

**Travel Acquired Infections and Illnesses in Canadians: Surveillance Report from
CanTravNet Surveillance Data, 2009—2011**

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Andrea K. Boggild contributed to study design, data collection, analysis, and interpretation, and was primarily responsible for writing and revising the manuscript.

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Conflict of Interest Statements:

Andrea K. Boggild – From 2008-2009, I served as a medical consultant to Shoreland Inc.

(<http://www.shoreland.com/>).

Jennifer Geduld – No conflicts to declare.

Michael Libman – I have served on the advisory board of Sanofi Pasteur in the past 2 years.

Brian Ward – In the past 5 years, I have: served as the medical officer for Medicago Inc.; held investigator-initiated grants shared with industrial partners (GlaxoSmithKline; Medicago Inc.); held contracts for clinical vaccine trials (Pfizer; Sanofi Pasteur; GlaxoSmithKline; Medicago Inc.); received honoraria approximately 5 times per year for delivering talks for which I have sole control over content; and served as an expert witness for Quebec and US Vaccine Injury Compensation programs.

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Susan Kuhn – I am a consultant to Shoreland Inc. (<http://www.shoreland.com/>)

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Abstract

Background: Important knowledge gaps exist in our understanding of migration medicine practice and the impact of imported pathogens by Canadian travellers. We herein provide a comprehensive, Canada-specific surveillance summary of illness in a cohort of returned Canadian travellers and new immigrants.

Methods: Data on ill returned Canadian travellers and new immigrants presenting to a Canadian GeoSentinel Surveillance Network site (CanTravNet) between September 2009 and September 2011 were extracted and analyzed.

Results: During the study period, 4365 travellers and immigrants presented to a CanTravNet site, 90% of whom were assigned a travel-related diagnosis. Latent tuberculosis (6.9%), chronic hepatitis B virus (4.4%), strongyloidiasis (2.5%), giardiasis (2.2%), and malaria (2.2%) were the most common specific etiologic diagnoses issued. Other potentially serious infections such as dengue fever and enteric fever (due to *Salmonella enterica* serotype Typhi or Paratyphi) were common, occurring in 61 and 36 travellers, respectively. Individuals travelling for the purpose of “visiting friends and relatives” (VFR) were over-represented among those diagnosed with malaria and enteric fever ($p<0.001$). Malaria was also over-represented among business travellers and males ($p<0.001$). Malaria was most likely acquired in Sub-Saharan Africa ($p<0.001$), while dengue was most likely imported from the Caribbean and southeast Asia ($p=0.003$), and enteric fever from South Central Asia ($p<0.001$).

Interpretation: Our analysis of surveillance data on ill returned Canadian travellers has detailed the spectrum of imported illness among this cohort and provides an epidemiologic framework for Canadian practitioners encountering ill returned travellers. We confirmed that VFR travel confers particularly high risks, underscoring the need to improve pre-travel intervention for a population

that is unlikely to seek specific pre-travel advice. Potentially serious and fatal illnesses such as malaria and enteric fever were common, as were illnesses of public health importance such as tuberculosis and hepatitis B.

INTRODUCTION

Canadians are an increasingly mobile population. The more affordable nature of air travel, globalization of trade and commerce, greater representation of developing-world immigrants among the Canadian population, and a trend towards “voluntourism” and ecotourism have all contributed to a greater number of Canadians crossing international borders than ever before. The stereotypical beach-destination vacationer is being increasingly replaced with off-the-beaten-path backpackers, new Canadian immigrants and their family members returning home to “visit friends and relatives” (VFR), last-minute business travellers, and researchers, missionaries, and volunteers heading to ever more exotic locales. This paradigm shift is supported by data from the World Tourism Organization and Statistics Canada: in 2011, Canadians spent 33.0 billion (US) dollars on international tourism, up from 29.6 billion dollars in 2010 [1]. Along with traditional destinations such as the United States, United Kingdom, and France, tropical and developing-world destinations including Mexico, Cuba, and the Dominican Republic are among the top 10 foreign destinations chosen by Canadian travellers [2].

