Malaria in Travellers Returning or Migrating to Canada: Surveillance Report from CanTravNet Surveillance Data, 2004—2014

Andrea K. Boggild[1,2], Jennifer Geduld[3], Michael Libman[4], Cedric P. Yansouni[4], Anne E. McCarthy[5], Jan Hajek[6], Wayne Ghesquiere[7], Jean Vincelette[8], Susan Kuhn[9], David O. Freedman[10], Kevin C. Kain[1,11]

[1]Tropical Disease Unit, Division of Infectious Diseases, Department of Medicine, University Health Network and the University of Toronto, Toronto;[2]Public Health Ontario Laboratories, Public Health Ontario, Toronto, Canada; [3]Office of Border and Travel Health, Public Health Agency of Canada, Ottawa; [4]Division of Infectious Diseases, Department of Microbiology, McGill University Health Centre, Montreal; [5]Tropical Medicine and International Health Clinic, Division of Infectious Diseases, Ottawa Hospital and the University of Ottawa, Ottawa; [6]Division of Infectious Diseases, Vancouver General Hospital, University of British Columbia, Vancouver; [7]Infectious Diseases, Vancouver Island Health Authority, Department of Medicine, University of British Columbia, Victoria; [8]Hôpital Saint-Luc du CHUM, Université de Montréal, Montréal; [9]Section of Pediatric Infectious Diseases, Departments of Pediatrics and Medicine, Alberta Children's Hospital and the University of Calgary, Calgary; [10]Center for Geographic Medicine, Department of Medicine, University of Alabama Birmingham, Birmingham, Alabama; [11]SAR Laboratories, Sandra Rotman Centre for Global Health, Toronto.

Address for Correspondence:

Andrea K. Boggild

200 Elizabeth Street, 13EN-218

Toronto, ON M5G 2C4

Phone - 416-340-3675

Fax - 416-340-3260

Email - andrea.boggild@utoronto.ca

Keywords: Malaria; Plasmodium falciparum; surveillance; travel medicine; vector-borne disease; VFR.

Word Count: Abstract: 250; Text: 3326.

Author Contributions: AKB conceived the study, contributed to study design, data collection, analysis, and interpretation, and was primarily responsible for writing the manuscript. JG contributed to study conception, data interpretation, and critical appraisal and revision of the manuscript. ML, CY, AEM, JV, JH, WG, SK, and KCK contributed to data collection and interpretation, and to critical appraisal and revision of the manuscript. DOF contributed to data interpretation and critical appraisal and revision of the manuscript. All authors take responsibility for the integrity of the manuscript.

Funding Source: CanTravNet is the Public Health Agency of Canada's corresponding network for tropical and travel medicine that has been funded through the Office of Border and Travel Health Division of the Public Health Agency of Canada (PHAC). It has been created by grouping the Canadian sites of GeoSentinel: the Global Surveillance Network of the International Society of Travel Medicine, which is supported by Cooperative Agreement U50/CCU412347 from the Centers for Disease Control and Prevention. The funding source of GeoSentinel had no role in study design, data analysis, data interpretation, or drafting the manuscript. The funding source of

CanTravNet contributed to study design and critical appraisal of the manuscript, but did not have access to raw data.

Conflicts of Interest and Disclosures:

Nothing to declare - AKB, JG, AEM, JV, JH, DOF, KCK, WG, SK, CPY, ML

Abstract

Background: Malaria remains the top specific cause of fever in returned travellers, and may be life-threatening. We present a Canada-specific surveillance summary of malaria in returned travellers and new immigrants.

Objectives: We examined demographic and travel correlates of malaria among Canadian travellers and immigrants to identify groups that may benefit from targeted pre-travel intervention.

Methods: Data on ill returned Canadian travellers and immigrants presenting to a CanTravNet site between 2004 and 2014 were analyzed.

Results: During the study period, 20,345 travellers and immigrants presented to a CanTravNet site, 93% of whom had a travel-related diagnosis. Of these, 437 (2.1%) received 456 malaria diagnoses, the most common species being *P. falciparum* (N=282, 62%). Those travelling to "visit friends and relatives" (VFR) were the most well-represented (N=169, 38.1%), followed by business travellers (N=71, 16.9%). Sub-Saharan Africa (SSA) was the most likely source region, accounting for 341 (N=75%) malaria diagnoses, followed by South central Asia (N=55, 12%). Nigeria was the most well represented source country, accounting for 41 cases (9%). India, a high volume destination for Canadians, accounted for 40 cases (8.8%), 36 of which were *P. vivax*. Of 456 malaria diagnoses, 26 (6%) were severe. Of 377 non-immigrant travellers with malaria, 19.9% (N=75) travelled less than 2 weeks, while 7.2% (N=27) travelled less than 1 week.

Conclusions: This analysis provides an epidemiologic framework for Canadian practitioners encountering prospective and returned travellers. It confirms the overwhelming importance of

travel to SSA and India, particularly by VFRs. Short duration travel confers important malaria risk.

INTRODUCTION

Malaria remains the top specific cause of fever in returned travellers (1), and may cause severe life-threatening illness, end-organ damage and cerebral complications. (2). Every year, North Americans die of imported malaria, mostly due to delays in diagnosis and treatment (2-4). However, malaria is preventable by adherence to strategies such as chemoprophylaxis, and personal protective measures including insecticide-treated bed nets, clothing, and insect repellants (5,6). Although bed nets and repellants are commercially available across Canada, chemoprophylactic medications require a prescription, and thus necessitate an encounter with a health care professional prior to travel in order to be obtained. Knowledge gaps exist in our understanding of migration medicine practice and the impact of imported pathogens by Canadian travellers and new immigrants, of which malaria is one of the most important. Barriers to the uptake of malaria preventive strategies, including chemoprophylaxis and personal protective measures, in the mobile Canadian population are poorly understood, but the first step to reducing these barriers is defining the scope and epidemiology of imported malaria to Canada.

