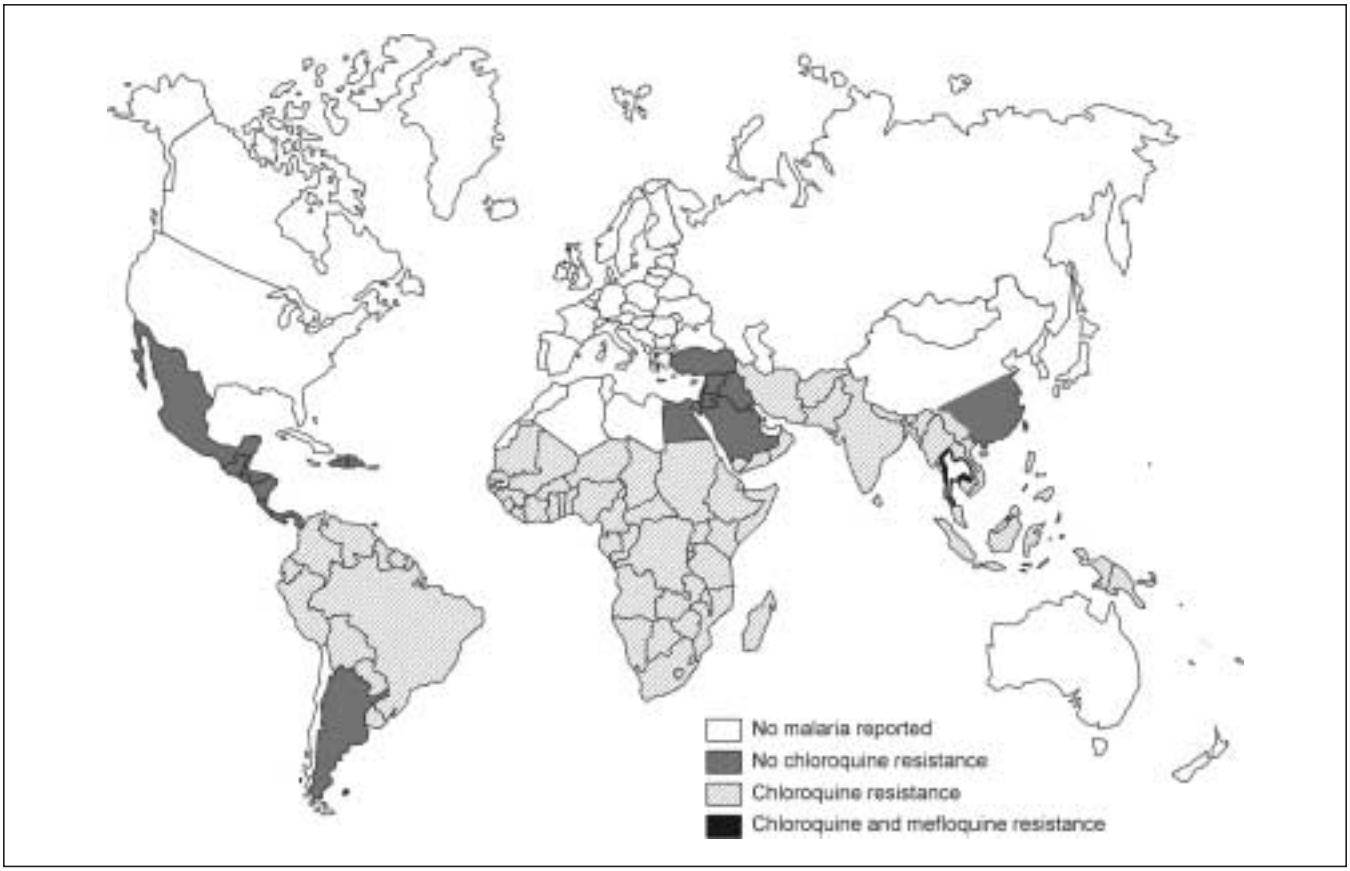

Fig. 1: World map showing areas where malaria is endemic, according to type of drug resistance, if any. This map is meant only as a visual aid, not as a definitive source of information about malarial endemicity. Additional important details about antimalarial drugs and country-specific malaria risk are available from Health Canada,[13] the Centers for Disease Control and Prevention,[14] the World Health Organization[15] and Kain.[19]

and airlines, which can already identify high-risk travellers through their itineraries. However, to date these partners have taken little if any leadership role in this important public health process.[26] Given that international travel and globalization of diseases will continue to escalate, provincial and federal health ministers must understand that maintaining funding and clinical and diagnostic expertise for globally important diseases such as malaria is essential for the welfare of all Canadians. On a positive note, physicians providing advice to travellers have access to the excellent evidence-based recommendations of Canada's Committee to Advise on Tropical Medicine and Travel. These recommendations can be obtained through a FAXlink service (613 941-3900) or through the Internet (www.hc-sc.gc.ca /hpb/lcdc/osh/tmp_e.html).[13]

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