A population-based case control study evaluating the risk of acquiring malaria in those visiting friends and relatives (VFR) in Calgary, Canada (2013 – 2017)

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Abstract

Background: The immigrant population from malaria endemic areas in Canada is steadily increasing and with this comes the increased risk of imported malaria. The primary objective of this study was to analyze the incidences of malaria in the Calgary area among those visiting friends and relatives (VFR) population in comparison to other travelers. Furthermore, we attempted to investigate if pediatric VFR travelers were at a higher risk of being diagnosed with malaria.

Methods: We conducted a case-control study of 1348 symptomatic returning travelers presenting for malaria testing in Calgary from 2013 – 2017, to compare the epidemiological risk factors between those who tested malaria positive and negative using routinely collected data from Calgary Laboratory Services database. Multivariable logistic regression was used to analyze the association between the presence of malaria and other risk factors.

Results: The odds of a VFR traveler being diagnosed with malaria was 2.82 [1.42-5.92] times greater than that of a non-VFR traveler. Adults travelers were 3.62 [1.66-8.84] more likely to be diagnosed with malaria compared to pediatric travelers controlling for other variables including traveler status. VFR travelers were significantly less likely to seek pre-travel advice (27%), take prophylaxis (18%) and more likely to stay longer than two weeks (93%) compared to other travelers.

Discussion: These data suggest that targeted strategies to provide pre-travel care to VFR travelers may aid in reducing the burden of malaria during and after travel. The potential savings to the health care system with reducing VFR malaria needs to be assessed further.

Introduction

In 2017, there were 219 million malaria cases and 435 000 fatalities worldwide, with $3.1 billion USD allocated globally for malaria eradication and management (1). 92% of all malaria cases and 93% of malaria deaths occurred in the WHO African Region (1). Even though Canada is not considered as an endemic malaria region, annually there are an approximately 488 imported malaria cases a year according to the 2010 – 2014 trends (2). Furthermore, the Canadian immigrant population from the malaria-endemic regions has been increasing over the past years. Specifically, in the Calgary metropolitan area, 4.3% of the population recognized themselves as belonging to an African ethnic origin and 27.9% of the population identified themselves as belonging to an Asian ethnic origin (3). Additionally, 37.5% of all Canadian children currently are either first- or second-generation immigrants (4).

Following the recommendations of Barnett et al. (2010), VFRs were defined for this study as the population of returning travelers who had recently visited a malaria endemic region for the purpose of visiting friends and relatives (5). Immigrants contribute to the VFR population, but not all immigrants will necessarily return to their country of origin. Moreover, other Canadians may be married to immigrants, and travel to visit in-laws with the same risk as the spouse. For the purpose of this study, VFR travel was not classified according to ethnic origin or immigration status but on the reason for travel. As such, this definition captured those who had connections to the local population, but did not qualify as a VFR under traditional definitions (5). The VFR population is known to be at a higher risk of being diagnosed with travel-related illnesses in general (6-8). VFRs are likely to make travel plans at short notice, likely to including dependent children, and stay in rustic family settings (9). The unique travel characteristics of this group put

them at increased risk of contracting malaria compared with groups traveling for other reasons. VFR travelers are more likely to visit malaria-endemic areas, make regular visits to same regions, and stay for long durations (6-10). Within malaria-endemic regions, VFR travelers are more likely to visit areas within countries defined by WHO as high risk for malaria such as rural remote locations (11). Local family accommodations are often more basic than that used by tourists, including less likelihood of air conditioning and indoor residual spraying (10, 11). VFR travelers are less likely to use personal protection such as long sleeve clothing, mosquito nets and insect repellent (10). Finally, some VFR travelers may downgrade their risk perception due to a faulty belief in ongoing protection from past exposure to malaria exposure prior to coming to Canada. This may be a reason that some may avoid taking effective antimalarial prophylaxis (6-12). Children of first and second-generation immigrants are also at a higher risk for travel-related illnesses than non-VFR travelers (9, 13). Canadian-born VFR travelers are exposed to the same hazards as their immigrant parents, but are naïve to many travel-related illnesses foreign to Canada. This places them at higher risk compared with recent immigrants of developing severe malaria with increased morbidity and mortality (9). Compared to adults, VFR children are also more likely to have delays in treatment due to greater likelihood of initial misdiagnosis, as well as higher parasitemia (14-17).

In Canada, the number of imported malaria cases has steadily risen since 2000 (12, 18). A previous study of returning travelers in Calgary done by this group found that the majority belonged to the VFR travel group (12). Therefore, the primary objective of the study was to rigorously investigate the epidemiological characteristics of VFR and compare them to other returning travelers using case-controlled multivariable logistic regression.