We aim to better inform pre-travel malaria risk assessment, and post-travel management, and to illuminate changing patterns of imported malaria. We present a Canada-specific surveillance summary of malaria in a cohort of returned travellers and new immigrants presenting for care at CanTravNet sites over a 10-year period.

METHODS

Data Source. Six Canadian sites from four provinces (British Columbia, Alberta, Ontario, and Quebec), also belonging to the GeoSentinel Global Surveillance Network, constitute CanTravNet, as described (7). These sites are large referral-based outpatient centres,

staffed by specialists in travel and tropical medicine, that serve the Greater Vancouver/Victoria, Calgary, Toronto, Ottawa, and Montreal metropolitan areas, which could account for service of almost 50% of the Canadian population. Network sites have been accrued over time, with inaugural sites in Toronto (1997) and Ottawa (1997), and more recent additional sites in Victoria/Vancouver (2009), Montreal (2007 and 2011), and Calgary (2012). Data were collected using the GeoSentinel Surveillance Network data platform. This network is comprised of 57 specialized travel/tropical medicine clinics on 6 continents, which contribute denominalized clinician- and questionnaire-based travel surveillance data on all ill travellers examined, to a centralized Structured Query Language database (8) (for additional details see www.geosentinel.org). Collected data include patient demographics, details of recent travel, 5-year travel history, purpose of travel, and pre-travel encounter history. Final diagnoses are made by attending physicians, and assigned a diagnostic code selected from a standardized list of >500 diagnostic entities, including etiologic (e.g., *Plasmodium falciparum*) and syndromic (e.g., fever) diagnoses. All CanTravNet sites contribute microbiologically confirmed data, where available, based on the best national reference diagnostic tests (including molecular diagnostics) available at the time. Further details regarding CanTravNet can be found at http://www.istm.org/cantravnet and additional details regarding the CanTravNet data source and definitions are as described (7).

Definitions and Classifications.

Reason for most recent travel. Six travel purpose designations are used, including immigration (including refugee); tourism; business; missionary/volunteer research/aid work; visiting friends and relatives (VFR); and "Other", which includes students, military personnel, and medical tourists. VFR travel is defined as an immigrant who is ethnically and/or racially

distinct from the majority population in their current country of residence, and who returns to his homeland to "visit friends and relatives". VFR travel also includes children of foreign-born parents (i.e., second generation immigrants) who return to their parent's homeland to visit friends and relatives. The term VFR is typically applied to individuals travelling from a high-income country of current residence to a low income country of origin (9).

Countries of exposure and travel were assigned to 1 of 8 hard-coded regional classifications (within the GeoSentinel database) where malaria is transmitted: Central America, the Caribbean, South America, North Africa, Sub-Saharan Africa, South Central Asia, Southeast Asia, and Oceania.

Inclusion criteria. Demographic, clinical, and travel-related data on Canadian citizens and new immigrants to Canada encountered after completion of their international travel or residence abroad and seen in any of six CanTravNet sites from September 2004 to September 2014 were extracted and analyzed. Only patients with probable or confirmed final diagnosis of malaria (specific etiology as described previously (7)) were included. A "returned traveller" refers to a single travel episode within the database, where an individual could appear more than once if they had more than one episode of malaria related to different trips, or if they were diagnosed with more than one species of malarial infection.

Analysis. Extracted data were managed in a Microsoft Access database, and analyzed descriptively. Travellers were described by purpose of travel, demographics, travel metrics including pre-travel encounter, diagnoses, country of exposure, and region of travel. Differences between groups of travellers were compared using Fisher's exact test or Chi-square analysis. All statistical computations were performed using SigmaStat 2.03 software (SPSS Inc., Chicago, IL) or GraphPad Prism software (GraphPad Software Inc., La Jolla, CA).

RESULTS

During the study period, 20,345 travellers and immigrants presented to a CanTravNet site, 93% of whom had a travel-related diagnosis. Of these, 437 (2.1%) received 456 diagnoses of malaria, which accounts for 11% of the total number of malaria cases (N=4190) reported in Canada through the national notifiable disease surveillance system over a similar 10-year period (10). The most common malaria species imported by ill returned travellers and new immigrants in this analysis was *P. falciparum* (N=282, 62%). Four cases of *P. falciparum-P. vivax* coinfection, and 2 cases of *P. falciparum-P. ovale* coinfection were documented. Figure 1 depicts imported malaria over time by causative *Plasmodium* species. Those travelling for the purpose of "visiting friends and relatives" (VFR) were the most well-represented (N=169, 38.7%), followed by business travellers (N=71, 16.2%), missionaries/volunteers/aid workers (N=69, 15.8%), immigrants (N=60, 13.7%), tourists (N=52, 11.9%), and students or military personnel (N=16, 3.7%). Demographic characteristics of the 437 ill returned travellers or new immigrants with a malaria diagnosis presenting to CanTravNet sites are summarized in Table 1.