Travelling to the developing world necessarily puts travellers and migrants at risk for communicable infectious diseases, with 20-70% of returned travellers suffering some sort of illness [3-5]. While single centre studies from other countries or multinational studies of travel-acquired illness have been conducted, a comprehensive multicentre comparison of the spectrum of illnesses acquired by a broad range of Canadian travellers returning from regions on all continents has been lacking. Our understanding of the range and frequency of infectious diseases in Canadian travellers is based primarily on existing synthesized knowledge of travel-acquired illness in other populations. Expert references such as the World Health Organization’s International travel and health book [6], the Centers for Disease Control and Prevention Yellow

Book [7], and the Public Health Agency of Canada's Committee to Advise on Tropical Medicine and Travel (CATMAT) (<http://www.phac-aspc.gc.ca/tmp-pmv/catmat-ccmtmv/index-eng.php>) provide guidance to practitioners, yet data specifically on Canadian travellers in support of these recommendations are lacking. And while many imported communicable diseases are nationally notifiable to PHAC [8], the quality of data accrued is hindered by delayed and under-reporting, which has led to “an incomplete picture of the incidence of communicable diseases in Canada” [9].

We have synthesized Canada-specific surveillance data on ill returned travellers in order to inform provincial and national-level public health policy and strategic initiatives to reduce the incidence of preventable infections, increase the efficiency of public health infrastructure, and improve uptake of preventive pre-travel care. In addition, accurate epidemiologic data about travel-associated infectious diseases in travellers returning to Canada are necessary to guide clinical decision-making by front-line Canadian practitioners. The analysis herein provides such an epidemiologic roadmap.

METHODS

Data Source. Data were collected using the GeoSentinel Global Surveillance Network platform. This network is comprised of 54 specialized travel/tropical medicine clinics on 6 continents, which contribute anonymous, de-linked clinician- and questionnaire-based travel surveillance data on all ill travellers examined, to a centralized Structured Query Language database [10] (for additional details see www.geosentinel.org). The GeoSentinel data-collection protocol is reviewed cyclically by the institutional review board officer at the National Center for Infectious Diseases at the Centers for Disease Control and Prevention and classified as public

health surveillance and not as human-subjects research requiring submission to institutional review boards. Six Canadian sites from four provinces, also belonging to the global GeoSentinel Global Surveillance Network have grouped together to form the core sites of CanTravNet.

The six sites in Canada are large referral-based outpatient clinics that primarily service the Greater Vancouver/Victoria, Calgary, Toronto, Ottawa, and Montreal areas, which account for 47% of the Canadian population (or, a catchment of ~15.5 million people). They are staffed by specialists in travel and tropical medicine, and are typically a secondary or tertiary point of care for patients, though immediate referral from the emergency departments attached to the parent hospitals is common. Collected data include patient demographics, detailed recent travel itinerary, all countries visited within 5 years, reason for travel, listing of affected organ system, and whether the patient had a pre-travel encounter with a healthcare provider. Final diagnoses are made by the attending physicians at the sites, and assigned a diagnostic code selected from a standardized list of >500 diagnostic entities, some of which are etiologic (e.g., *Campylobacter*), and some of which are syndromic (e.g., acute diarrhea). Syndromic codes are entered where an etiologic code cannot be assigned due to use of empiric therapy, self-limited disease, or inability to justify complete or sophisticated workup as part of routine clinical practice. All CanTravNet sites contribute microbiologically confirmed data, where available, based on the best reference diagnostic tests (including serologic assays and PCR) available in Canada at the time. ‘Probable’ diagnoses are restricted to patients with pathognomonic physical findings (e.g., tick eschar), clinical response to highly specific therapy, or classical presentation and exposure history with laboratory exclusion of other possible etiologies.