Methods

Study design

We conducted a case-control study of symptomatic returning travelers presenting for malaria testing in Calgary (Alberta, Canada) from 2013 – 2017, to compare the epidemiological risk factors between those who tested malaria positive and negative. Calgary is a city of 1.4 million people with a growing immigrant population. Malaria testing is handled by the centralized Calgary Laboratory Services (CLS). When a malaria test is ordered, a malaria history form (MHF) was required according to CLS protocol, to allow for data collection on epidemiological risk factors. The CLS database was reviewed, which contained a record of all malaria diagnostic tests requested during the study period. Subjects from the CLS database was linked to the MHF using the laboratory accession number. Data collection took place between May-August 2018. Observers recording information on MHFs were inherently blinded to the outcome of the patient as they were completed before the diagnostic test was conducted, but investigators conducting the analysis were not blinded. Individuals who were not symptomatic and undergoing testing for alternative reasons (e.g. visa requirement) were excluded from the study. Ethical approval was obtained from the Conjoint Health Research Ethics Board at the University of Calgary (REB 15-1160).

Case definition

A case was defined as someone who had a clinical diagnosis of malaria. Each malaria test was performed as per standard operating procedure at the time with three Giemsa-stained thick and thin peripheral blood smears at least 6-8 hours apart and rapid diagnostic tests (RDTs)

(BinaxNOW®Malaria, Alere, USA). Malaria species were identified by microscopy. In house polymerase chain reaction (PCR) was performed in cases where further confirmation was required. Individuals undergoing repeated malaria tests within a three-month period were included only once. All cases from 2013 – 2017, except for those that were excluded due to malaria screening tests were included in the study.

Selection of controls

From individuals who tested negative using the same methods as described for a case, roughly five controls were selected for each case matched to the year when the case was diagnosed. The main purpose of this was to reduce the time taken performing chart reviews on the MHFs. Further information regarding the randomization process and selection of controls is available in the online supplementary material.

Epidemiological risk factors

Epidemiological data were collected on enrolled individuals prospectively by the testing clinician on the MHF so that the relationship between malaria positivity and epidemiological risk factors could be examined. Data entry into the study database was performed retrospectively via review of the MHFs. Information from the original MHFs was complemented with information from repeated MHFs and CLS database to reduce recall bias. Further information of the epidemiological risk factors can be found in the supplementary material and a copy of the standardized MHF is shown in supplementary figure 1.

Statistical Analysis

An initial descriptive analysis was conducted of the epidemiological risk factors of the study population based on the outcome status. A multivariable analysis was conducted using only those who traveled for the purpose of VFR, tourism or business. Other categories such as new immigrants and visitors to Canada were excluded because they were not considered as returning travelers. Differences in predisposing conditions between VFR and other travelers were examined using Chi-square tests. Multivariable logistic regression was used to compare the odds ratio for being in the VFR group versus other returning travelers and other risk factors/ potential confounders between cases and controls.

Results

Descriptive epidemiological analysis

As seen in figure 1, there were 219 confirmed malaria cases and 1129 controls enrolled in this study. Basic demographic and clinical characteristics of the study population stratified by malaria status are described in table 1. *P. falciparum* was the most commonly detected malaria parasite (65.8%) in this study, followed by *P. vivax* (24.7%). Percentage of males in the malaria positive group (64.8%) was significantly higher compared to the control group (51.3%; p-value <0.001). The most common age of travel was 33 years-old for cases and 35 for controls and this was not significantly different between the two groups (p-value 0.147). VFR was the most common type of traveler among both cases (49.7%) and controls (46.6%). Among those who tested positive for malaria, Africa was the most common travel destination (79.7%) whereas Asia was the most

commonly traveled destination among those who tested negative for malaria (48.7%). Those who tested negative for malaria sought pre-travel advice significantly more often (35.9%) compared to those who tested positive (19.6%; p-value <0.001). The percentage taking prophylaxis was not significantly different between cases and controls (p-value 0.267). Percentage of participants that reported headache as a symptom was significantly higher in cases (65%) compared to controls (51%; p-value 0.001). Sore throat was observed significantly more among controls (25%) as oppose to cases (12%; p-value <0.001). Other symptoms such as fever, cough and diarrhea were marginally significant between cases and controls with only fever being observed at a higher percentage among cases. Duration of travel (in days) for those who tested positive for malaria was significantly higher (239) compared to those who tested negative (49; p-value <0.001. The incidence of malaria was highest in municipal Ward 5, followed by Ward 9 and 10, which corresponded to North East (NE) and South East (SE) quadrants in City of Calgary (Figure 2).

Multivariable analysis

VFR travelers were less likely to seek pre-travel advice (p-value < 0.001), take prophylaxis (p-value = 0.002), and more likely to stay longer than 2 weeks (p-value < 0.001) compared with non-VFR travelers (Figure 3). Controlling for other factors, being an adult (OR: 3.62 [1.66-8.84]), male (OR: 2.70 [1.56-4.80]), belonging to VFR population (OR: 2.82 [1.42-5.92]) and traveling to Africa (OR: 11.52 [6.33-22.05]) were factors that were significantly associated with testing positive for malaria in this study population (Table 2). Seeking pre-travel advice was associated with testing negative for malaria (OR: 0.38[0.20-0.70]; Table 2). There was no significant evidence to suggest

duration had an impact of being a case or a control (OR: 1.40 [0.60-3.67]; Table 2). Similarly, there was no significant evidence of effect measure modification on the multiplicative scale between VFR status and gender or region traveled to (Supplementary table 1 and 2).