Figure 2 depicts countries of acquisition of malaria in this analysis. Sub-Saharan Africa (SSA) was the most likely source region, accounting for 326 (N=75%) of cases, followed by South central Asia (N=55, 12.6%), South America (N=10, 2%), and North Africa (Sudan and South Sudan) (N=10, 2%) (Table 1). Nigeria was the single most well represented individual source country, accounting for 41 cases (9.4%). India, a particularly high volume destination for Canadians, accounted for 40 total cases (9.2%), 36 of which were *P. vivax*. Sixty-one percent of *P. vivax* cases were imported from the Indian sub-continent (51/84). Five cases of *P. falciparum* were imported from Haiti, and 3 from Dominican Republic. Top source regions by purpose of

travel are listed in Table 1, and top source countries by type of malaria are listed in Table 2. Table 3 lists top source countries by year of import to Canada.

Of 456 malaria diagnoses among ill returned travellers or new immigrants with malaria presenting for care at a CanTravNet site, fever was the presenting symptom in 83.1% (N=379), though this presentation also varied by causative species (Table 2). Malaria was also the top specific cause of fever in this analysis, occurring in 15% of ill returned travellers or new immigrants presenting with fever. Other common presenting symptoms in those with malaria diagnoses included fatigue (N=153, 33.6%), abnormal laboratory tests (N=146, 32%), and gastrointestinal (N=114, 25%). Of the total 456 malaria diagnoses, 26 (6%) were classified as severe, but varied by travel reason, with 10% (N=7) of cases in missionaries classified as severe, 10% (N=7) in business travellers, 7.4% (N=4) in tourists, 3.2% (N=2) in immigrants, and 2.9% (N=5) in VFRs (Table 4). Collectively, severe malaria was over-represented in the non-VFR/non-immigrant group of travellers (19/221 diagnoses) compared to the VFR/immigrant travellers (7/236 diagnoses) (p=0.014). Approximately one-third of travellers and new immigrants with malaria (N=154) required inpatient management of their illness, 81% of which was caused by *P. falciparum* (N=125) (Table 1).

Approximately 30% (N=131) of travellers with malaria in this analysis had received pre-travel care (Table 1). The most well-represented group of travellers with malaria, VFRs, had the lowest rate of pre-travel encounter (Table 1). Interestingly, the 2nd and 3rd most well represented groups of travellers, those travelling for business and missionary/volunteer/research/ or aid work, had the highest uptake of pre-travel encounters, at 54.9% and 56.5%, respectively. Of those with malaria who had received pre-travel care (N=131), only 68 (15.6%) had reported taking some sort of malaria chemoprophylaxis (Table 4). While it is unknown how many

travellers with malaria were reportedly adherent to their prophylaxis, at least 5 (1%) were specifically noted to have either missed doses of doxycycline throughout travel, or ran out of pills prior to departure from the malarious area (Table 4).

Of 377 ill returned non-immigrant travellers with malaria presenting for care at a CanTravNet site, 19.9% (N=75) had a trip duration less than 2 weeks, while 7.2% (N=27) travelled less than 1 week. Of malaria diagnoses among those ill non-immigrant travellers with short-duration travel (<2 weeks), malaria was caused by *P. falciparum* in 68% (N=51), and was severe in 9.3% (N=7). Pre-travel advice had been obtained in 34.7% (N=26) of travellers with malaria who had travelled less than 2 weeks, which was similar to those with any duration of travel (Table 1).

INTERPRETATION

The data provide an epidemiologic framework for prospective travellers

Our analysis of surveillance data on ill returned Canadians provides an epidemiologic framework for Canadian practitioners encountering prospective travellers. Approximately two-thirds of cases of malaria in this analysis occurred in males, a phenomenon noted previously (11,12). Higher rates of malaria and deaths due to malaria among male travellers may reflect both biological (e.g., attractiveness to vectors) and behavioural (e.g., adherence to chemoprophylaxis) risk factors (11,13-17), though their continued over-representation in epidemiologic analyses speaks to the need for better, targeted prevention initiatives.

Business travellers were also over-represented among ill returned travellers with malaria presenting for care at a CanTravNet site, accounting for 16% of cases. As a group, these

business travellers tended to be born in Canada, and conducting business in West Africa, the region with the highest overall relative risk of malaria (18). Two-thirds of cases of malaria in business travellers in this analysis were caused by potentially fatal *P. falciparum*. More than half of business travellers with malaria had received pre-travel advice, yet only 10% actually reported taking chemoprophylaxis. Thus, there is a clear disconnect between known travel to a risk area and adherence to malaria chemoprophylaxis among this group of travellers. Understanding barriers to uptake of malaria preventive measures, which includes chemoprophylaxis (5) and insect precautions (6) following the pre-travel encounter among business travellers should be strategically prioritized so as to reduce morbidity and potential mortality.

VFR travellers constitute a particular group at high-risk for malaria, (1,8,9,19,20) and were the most well represented group of travellers with malaria in this analysis. Unlike business travellers, VFRs had the lowest rates of pre-travel encounter (17%) of any type of traveller, a finding that has been noted in past studies (9). As malaria is preventable with appropriate chemoprophylaxis and insect precautions, poor uptake of pre-travel advice and intervention may translate into a proportionately higher burden of malaria among VFRs. Understanding the barriers to obtaining a pre-travel consultation in the VFR population is necessary to inform strategic initiatives aimed at reducing the burden of imported malaria among this group of highly mobile Canadians and their children.