Definitions. The following definitions were used in this study:

- i) Reason for most recent travel. Six possible travel purpose designations are available in GeoSentinel: these include 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 their homeland to “visit friends and relatives”. The term VFR 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 [11]. “Medical tourists” were defined as those for whom the primary purpose of travel was to seek emergency or elective care and as a consequence of travel, acquired an infectious complication secondary to the medical care received OR became ill with an infectious or non-infectious disease while abroad.
- ii) Countries of exposure and travel were assigned to 1 of 14 regional classifications: North America, Central America, the Caribbean, South America, Western Europe, Eastern Europe, the Middle East, North Africa, Sub-Saharan Africa, South Central Asia, Southeast Asia, Northeast Asia, Australia/New Zealand, 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 five CanTravNet sites from September 2009 to September 2011 were extracted and analyzed. Only patients with probable or confirmed final diagnoses (specific etiology or syndrome as described above) were included. “The cohort of travellers”

refers to the entire cohort of travellers encountered at CanTravNet sites, including immigrants. “Ill returned travellers” refers to the travellers or immigrants within the larger cohort who were deemed to have a definitive “travel related” diagnosis, rather than one which was unrelated to travel or not ascertainable.

Statistical Analysis. Extracted data were managed in a Microsoft Access database, and analyzed using standard parametric and non-parametric techniques. Comparisons between categorical variables were made using Yates’ corrected Chi-square analysis, while continuous variables were analyzed for significant differences using the Student’s t-test, and in the case of non-normally distributed parameters, the Mann-Whitney Rank Sum test. Differences between groups of continuous variables were compared using One Way ANOVA or Kruskal Wallis One Way ANOVA on ranks. All statistical computations were performed using SigmaStat 2.03 software (SPSS Inc., Chicago, IL). Level of significance was set at $p < 0.05$.

RESULTS

Patients and Demographics. For the surveillance period reported, the cohort of 4365 travellers presented to a CanTravNet site, and were assigned 4776 confirmed and 535 probable diagnoses. Of 4365 travellers seen, 3943 (90.3%) had a definitive travel-related diagnosis (hereafter referred to as “ill returned travellers”), 363 (8.3%) had a non-travel related diagnosis, and 59 (1.4%) had a diagnosis whose relatedness to travel could not be ascertained. The cohort of 4365 travellers presented to 1 of 5 CanTravNet sites as follows: Montreal-McGill (N=1899, 43.5%), Toronto (N=1088, 24.9%), Ottawa (N=850, 19.5%), Vancouver (N=320, 7.3%), and Montreal-Centre Hospitalier de l’Université de Montreal (CHUM) (N=208, 4.8%). The Calgary site is new to GeoSentinel as of 2012 and did not contribute cases during the study period. Major

demographic variables for the cohort of 4365 travellers are summarized in Table 1. Fifty-five percent of the cohort was born in Canada. Top countries of emigration for individuals born outside of Canada were: India (N=174, 4%), China (N=91, 2.1%), United States (N=75, 1.7%), Philippines (N=75, 1.7%), France (N=72, 1.6%), Haiti (N=69, 1.6%), United Kingdom (N=53, 1.2%), Vietnam (N=50, 1.1%), and Somalia (N=47, 1.1%).

Non-immigrant travellers in the cohort (i.e., all travellers in the cohort except those travelling for the purpose of immigration) for whom exposure country was known (N=3439) visited 154 different countries, the most frequently visited of which included: India (N=287, 8.3%), Mexico (N=231, 6.7%), Cuba (N=153, 4.4%), Dominican Republic (N=138, 4%), Costa Rica (N=92, 2.7%), the United States (N=73, 2.1%), Ghana (N=72, 2.1%), Thailand (N=71, 2.1%), Peru (N=65, 1.9%), and China (N=58, 1.7%). Immigrant travellers in the cohort (i.e., those travelling for the purpose of immigration) (N=876) emigrated from 113 different countries, the most frequent of which included: China (N=66, 7.5%), India (N=66, 7.5%), Philippines (N=55, 6.3%), Haiti (N=48, 5.5%), Somalia (N=33, 3.8%), Viet Nam (N=31, 3.5%), Thailand (N=27, 3.1%), Burundi (N=23, 2.6%), Congo (N=23, 2.6%), Cameroon (N=19, 2.2%), and Myanmar (N=19, 2.2%). Figure 1 depicts regional exposure for the cohort of travellers.