Discussion

The primary aim of this study was to investigate risk factors associated with testing positive for malaria among VFR travelers in the Calgary metropolitan area. 47% of the study population belonged to the VFR population excluding those who did not have a traveler status reported in MHFs. The highest proportion of those who were diagnosed with malaria also belonged to this population. It was observed that VFRs were also less likely to seek pre-travel advice, take prophylaxis, and stay less than 2 weeks compared to non-VFR travelers. These factors were hypothesized to make the VFR population a high-risk group in acquiring malaria during their travels (7, 12). Consequently, after controlling for other factors, VFRs were also more likely to be diagnosed with malaria compared with other travelers. Travelling to Africa as well as being male also increased the odds of being diagnosed with malaria independent of other factors.

Currently, Sub-Saharan Africa has the highest malaria burden among WHO regions with 95% of malaria cases in 2016 originating from this region (1). Additionally, previous studies also found that those who travel to the African continent carried the highest burden of imported malaria (13, 19, 20). Thus, the observation in this study that those who traveled to the African continent carry higher odds of being diagnosed with malaria corresponds to what has been previously reported in other jurisdictions. Males were more likely to be diagnosed with malaria in this study

population. Likely explanations for this could be that they may disproportionately travel to the highest risk malaria areas within risk destinations (e.g., rural, remote and repetitive travel) and/or that they might take fewer personal protective measures (e.g., bed nets, repellant use) (21, 22) Therefore, disparities between men and women regarding malaria diagnosis is an important finding, where VFR men may be a hard-to-reach population that may need greater outreach regarding pre-travel clinical prevention.

We were also interested in investigating VFR children being tested positive for malaria. It was observed that children were less likely to be diagnosed with malaria compared with adults, when controlled for the traveler status and other confounders. However, 7.8% of VFR children tested in our study were diagnosed with malaria, as opposed to 0% of non-VFR pediatric travelers. Regardless of the type of travel, parents are more likely to seek medical care for children presenting with febrile symptoms than for themselves. Therefore, it is likely that this dataset would represent a higher proportion of children with non-malaria causes for their febrile illnesses compared with adults presenting with the same (23-25). This is likely to produce bias in the effect measure, and to erroneously suggest that children are at a disproportionately lower risk of malaria in comparison to adults. Due to the lack of a sufficient sample of non-VFR pediatric travelers in our study, we could not establish evidence to support effect measure modification between being a child and belonging to VFR population.

A major limitation of this study was that we only had information on those subjects, who presented with malaria-like symptoms to a care facility. This likely introduced selection bias, exaggerating the effect measure. Additionally, VFR travelers were not distinguished according to first- or second-generation immigration status. It would have been valuable to make this

distinction, because risk perception about malaria and the use of personal protective measures may differ between these subpopulations. Similarly, another subgroup that could be considered is those who travel to malaria-endemic versus non-endemic areas. The potential for information bias was overlooked in this study due to missing information. Despite these limitations, this study is consistent with the findings previously published from other industrialized non-malarial countries (6-8, 12, 18, 26). Therefore, this study adds to the growing body of knowledge regarding the travel-related health burden among VFR travelers, and the need for better access to pre-travel clinical prevention that suits the specific needs of various immigrant populations. This study also directly investigated predisposing factors such as malaria prophylaxis use and utilization of pre-travel health services within the international travel population presenting with malaria-like symptoms in Calgary. Furthermore, the use of CLS database from the Calgary metropolitan area may allow key findings to be generalizable to other major metropolitan areas in Canada that have similar immigrant population demographics.

Even with published evidence to suggest that pre-travel clinical prevention in general helps to reduce commonly-encountered health risks such as malaria, little has been done to create programs or interventions tailored to the specific needs of high-risk VFR travelers regarding low-cost immunization and chemoprophylaxis especially for dependent vulnerable children (10, 19, 26). Instead, VFR travelers are often treated health policy decision-makers as having the same needs and ability to pay as well-headed tourists traveling to all-inclusive resorts for vacation. By creating financial and structural barriers to pre-travel clinical prevention for high-risk groups such as VFR travelers, an unnecessary burden is also placed on the publicly-funded health care system in Canada dealing with expensive post-travel medical interventions for completely preventable