Sub-Saharan Africa and India contribute substantially to the burden of imported malaria

Our data confirm the overwhelming importance of travel to Sub-Saharan Africa and the Indian sub-continent, particularly by VFRs but also other traveller categories. The top represented source countries for malaria in this analysis were Nigeria and India, though countries

such as Ghana, Ivory Coast, Cameroon, and Burkina Faso were also well represented, and mostly accounted for imports of *P. falciparum*. While 75% of malaria was imported from sub-Saharan Africa in this analysis, only 54% of tourists acquired their malaria in this region. Compared to other types of travellers, tourists appeared to have acquired their malaria in regions such as Central America, the Caribbean, and Oceania, which may reflect the perception of low risk for malaria in these areas, and consequent poor adherence to prophylaxis and personal protective measures. Continued reinforcement of personal protective vigilance, including insect precautions, in the pre-travel setting, even for possibly low-risk itineraries, is important.

India was the 2nd most common source country in our analysis and contributed mostly to the burden of imported *P. vivax* infection, which raises the issue of how to best address malaria prevention in Canadian travellers to the Indian sub-continent. Although clearly a risk in many parts of the Indian sub-continent, the true epidemiology of malaria in India is complex due to seasonal variability, widespread urban and rural transmission, and the difficulty in separating multiple relapses of *P. vivax* from new infections. These factors contribute to confusion and inconsistent recommendations around malaria prevention strategies for travelers to India. An individualized approach to malaria prevention is needed for travellers, taking into account multiple relevant factors including the season, duration, regions visited, and type of travel.

Malaria chemoprophylaxis is typically focused on *P. falciparum* and includes atovaquone-proguanil, doxycycline, or mefloquine. However, primaquine is becoming increasingly offered to travellers to parts of countries where *P. vivax* predominates, such as the Andhra Pradesh, Orissa, and Andaman regions of India. Primaquine requires G6PD testing before use, cannot be used in pregnancy, and must be dosed correctly; but it is effective as chemoprophylaxis for *P. vivax*, and offers the unique advantage of eradicating the liver stages

that can persist in *P. vivax* or *P. ovale* infection. It needs to be continued for 7 days after departure from the malaria endemic region, rather than the 4-weeks of post-travel dosing required with doxycycline and mefloquine. Primaquine is listed by both Canadian (4) and US (21) guidelines as an effective 2nd line alternative for malaria chemoprophylaxis.

Finally, conventional practice is to recommend primaquine anti-relapse therapy (PART) only for travellers returning from long-term residence in areas at very high relative risk of vivax malaria, such as Papua New Guinea (22). However, given the high numbers of Canadians travelling to the Indian sub-continent for the purpose of VFR, data on the true incidence of vivax malaria in this group are needed, and may lead to reconsideration of this practice for certain itineraries at high risk of vivax malaria, understanding that primaquine is not entirely benign, and may cause potentially severe hemolysis in some patients. Physicians should be aware that vivax malaria may present many months, and even years, after leaving the malaria risk area.

Risk of malaria to Canadian travellers is a complex combination of local transmission intensity, type and duration of travel, total numbers of Canadian travellers to the malarious regions, and other factors. As illustrated by Figure 2, India has far lower transmission intensity than that of most countries of sub-Saharan Africa, yet was the 2nd most common source country in this analysis. Thus, local transmission intensity, while important when advising travellers, does not directly translate into overall risk for importing malaria into Canada.

Malaria was the most common specific cause of fever after travel

Malaria was diagnosed in 15% of ill returned travellers and new immigrants presenting with fever in this analysis. While malaria may present with myriad symptoms and signs, including common post-travel syndromes such as diarrhea, abdominal pain, and cough, fever in

the returned traveller should be construed as a medical emergency until malaria is excluded by serial thick and thin blood smears and rapid diagnostic tests (4). It is important to remember that the clinical presentation of malaria may be atypical in individuals with semi-immunity, and in those who have taken partial doses of antimalarials, or even antibiotics with antimalarial activity (e.g., macrolides, tetracyclines). Access to first line medications for the treatment of malaria is restricted in Canada. To improve access, the Canadian Malaria Network (http://www.phac-aspc.gc.ca/tmp-pmv/quinine/index-eng.php) provides depot sites for intravenous artesunate and quinine at several major centres across the country for the emergent management of patients demonstrating signs of severe malaria. The Committee to Advise on Tropical Medicine and Travel (CATMAT) provides comprehensive guidance on the assessment and management of malaria in Canadian travellers and migrants (http://publications.gc.ca/collections/collection_2014/aspc-phac/HP40-102-2014-eng.pdf), and maintains updated online tables for Malaria Risk and Recommended Chemoprophylaxis by Geographic Area (http://www.phac-aspc.gc.ca/tmp-pmv/malaria_catmat-paludisme_ccmtmv-eng.php), as well as Drugs for the Treatment and Prevention of Malaria (http://www.phac-aspc.gc.ca/tmp-pmv/malaria_dosage-paludisme_posologie-eng.php). Unfortunately, first-line oral artemisinin-based combination therapy for uncomplicated falciparum malaria is unavailable in Canada.

Malaria prevention strategies are required for even short duration of travel

Short duration travel to malaria risk areas was confirmed to require malaria prevention, which may include chemoprophylaxis and personal protective measures such as insecticide-treated bed nets, clothing, and/or insect repellants (6). Twenty-percent of malaria in this analysis

was acquired on trips lasting less than 2 weeks, most of which was caused by *P. falciparum*, and 9% of which was severe. Even trips lasting less than 1 week carried risk, accounting for 7% of cases of malaria in this analysis. Again, poor uptake of pre-travel consultation, the perception of lower risk with shorter itineraries, and poor translation of pre-travel counselling into preventive action on the part of the traveller all may have contributed to the malaria burden among short-term travellers. The serial short-term traveller (e.g., frequent business traveller) also presents a challenge to current standard of pre-travel care. Many of these travellers anecdotally report that they are loathe to be on antimalarials continuously or near continuously, and are either non-adherent to post-travel 1- or 4-week dosing of chemoprophylaxis, or do not take chemoprophylaxis at all.