Diagnoses. A total of 4774 travel related diagnoses were issued to 3943 ill returned travellers. Of these, 4278 were confirmed and 496 were probable. The most frequently issued travel related etiologic diagnoses were: latent tuberculosis (N=302, 6.9%), chronic hepatitis B (N=192, 4.4%), strongyloidiasis (N=107, 2.5%), acute bacterial diarrhea (N=99, 2.3%), giardiasis (N=96, 2.2%), and malaria (N=94, 2.2%). Common travel related syndromic diagnoses included: chronic diarrhea (N=249, 5.7%), post-infectious irritable bowel syndrome (N=235, 5.4%), acute diarrhea (unspecified etiology) (N=133, 3.0%), and abdominal pain (N=110, 2.5%). Cases of

potentially serious imported infections, such as dengue fever, and enteric fever (due to *S. Typhi* or *S. Paratyphi*) were also common, occurring in 61 and 36 ill returned travellers, respectively. Table 2 summarizes the top travel related diagnoses by travel reason, while Table 3 lists the top 10 travel related diagnoses issued to children <13 years of age.

Travel related tuberculosis (TB) was a common diagnosis, the majority of cases of which were classified as latent TB as indicated by a positive tuberculin skin test (N=302, 71.1%). Other types of tuberculosis documented among ill returned travellers include: pulmonary (N=82, 19.3%), extrapulmonary (N=31, 7.3%), CNS or meningeal TB (N=7, 1.6%), disseminated TB (N=2, 0.5%), and multi-drug resistant or XDR TB (N=1, 0.2%).

Between 2009 and 2011, 348 cases of travel-related blood-borne and sexually transmitted infections were diagnosed in this group of ill returned travellers. This includes 200 cases of hepatitis B virus and 97 cases of hepatitis C virus, most of which were diagnosed in immigrant ill returned travellers, and 15 cases of HIV.

The diagnosis of tuberculosis (both latent and active), hepatitis B virus, and hepatitis C virus were all over-represented among those travelling for the purpose of immigration ($p<0.0001$). Malaria and enteric fever were both over-represented among those travelling for the purpose of VFR ($p<0.0001$). Malaria was also over-represented among those travelling for the purpose of business ($p<0.0001$) and among males ($p<0.001$). Of the 22 cases of malaria in business travellers, 15 (68%) had received pre-travel consultation, yet only 3 took appropriate malaria prophylaxis. Of 7 cases of malaria that were diagnosed in ill returned pediatric travellers, 71% were caused by *P. falciparum*, and all occurred in children travelling for the purpose of immigration (N=5) or VFR (N=2).

The proportion of ill returned VFR travellers requiring inpatient management of their travel-acquired illness was double that of ill returned non-VFR travellers ($p<0.0001$). VFRs also had the lowest proportionate uptake of pre-travel consultation among all ill returned non-immigrant travellers ($p<0.0001$) [Table 1]. In addition, VFRs traveled for longer periods of time compared to non-VFR travellers (31 versus 19 days; $p<0.001$). While VFR travellers constituted 11.4% of the cohort reported herein, they accounted for 36.2% of cases of malaria and almost 52% of cases of enteric fever due to *S. Typhi* or *S. Paratyphi*.

The single case of measles in this study was imported by a VFR traveller to India. During the surveillance period reported herein, cases of highly communicable influenza ($N=21$) and varicella ($N=1$) were also reported, as was one case of Japanese encephalitis, which occurred in a tourist traveller to Thailand.

Table 4 summarizes the top travel related diagnoses and source countries among those ill returned travellers who presented for care complaining of fever, skin rash, or gastrointestinal symptoms.

Malaria and blood-borne pathogens, such as hepatitis B virus and hepatitis C virus, were over-represented among those who traveled to, or immigrated from sub-Saharan Africa ($p<0.001$). Vaccine preventable diseases were over-represented among those who traveled to, or immigrated from Southeast and Northeast Asia ($p<0.0001$). Dengue fever was over-represented among those who traveled to the Caribbean or Southeast Asia ($p=0.003$). Enteric fever was most likely acquired in South Central Asia ($p<0.0001$).