conditions. Previous studies suggest that financial support rather than education and awareness is a more effective strategy in dealing with the health risks of the VFR population (27-30). Currently in Canada, pre-travel clinical prevention has been defunded or delisted from publicly-funded provincial health care services. VFR travelers and parents must pay completely out-of-pocket for pre-travel health services as well as most if not all travel-related immunizations and prophylaxis with or without public or private drug benefit plans. In addition, very few private health organizations have access to publicly-funded language services to assist in reducing iatrogenic mistakes with travelers where English is a second language. Finally, many VFR travelers are working-class with limited funds for more than the cost of air fare. The cost of travel-related vaccines and chemoprophylaxis can be more than one household can afford, especially if parents are taking several children to visit grandparents, uncles and aunts. Until financial barriers to good quality and appropriate VFR travel health services are reduced, we cannot assume that all cases of malaria in this high-risk population is due solely to lack of awareness or lack of concern. We advise that policy makers be more aware of the disparities of health outcomes in the traveler population according to travel status (VFR vs non-VFR), and suggest providing financial support to cover travel-related health expenses for those at greatest risk including children. Incidences of malaria in the Calgary area during the study period was highest along the city's NE and SE quadrant border, where most new Canadians now reside. Traveling populations in this area of the city should be the focus of further study to determine community-based needs to reduce the prevalence of malaria and other preventable conditions in these regions. Further investigation regarding social factors such as risk perceptions, socioeconomic status and ability to pay, and

language barriers should be conducted to determine their impact on timely access to appropriate pre-travel clinical prevention in Canada.

Conclusion

In this study, it was observed that VFR travelers were less likely to seek pre-travel advice, take prophylaxis and were more likely to stay in a malaria-endemic area for a longer duration in comparison to non-VFR recreational or business travelers. VFR travelers were also more likely to be diagnosed with malaria than non-VFR travelers. We highlight the need for targeted and subsidized pre-travel health services for the VFR population that goes beyond providing awareness of risk factors when traveling internationally.

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Figure Legends

Figure 1: Overview of study design. Only cases and controls who had the reason as “VFR”, “Tourism” or “Business” were included in the multivariate analysis. Those who were excluded due to “Missing Information” did not have their purpose of travel status specified in the malaria history form (MHF). False positives were discrepant cases that were confirmed by PCR.

Figure 2: The incidences of Malaria in the Calgary area between 2013 - 2017 by municpal ward boundaries. The locations for ward boundaries and population demographics were obtained from The City of Calgary (Open Calgary, open data source).

Figure 3: The proportions of observing the specified predisposing conditions; (i) duration of stay longer than two weeks (n = 241), (ii) seeking pre-travel advice (n = 779) and (iii) taking prophylaxis (n = 736) within each traveler groups. P-values were calculated using Chi-square tests comparing the two traveler groups

Tables

Table 1: Characteristics of the study population stratified by Malaria Status for symptomatic individuals (n = 1348)

Characteristic	**Malaria Status**		**p value[a]**
	No	**Yes**	
n	1129	219	
Gender Male (n) (%)	579 (51.3)	142 (64.8)	< 0.001
Age (mean (sd))	34.80 (21.05)	32.59 (18.01)	0.147
Reason (n[b]) (%)			< 0.001
Business	59 (6.3)	10 (5.6)	
New Immigrant	96 (10.3)	49 (27.7)	
Tourism	325 (34.9)	16 (9.0)	
VFR	433 (46.6)	88 (49.7)	
Visitor	17 (1.8)	14 (7.9)	
Continent (n[b]) (%)			< 0.001
Africa	313 (32.5)	145 (79.7)	
Americas	175 (18.2)	5 (2.7)	
Asia	469 (48.7)	31 (17.0)	
Europe	2 (0.2)	0 (0.0)	
Oceania	4 (0.4)	1 (0.5)	
Pre-Travel Advice (n[b])	774	148	< 0.001
Yes	278 (35.9)	29 (19.6)	
Prophylaxis (n[b])	214	82	0.267
Yes	54 (25.2)	15 (18.3)	
Symptoms (n[b])	964	181	
Fever			0.049
Yes	829 (86.0)	166 (91.7)	
Night Sweats			0.850
Yes	336 (34.9)	65 (35.9)	
Headache			0.001
Yes	492 (51.0)	117 (64.6)	
Sore Throat			< 0.001
Yes	243 (25.2)	22 (12.2)	
Cough			0.019
Yes	323 (33.5)	44 (24.3)	
Arthralgia/ Myalgia			0.084
Yes	342 (35.5)	77 (42.5)	

Diarrhea			0.032
Yes	257 (26.7)	34 (18.8)	
Splenomegaly			0.277
Yes	21 (2.2)	7 (3.9)	
Duration [c] (mean days [sd])	48.98 (77.74)	239.00 (665.62)	< 0.001
Plasmodium Species Type (n) (%)			
P. falciparum	-	144 (65.8)	
P. vivax	-	54 (24.7)	
P. ovale	-	17 (7.76)	
P. malariae	-	4 (1.83)	