Severe malaria is over-represented among non-immigrant/non-VFR travellers

Business travellers had the highest rates of hospitalization for their malaria among all groups of travellers and new immigrants presenting for care at a CanTravNet site, and 10% suffered from severe malaria. Similarly, missionaries, volunteers, researchers, and aid workers, 85% of whom were Canadian-born, also suffered high rates of severe malaria (10%). Conversely, only 3% of malaria in immigrants or VFRs was severe, supporting the hypothesis that at least some long-term semi-immunity to malaria in individuals born and raised in an endemic area persists, and translates into less severe clinical manifestations of malaria (23). Interestingly, the proportion of severe malaria appeared to marginally decrease over time, which may reflect the greater proportionate burden of malaria among VFR travellers, though this should be interpreted with caution given the low absolute numbers of severe cases documented in this analysis.

Limitations

Analysis of CanTravNet data has several limitations, which have been described previously (7). This analysis pertains only to the sample of ill returned travellers and new immigrants who presented to a CanTravNet centre, thus, our conclusions may lack generalizability. Our network captured 11% of all malaria cases imported to Canada over a 10-year period, with 19% captured during the final year of this analysis. Our ability to comment on changing rates of imported malaria over time is hindered by our accrual of additional sites in the network. Our data cannot estimate incidence rates or destination-specific numerical risks for malaria (8,24). As the Calgary site was new to CanTravNet in 2012, travellers and new immigrants to Alberta are under-represented, which may have introduced bias given the inter-Provincial variation in travel patterns and preferences. The over-representation of severe cases of malaria in this analysis likely relates to referral bias, though we are unable to comment on other possibly contributory factors, such as delayed care-seeking, as we lack the data to do so. Data on pre-travel medical consultation was missing for 20% of ill returned travellers. Finally, our network does not capture significant numbers of pediatric malaria cases, and as such, our data may not be generalizeable to the pediatric population in Canada.

Conclusions

The data collected by the CanTravNet Surveillance Network can be used to better inform pre-travel malaria risk assessment, and post-travel management, and to illuminate changing patterns of imported malaria. Malaria remains the top specific cause of fever in returned travellers, and although still mostly acquired in sub-Saharan Africa, India was the second most

common source country of imported malaria over the 10-year period studied. Barriers to the uptake of effective chemoprophylaxis by particular risk groups, such as VFRs and business travellers, and the use of insect repellent, bed nets, and other preventative measures should be systematically assessed. Malaria continues to be imported into Canada. Front-line physicians managing patients with fever must remain vigilant for malaria, and always obtain a full travel history. Fever in the returning traveller from areas where malaria is a risk should be construed as a medical emergency and malaria until proven otherwise.

REFERENCES

1. Wilson ME, Weld LH, Boggild A, Keystone JS, Kain KC, von Sonnenburg F, et al. Fever in returned travelers: Results from the GeoSentinel Surveillance Network. Clin Infect Dis 2007;44:1560-1568.
2. Kain KC, MacPherson DW, Kelton T, et al. Malaria deaths in visitors to Canada and in Canadian travellers: a case series. CMAJ 2001;164:654-9.
3. Cullen KA, Arguin PM; Centers for Disease Control and Prevention (CDC). Malaria surveillance--United States, 2012. MMWR Surveill Summ. 2014;63(12):1-22.
4. McCarthy AE, Morgan C, Prematunge C, Geduld J. Severe malaria in Canada, 2001–2013. Malaria J 2015; 14:151.
5. Boggild A, Brophy J, Charlebois P, et al for the Committee to Advise on Tropical Medicine and Travel (CATMAT). Canadian recommendations for the prevention and treatment of malaria: An advisory committee statement of the Committee to Advise on Tropical Medicine and Travel (CATMAT). Available at (accessed September 29, 2015): http://publications.gc.ca/collections/collection_2014/aspc-phac/HP40-102-2014-eng.pdf
6. Schofield S, Plourde P, for the Committee to Advise on Tropical Medicine and Travel. Statement on personal protective measures to prevent arthropod bites. Canada Commun Dis Rep(CCDR) 2012; 38(ACS-3):1-18. Available at (accessed March 5, 2015): http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/12vol38/acs-dcc-3/index-eng.php
7. Boggild AK, Geduld J, Libman M, McCarthy A, Doyle P, Ghesquiere W, Vincelette J, Kuhn S, Freedman DO, Kain KC. Travel acquired infections and illnesses in Canadians: Surveillance report from CanTravNet surveillance data, 2009—2011. Open Medicine 2014; 8(1):e20-e32.