INTERPRETATION

Analysis of surveillance data on ill returned travellers presenting to a CanTravNet site between September 2009 and September 2011 has revealed the spectrum of travel-acquired illness encountered at CanTravNet sites. To date, this is the largest surveillance report on illness in ill returned Canadians from abroad.

Serious Imported Infections are Common among Ill Returned Canadian Travellers.

Potentially life-threatening infections such as malaria, enteric fever, and dengue are commonly imported infections with specific demographic and geographic preponderances. Ill returned travellers with malaria were proportionately more likely to require inpatient management compared to those with alternate diagnoses (44% versus 5%). Of the 94 cases of malaria in ill returned travellers, 60% were caused by *P. falciparum*, which can lead to severe and fatal disease. Moreover, 8.5% of those with malaria in this cohort of ill returned travellers had complicated or cerebral malaria, underscoring the potential severity of this highly preventable illness among travellers, as outlined in the Canadian recommendations for the management of falciparum malaria in Canada [12]. In Canada, of the 174 cases of imported severe or cerebral malaria reported by the Canadian Malaria Network between 2001 and 2012, 95% were due to *P. falciparum* (Anne McCarthy, pers. commun). Cases of severe or cerebral malaria have also increased year-to-year, from 11 in 2001 to 26 in 2012 (Anne McCarthy, pers. commun.). And while children comprised only 2% of ill returned travellers in this study, they contributed 7.5% of cases of malaria, underscoring the need for improved access to and delivery of preventive strategies in this vulnerable population.

Relative risks for malaria among travellers are consistently highest in sub-Saharan Africa [13]. We have confirmed that sub-Saharan Africa is the source region for most malaria among ill

returned Canadian travellers, accounting for almost 77% of cases in this cohort. Of the 22 cases of malaria in business travellers, 95% were acquired in sub-Saharan Africa. In contrast, dengue was more often associated with travel to the Caribbean and Southeast Asia [14]. Other potentially serious infections such as typhoid and paratyphoid fevers were likely acquired in South Central Asia, a finding supported by previously published data [10,15,16].

Cosmopolitan and Vaccine Preventable Diseases were Observed.

While serious and transmissible infections of particular public health importance such as viral hemorrhagic fever due to Ebola or Lassa, anthrax, and meningococcal meningitis were not observed in this cohort of ill returned travellers, other cosmopolitan and potentially vaccine-preventable infections were noted. Sporadic cases of highly communicable yet vaccine preventable infections such as measles, varicella, and influenza are imported by travellers on an annual basis. Since the mid-1990s, more than 80% of all cases of measles in the US and Canada were imported from measles-endemic countries, or were epidemiologically related to an imported case [17-20]. A single imported case of measles to Quebec in 2011 led to a superspreading event with sustained transmission and 678 local cases in the largest measles epidemic in North America over the past decade [20]. Thus, while emerging imported infections such as SARS receive considerable public attention, other travel-acquired illnesses that are imported into North America also exact a heavy cumulative personal and public health toll.

Travelling to “Visit Friends and Relatives” is a Risk Factor for Travel-Acquired Illness.

Travelling for the purpose of VFR is a particular documented risk factor for the acquisition of travel-related illness as these travellers tend to stay in local homes, travel for longer

durations, and may fail to recognize the health risks inherent to travel to their country of origin [3,4,10,11,15]. It has been previously documented that 40->90% of imported cases of typhoid in the North America occur in VFRs [16,21]. In this study, double the proportion of VFR travellers required inpatient management of their travel-acquired illness and they traveled for a longer period of time compared to ill returned non-VFR travellers, highlighting the unique nature of this particular type of traveller. In 2010, VFR travellers accounted for 17.4% of trips taken by Canadian travellers to overseas countries with 1.83 million overnight visits, thus, the scale of VFR travel is substantial [22].