[a] The tests used for categorical variables are chi-square with continuity correction and ANOVA for continuous variables with equal variance assumption
[b] Missing values are excluded from the table
[c] The duration of stay in the malaria-endemic areas for travelers in days

Table 2: The odds ratios and corresponding 95% CIs and p-values for the multivariate regression analysis of cases and controls for various exposure measures (N = 931)

Variable	OR (95% CIs)	Pr (>|z|)
Gender		
Female	1.00	
Male	2.70 (1.56 - 4.80)	**< 0.001**
Age		
Children	1.00	
Adults	3.62 (1.66 - 8.84)	**< 0.001**
Reason		
Tourists	1.00	
Business	1.12 (0.35 - 3.26)	0.84
VFR	2.82 (1.42 - 5.92)	**< 0.001**
Continent		
Other	1.00	
Africa	11.52 (6.33 - 22.05)	**< 0.001**
Pre-Travel Advise		
No	1.00	
Yes	0.38 (0.20 - 0.70)	**< 0.001**
Duration (> 2 weeks)		
No	1.00	
Yes	1.40 (0.60 - 3.67)	0.46

Bolded p-values are those variables with a significant p-value, using an $\alpha = 0.05$, in comparison to its reference

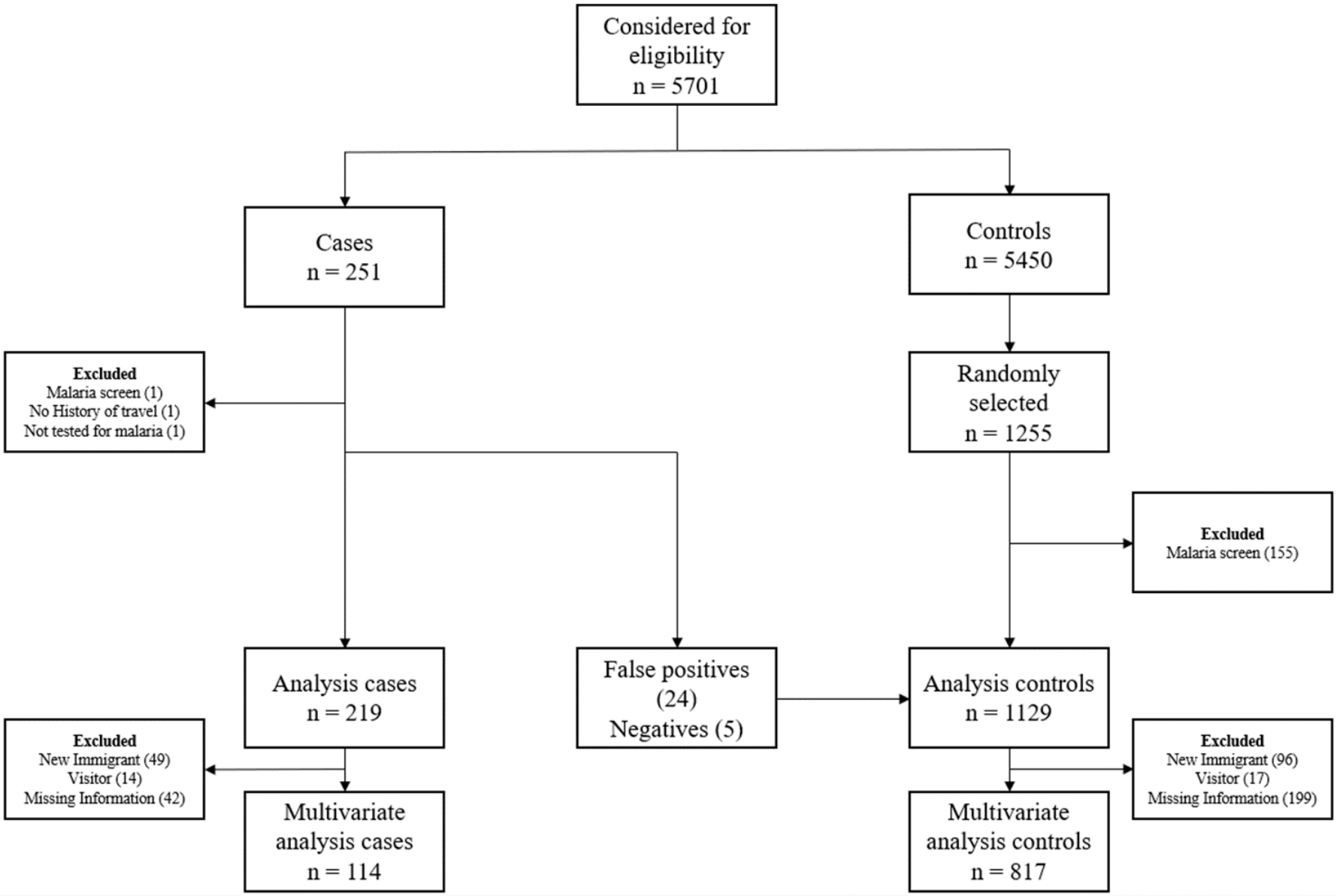

Considered for eligibility n = 5701
Cases n = 251
Controls n = 5450
Excluded
Malaria screen (1)
No History of travel (1)
Not tested for malaria (1)
Randomly selected n = 1255
Excluded
Malaria screen (155)