8. Freedman DO, Weld LH, Kozarsky PE, Fisk T, Robins R, von Sonnenburg F, et al. Spectrum of disease and relation to place of exposure among ill returned travelers. N Eng J Med 2006;354:119-130.
9. Leder K, Tong S, Weld L, Kain KC, Wilder-Smith A, von Sonnenburg F, et al. Illness in travelers visiting friends and relatives: a review of the GeoSentinel Surveillance Network. Clin Infect Dis 2006;43:1185-1193.
10. Public Health Agency of Canada. Notifiable diseases online - Malaria, 2004-2013. Available at (accessed September 29, 2015): http://dsol-smed.phac-aspc.gc.ca/dsol-smed/ndis/index-eng.php
11. Schlagenhauf P, Chen LH, Wilson ME, Freedman DO, Tcheng D, Schwartz E, Pandey P, Weber R, Nadal D, Berger C, von Sonnenburg F, Keystone J, Leder K; GeoSentinel Surveillance Network. Sex and gender differences in travel-associated disease. Clin Infect Dis. 2010;50(6):826-32.
12. Jensenius M, Han PV, Schlagenhauf P, Schwartz E, Parola P, Castelli F, von Sonnenburg F, Loutan L, Leder K, Freedman DO; GeoSentinel Surveillance Network. Acute and potentially life-threatening tropical diseases in western travelers--a GeoSentinel multicenter study, 1996-2011. Am J Trop Med Hyg 2013;88(2):397-404.
13. Stienlauf S, Segal G, Sidi Y, Schwartz E. Epidemiology of travel-related hospitalization. J Travel Med 2005; 12(3):136–141.
14. Lüthi B, Schlagenhauf P. Risk factors associated with malaria deaths in travellers: A literature review. Travel Med Infect Dis. 2015;13(1):48-60.
15. Legros F, Bouchaud O, Ancelle T, et al. Risk factors for imported fatal Plasmodium falciparum malaria, France, 1996–2003. Emerg Infect Dis 2007; 13(6):883–888.

16. Christen D, Steffen R, Schlagenhauf P. Deaths caused by malaria in Switzerland, 1988–2002. Am J Trop Med Hyg 2006; 75:1188–1194.

17. Nicastri E, Paglia MG, Severini C, Ghirga P, Bevilacqua N, Narciso P. Plasmodium falciparum multiple infections, disease severity and host characteristics in malaria affected travellers returning from Africa. Travel Med Infect Dis 2008; 6(4):205–209.

18. Freedman DO. Malaria prevention in short-term travelers. N Engl J Med 2008;359:603-12.

19. Leder K, Torresi J, Libman M, Cramer JP, Castelli F, Schlagenhauf P et al. GeoSentinel surveillance of illness in returned travelers, 2007-2011. Ann Int Med 2013; 158:456-468.

20. Bui YG, Trépanier S, Milord F, Blackburn M, Provost S, Gagnon S. Cases of malaria, hepatitis A, and typhoid fever among VFRs, Quebec (Canada). J Travel Med. 2011;18:373-378.

21. Arguin PM, Tan KR. Malaria. Chapter 3, Infectious diseases related to travel. IN: 2016 Yellow Book - Health Information for International Travel. Centers for Disease Control and Prevention. Atlanta, GA. Available at (accessed September 29, 2015): http://wwwnc.cdc.gov/travel/yellowbook/2016/infectious-diseases-related-to-travel/malaria#1939

22. Hill DR, Baird JK, Parise ME, Lewis LS, Ryan ET, Magill AJ. Primaquine: Report from the CDC expert meeting on malaria chemoprophylaxis I. Am J Trop Med Hyg 2006;75(3):402-415.

23. Pistone T, Diallo A, Mechain M, Receveur MC, Malvy D. Epidemiology of imported malaria give support to the hypothesis of 'long-term' semi-immunity to malaria in sub-Saharan African migrants living in France. Travel Med Infect Dis 2014;12(1):48-53.

24. Leder K, Steffen R, Cramer JP, Greenaway C. Risk assessment in travel medicine: how to obtain, use, and interpret risk data for informing pre-travel advice. J Travel Med 2014; Nov 6. doi: 10.1111/jtm.12170.

FIGURE LEGENDS

Figure 1. Cases of malaria by causative *Plasmodium* species imported to Canada and evaluated at CanTravNet sites between 2004 and 2014. Total number of malaria cases by year are as follows: 2004 (last 4 months of 2004), N=4; 2005, N=10; 2006, N=21; 2007, N=31; 2008, N=45; 2009, N=36; 2010, N=41; 2011, N=60; 2012, N=64; 2013, N=95; 2014 (first 8 months of 2014), N=49.

Figure 2. Total number of imported cases of malaria evaluated at CanTravNet sites between 2004 and 2014 by source country. Shading represents local transmission intensity (cases per 1000 population). Figure adapted from the World Health Organization's "World Malaria Report, 2014" Figure 1.1 (available at: http://www.who.int/malaria/publications/world_malaria_report_2014/wmr-2014-no-profiles.pdf)

Table 1
Demographic characteristics of 437 returned travellers or new immigrants diagnosed with 456 cases of malaria presenting to a CanTravNet site for care, 2004–2014*

Characteristic	All travellers n = 456 diagnoses of malaria in 437 travellers		Purpose of travel; no. (%) of travellers‡											
			Visiting friends and relatives n = 174 diagnoses of malaria in 169 travellers		Business n = 77 diagnoses of malaria in 71 travellers		Missionary, volunteer, researcher, aid n = 73 diagnoses of malaria in 69 travellers		Immigration n = 62 diagnoses of malaria in 60 immigrants		Tourism n = 54 diagnoses of malaria in 52 travellers		Other‡ n = 16 diagnoses of malaria in 16 travellers	
Sex														
Male	278	63.6	101	59.8	62	87.3	38	55.1	39	65.0	26	50.0	12	75.0
Female	159	36.4	68	40.2	9	12.7	31	44.9	21	35.0	26	50.0	4	25.0
Age, yr, median (range)	33.5	1-82	37	2-82	42	21-71	28	12-68	22	1-64	39	1-75	22	14-48
Type of patient														
Inpatient	141	32.3	52	30.8	28	39.4	21	30.4	18	30.0	16	30.8	6	37.5
Outpatient	296	67.7	117	69.2	43	60.6	48	69.6	42	70.0	36	69.2	10	62.5
Travel duration, d, median (range)	35	0-7256	34	0-884	33	0-1065	61	3-831	NA	NA	19	0-547	90	1-7256
Pretravel medical encounter														
Yes	131	30.0	29	17.1	39	54.9	39	56.5	NA	NA	16	30.8	6	37.5
No	217	49.7	110	65.1	19	26.8	14	20.3	NA	NA	24	46.2	5	31.3
Unknown	89	20.4	28	16.6	13	18.3	16	23.2	NA	NA	12	23.1	5	31.3
Geographic region of exposure														
Sub-Saharan Africa	326	74.6	133	78.7	57	80.3	58	84.1	38	63.3	28	53.8	11	68.8
South Central Asia	55	12.6	30	17.8	1	1.4	0	0	15	25.0	4	7.7	5	31.2
South America	9	2.1	2	1.2	3	4.2	1	1.4	1	1.7	2	3.8	0	0
Caribbean	9	2.1	1	0.6	1	1.4	2	2.9	0	0	5	9.6	0	0