The behaviour of individual travellers dictates the potential for exposure to, and acquisition of, infectious diseases abroad [23-27]. Travellers are much more likely to be exposed to blood and body fluids while travelling than at home [27], and more likely to engage in risk taking behaviours during which blood and body fluid exposures may occur [26,27]. The data reported herein illuminate the frequency of some of these blood-borne and sexually-acquired illnesses in travellers, several of which are chronic and expensive to manage.

Diarrheal Illness is a Common Cause of Morbidity among Travellers.

The most common and well-represented group of infectious illnesses among travellers are those that are food- and water-borne [28]. Food- and water-borne illnesses predominate in the developing world for one main reason: inadequate sewage and sanitation systems. Non-potable water that is used as drinking water or water to wash fruits and vegetables, as well as hands contaminated with fecal matter, place travellers at risk for common illnesses such as bacterial gastroenteritis and parasitic causes of diarrhea and dysentery. A gastrointestinal chief complaint predominated in this cohort of travellers, with a full 45% presenting with gastrointestinal

symptoms. Furthermore, chronic diarrhea, post-infectious irritable bowel syndrome, acute diarrhea, acute bacterial diarrhea, and giardiasis were all among the top diagnoses issued. For tourists, missionaries, volunteers, researchers, aid workers, and other travellers, in particular, 4 to 6 of the top 10 diagnoses were gastrointestinal related.

Traveller's diarrhea, while usually self-limited, is known to trigger post-infectious irritable bowel syndrome (IBS), a chronic and potentially debilitating condition, the median duration of which is approximately 2-3 years [29]. The diagnosis of post-infectious IBS is one of exclusion, and therefore requires elimination of other etiologies by stool microbiology and possibly more costly diagnostic interventions such as imaging and colonoscopy. Chronic diarrhea necessarily imposes a heavy burden on the Canadian healthcare system given that approximately half of travellers to tropical and sub-tropical destinations develop infectious diarrhea while travelling [30-32], and 10% of those cases likely develop post-infectious IBS [33].

Study Limitations and Conclusions.

This analysis has several limitations. First, the population analyzed represents only those ill returned travellers who presented to a CanTravNet clinic, thus, our conclusions may not extend to all ill returned travellers. However, it should be noted that the top countries of exposure for non-immigrant travellers paralleled the top countries visited by travelling Canadians in general, with Mexico, Cuba, Dominican Republic, and China as top 10 destinations for both this cohort and the general Canadian population [34]. The top 3 source countries for new immigrants to Canada (Philippines, China, and India) [35] were also represented among the top 4 countries of emigration for immigrant travellers in this cohort. Travellers with mild or self-limited illnesses or illnesses with very short or very long incubation periods may have sought care in different

settings. Our study does not capture illnesses for which care was sought during travel. Similarly, ill travellers returning from destinations perceived to be low-risk may be under-represented in the CanTravNet database. Third, data on inpatient versus outpatient management may be influenced by regional variations in management guidelines. Fourth, our data do not permit estimation of incidence rates or destination-specific numerical risks for particular diseases [10,36]. Finally, inter-site variation in screening protocols for new immigrants and refugees may have led to over- or under-contributions of particular diagnoses from individual sites. Forty-eight percent of cases were contributed by Montreal sites, which may have introduced bias given the inter-Province variation in travel patterns.

The impact and importance of travel-acquired illness is considerable. At an individual level, it can lead to reduced work and school productivity, home convalescence, hospital admission, and potentially death, while incurring costs related to diagnostic tests and other medical visits that occur during the evaluation of such illnesses. At a population level, the potential for importation of public health threats by travellers, such as measles, sexually transmitted infections, and blood borne and vector borne diseases, is substantial. An accurate knowledge of the health problems that are faced by international travellers in different geographical destinations provides a robust evidence base for physicians to deliver effective preventative advice, immunizations, and prophylactic medications to travellers. This profile further informs post-travel diagnosis and therapy, as well as prioritization of pre-travel intervention strategies for the most significant illnesses. The Canada-specific surveillance data should inform public health policy and strategic initiatives around defining, monitoring, and preventing travel-acquired illness in Canadians.

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