Analysis cases n = 219
False positives (24)
Negatives (5)
Analysis controls n = 1129
Excluded
New Immigrant (49)
Visitor (14)
Missing Information (42)
Excluded
New Immigrant (96)
Visitor (17)
Missing Information (199)
Multivariate analysis cases n = 114
Multivariate analysis controls n = 817

Figure 1

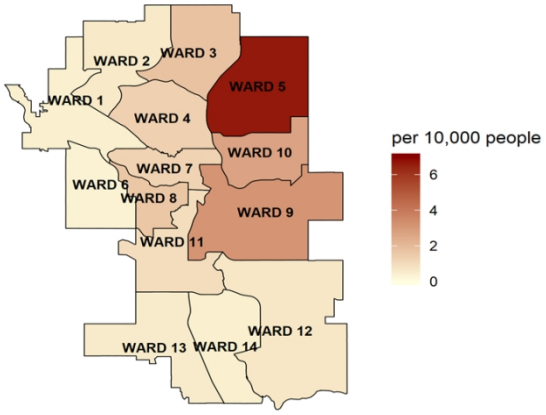


Figure 2

338x190mm (96 x 96 DPI)

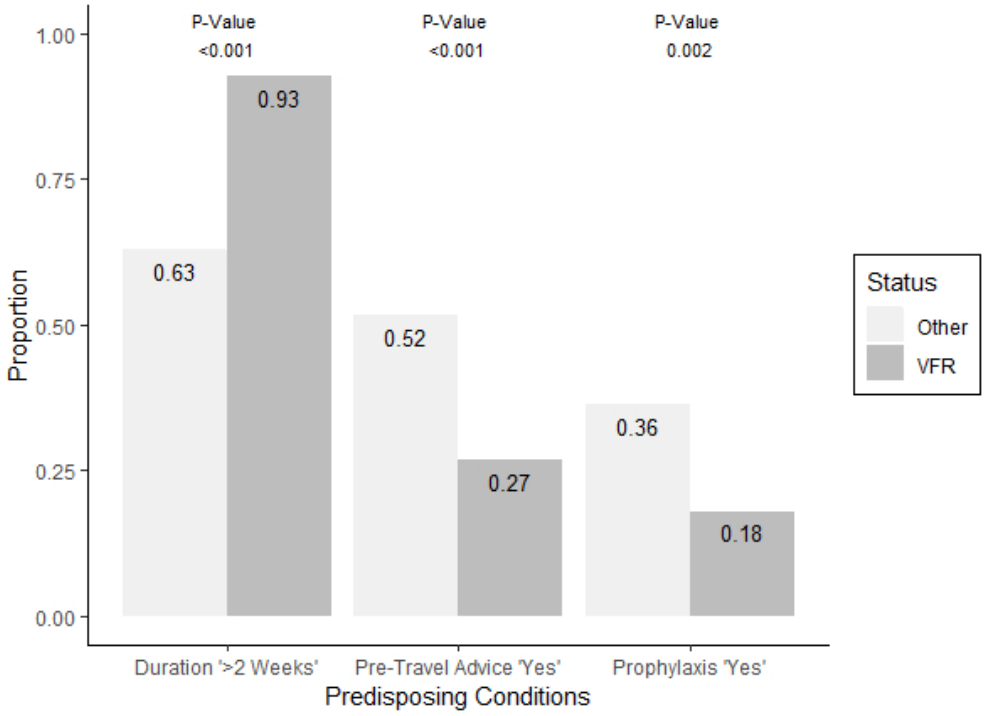

P-Value
<0.001
P-Value
<0.001
P-Value
0.002
1.00
0.75
0.50
0.25
0.00
Proportion
0.63
0.93
0.52
0.27
0.36
0.18
Status
Other
VFR
Duration '>2 Weeks'
Pre-Travel Advice 'Yes'
Prophylaxis 'Yes'
Predisposing Conditions

Figure 3

Supplementary Material

Random selection of controls

Using software R version 1.1.453, random numbers were generated between 1 and the maximum number of malaria tests conducted for the year, such that five controls could be selected for each case within that specific year. This number corresponded to the laboratory accession number from the Calgary Laboratory Services (CLS) database which was used to identify the participant. A ratio of greater than 4 controls to 1 case was felt unlikely to increase the study power further, yet a 5:1 ratio was selected to allow for missing data.