North Africa	10	2.3	1	0.6	1	1.4	3	4.3	4	6.7	1	1.9	0	0
Southeast Asia	7	1.6	0	0	1	1.4	3	4.3	2	3.3	1	1.9	0	0
Central America	8	1.8	1	0.6	1	1.4	1	1.4	0	0	5	9.6	0	0
Oceania	4	0.9	0	0	1	1.4	0	0	0	0	3	5.8	0	0
Unknown	10	2.3	1	0.6	5	7.0	1	1.4	0	0	3	5.8	0	0
Birth country														
Canada	148	33.9	11	6.5	43	60.6	59	85.5	0	0	29	55.8	6	37.5
Outside Canada	289	66.1	158†	93.5	28	39.4	10	14.5	60	100	23	44.2	10	62.5

*The total cohort of travellers consisted of 18,870 travellers with a definitive travel-related diagnosis, 931 with a non-travel–related diagnosis, and 544 with a diagnosis for which relation to travel could not be ascertained. This analysis includes only those travellers with a final diagnosis of malaria, except where indicated otherwise.

†Among those born outside of Canada, people who travelled for the purpose of visiting friends and relatives were defined as immigrants who were ethnically and/or racially distinct from the majority population in their current country of residence and who returned to their homeland to visit friends and relatives. This group also included children of foreign-born parents (i.e., second-generation immigrants) who returned to their parents' homeland to visit friends and relatives.

‡ includes 15 students and 1 military personnel

Table 2
Top diagnoses and source countries for malaria species among 437 ill returned travellers with 456 malaria diagnoses seen at CanTravNet sites, 2004-14.

Diagnosis	No. (%) of malaria diagnoses* in travellers with presenting complaint of fever		Total no. of malaria diagnoses in database	Top 3 source countries for diagnosis
Chief complaint fever (n = 2902)				
Malaria	379	83.1	456	
Plasmodium falciparum	237	84.0	282	Nigeria, Ghana, Ivory Coast (includes severe malaria)
Severe (complicated)	23	88.5	26	
Plasmodium vivax	77	90.6	85	India, Pakistan, Guyana
Plasmodium species unknown	22	56.4	39	Burkina Faso, Sierra Leone
Plasmodium ovale	18	85.7	21	Nigeria, Ghana, Cameroon
Plasmodium malariae	2	66.7	3	Nigeria, Ghana, Cameroon

*Percentages are calculated using total number of diagnoses in database as denominator. An ill returned traveller could present with more than one chief complaint, and have more than 1 diagnosis.

Table 3
Top 3 source countries by year of import for 456 malaria diagnoses among 437 ill returned travellers and new immigrants evaluated at CanTravNet sites between 2004 and 2014.

Year of Import	Total Diagnoses of Malaria in Year of Import seen at CTN Sites (no. travellers with malaria)	Total Cases of Malaria in Year of Import Reported to PHAC[10]	Percentage of Cases reported to PHAC seen at CTN Sites	Top 3 Source Countries (N)§		
				First	Second	Third¶
2004*	4 (4)	375	4.3‡	Afghanistan (1)	Guatemala (1)	Venezuela (1)
2005	10 (9)	365	2.7	Ghana (2)	Guinea (2)	--
2006	21 (20)	333	6.3	Nigeria (6)	Ivory Coast (4)	Mozambique (4)
2007	31 (28)	384	8.1	India (5)	Ivory Coast (3)	Cameroon (2) = Nigeria (2)
2008	45 (42)	372	12.1	Kenya (5)	Nigeria (5)	--
2009	36 (35)	364	9.9	India (5)	Ghana (4)	--
2010	41 (40)	514	8.0	Cameroon (3)	Ghana (3)	Honduras (3) = Nigeria (3)
2011	60 (58)	517	11.6	India (10)	Ghana (7)	Nigeria (6)
2012	64 (62)	477	13.4	India (7)	Pakistan (6)	Sierra Leone (5)
2013	95 (90)	489	19.4	Cameroon (12)	Guinea (7)	Nigeria (7)
2014†	49 (48)	Unavailable	Unavailable	Benin (4)	Ghana (4)	--
TOTAL	456 (437)	4190	11.3	Nigeria (41)	India (40)	Ghana (32)

*data for September 1, 2004 to December 31, 2004
†data for January 1, 2014 to August 31, 2014
‡extrapolated to 1 year
§country of exposure may be unknown or unattributable with multi-country itineraries
¶not noted if >5-way tie for 3rd place

Table 4.
Cases of malaria by travel reason among 18,870 ill returned travellers presenting to a CanTravNet site, 2004--2014.