The rationale for cases and controls

Given the objective of the study, malaria positive individuals presented themselves as the outcome of interest. Hospital controls were selected from the CLS database from among those who have undergone a malaria test to ensure that both the cases and controls got tested for malaria by the same diagnostic methods and that controls only included those who did not have malaria within the specificity of the diagnostic tests used. This was to limit the information bias due to incorrect outcome ascertainment. No measures were taken to mitigate selection bias that arose due to hospital control selection in this study. Controls and cases were matched by year to eliminate any variation due to immigration/emigration rates and other factors that impact travel by year.

Epidemiological risk factors

Variables that were analyzed for this study included age, gender, the reason for visit, continent visited, if pre-travel advice was sought, if malarial prophylaxis was taken and duration of stay. Symptoms of cases and controls were also recorded. Our primary exposure of interest, VFR was defined as those who travelled primarily for the purpose of visiting friends and relatives and those who had a difference in risk for malaria exposure due to a history of recent travel to a malaria endemic region, disregarding the differences in ethnicity and immigration status of this population (1).*VFR* was a category under Reason for Visit variable in the Malaria History Form (MHF) and other categories included *Tourists, Business, New Immigrant* and *Visitor*. The two main other purposes of visit categories were *Tourist* travelers and *Business* travelers which included those who self-declared themselves as visiting a malaria endemic region for pleasure (without visiting family or friends) or for work-related purposes respectively. Information regarding age and gender was obtained from the CLS database. Age was a categorical variable of *Child* or *Adult*, where participants who are under 16 years of age were defined as a child. Gender was a categorical variable of *Female* and *Male*. Continent visited was derived from the country indicated in the *Travel Destination* section in MHF and categorized as either visiting *Africa* or *Other* continent for the statistical analyses. Africa was used as a primary comparator to other continents due to past evidence suggesting imported malaria mainly resulted from travel to the

African continent (2-4). Pre-travel advise sought was also a categorical variable of *Yes* or *No* which was collected from the MHF questionnaire that was completed before malaria testing. Malaria prophylaxis taken was a *Yes* or *N*o categorical variable and information for this was also collected from the MHF. Participants were categorized under *Yes* if they indicated that they have taken any one or more of the malaria prophylaxes listed under *Malaria Prophylaxis Taken* in the MHF and *No* if they indicated *None*. Duration of stay was derived from information provided in the MHF under *Departure Date* and *Date of Arrival in Canada*. This was calculated in days and later categories as less than or equal to two weeks of stay (*≤ 2 weeks*) or longer than 2 weeks of stay (*>2 weeks).* First three digits of the zip code obtained from the CLS database, complemented by MHFs was used to determine the Ward of residence in Calgary and to develop an incidence map of Malaria cases in Calgary according to 2016 census population data.

Statistical analysis

For descriptive analysis, chi-square tests with continuity correction were used for categorical variables whereas ANOVA with the assumption of equal variance was used for continuous variables. This included all the cases and controls (N = 1348) selected for this study. Incidences of malaria map were drawn according to population demographics from the census in 2016 and using geographical boundaries of Wards from Open Calgary (5). For the multivariable logistic regression, numerous variables were examined including the effects of age, VFR status, region traveled to, pre-travel advice, duration and gender on testing positive for malaria. Evidence for effect measure modification between gender and VFR and continent travel to and VFR on a multiplicative scale was analyzed by including interaction variables in multivariate regressions. A chi-square test was used to analyze the differences in taking prophylaxis, taking pre-travel advice and duration of stay between VFR travelers and other travelers. Missing data were not examined further using imputations methods or sensitivity analysis.

Data access and cleaning methods

Investigators only had access data extracted from the CLS database regarding all malaria tests conducted in the CLS during the study period. They were stored and cleaned using Microsoft Excel (Version 1808) to remove repeated tests for individuals occurring within three months. Individuals from the CLS database was linked to individuals from the MHF using MIL numbers.