		Type of malaria; no. of diagnoses							
Reason for travel	Total no. of malaria diagnoses (travellers)	*P. falciparum*	Severe malaria	*P. vivax*	*P. ovale*	*Plasmodium* species unknown	*P. malariae*	Top 3 countries of exposure	Received prophylaxis
All (n = 18,870)	456 (437)	282	26	85	21	39	3	See Table 2	68†
Tourism (n = 8136)	54 (52)	29	4	16	2	3	0	Ghana, Uganda, Ivory Coast	8
Immigration (n = 4967)	62 (60)	35	2	15	4	5	1	India, Nigeria, Liberia	NA
Visiting friends and relatives (n = 1966)	174 (169)	117	5	38	7	7	0	Nigeria, India, Cameroon	28
Missionary, volunteer, researcher, aid (n = 1656)	73 (69)	42	7	5	5	13	1	Ghana, Burkina Faso, Cameroon	19
Business (n = 1643)	77 (71)	51	7	7	3	8	1	Burkina Faso, Ghana, Guinea	7
Other§ (n = 498)	16 (16)	8	1	4	0	3	0	India, Benin, Burkina Faso,	2

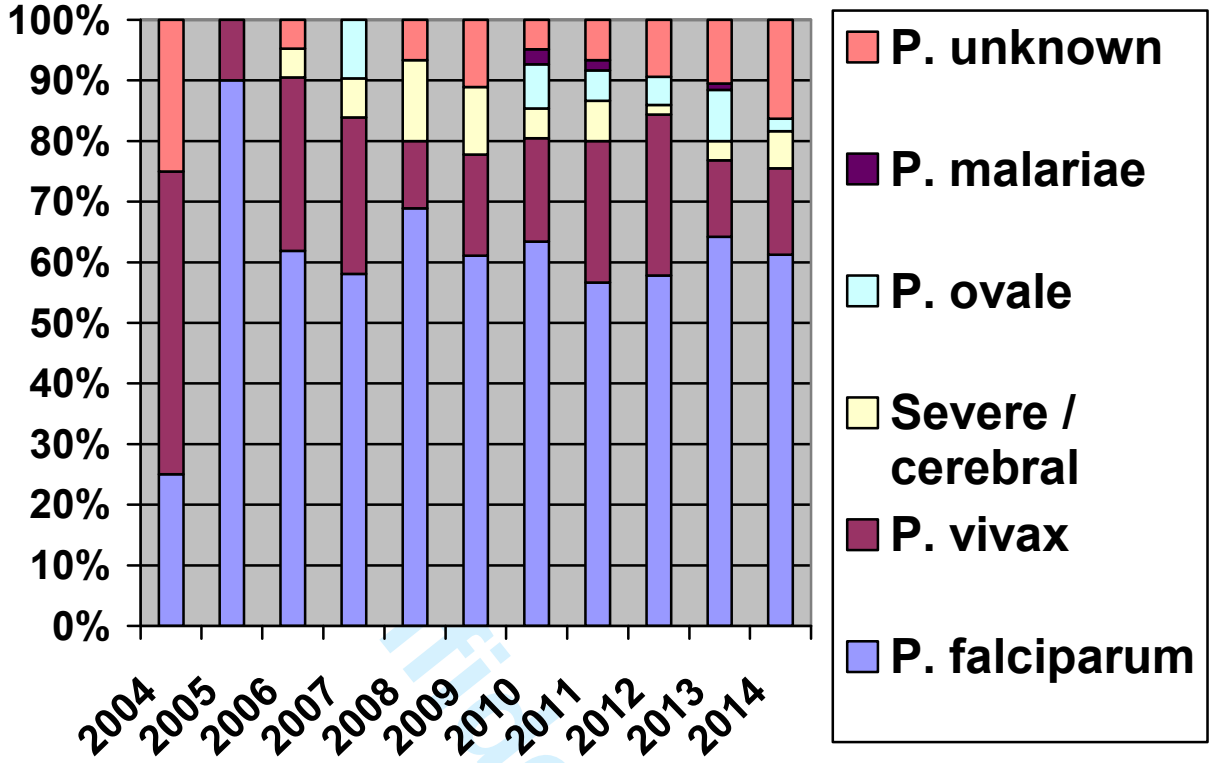
	Tanzania

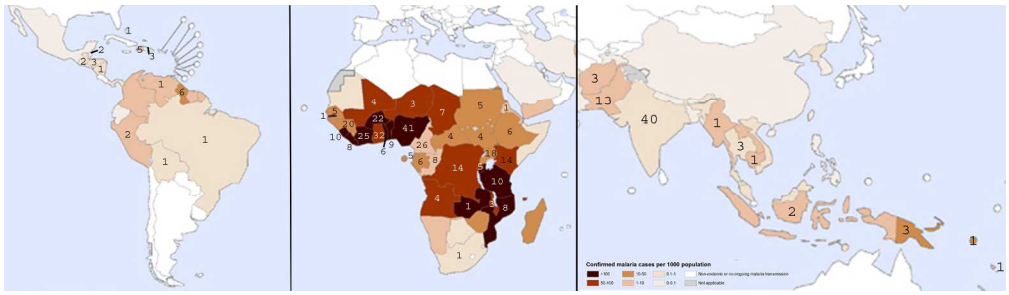
Abbreviations: NA, not applicable

†Includes 5 travellers who either missed doses of doxycycline throughout travel or ran out of doxycycline prior to the end of travel.

§ Includes 355 students, 122 military personnel, and 21 individuals travelling for medical tourism

Figure 1.





266x76mm (300 x 300 DPI)