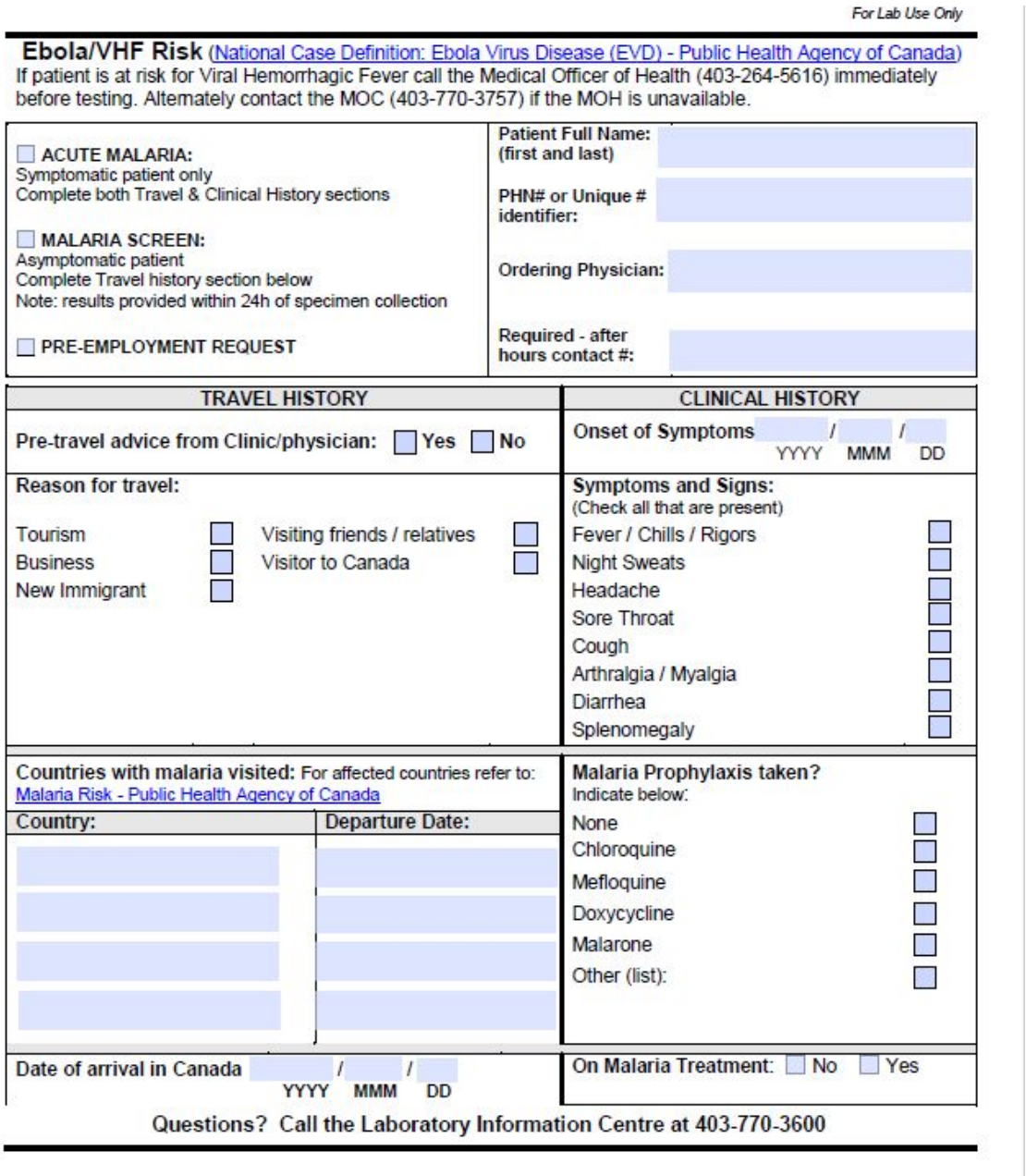
Supplementary Table 1: Odds ratios, 95% CIs and p-values for the multivariate regression examining the evidence for EMM between VFR status and Gender (N = 931)

Variable	**OR**	**95 % (CIs)**		**Pr(>|z|)**
		2.50%	97.50%	
Gender				
Female	1.00			-
Male	2.77	1.19	7.23	0.02
EMM Male & VFR				
No	1.00			-
Yes	0.59	0.21	1.58	0.31
Reason				
Tourist	1.00			-
VFR	4.22	1.93	10.62	<0.001

Supplementary Table 2: Odds ratios, 95% CIs and p-values for the multivariate regression examining the evidence for EMM between VFR status and region visited (N = 931)

Variable	**OR**	**95 % (CIs)**		**Pr(>|z|)**
		2.50%	97.50%	
Continent				
Other	1.00			-
Africa	8.36	3.46	23.39	<0.001
Africa & VFR				
No	1.00			-
Yes	1.30	0.41	3.80	0.64
Reason				
Tourist	1.00			-
VFR	2.39	0.97	6.73	0.07

Supplementary Figure 1: A copy of the malaria history form where information regarding the cases and controls were collected from. Missing information was supplemented with data from the CLS database when available.



For Lab Use Only

Ebola/VHF Risk (National Case Definition: Ebola Virus Disease (EVD) - Public Health Agency of Canada)
If patient is at risk for Viral Hemorrhagic Fever call the Medical Officer of Health (403-264-5616) immediately before testing. Alternately contact the MOC (403-770-3757) if the MOH is unavailable.

☐ **ACUTE MALARIA:**
Symptomatic patient only
Complete both Travel & Clinical History sections

☐ **MALARIA SCREEN:**
Asymptomatic patient
Complete Travel history section below
Note: results provided within 24h of specimen collection

☐ **PRE-EMPLOYMENT REQUEST**

Patient Full Name: (first and last)

PHN# or Unique # identifier:

Ordering Physician:

Required - after hours contact #:

TRAVEL HISTORY

Pre-travel advice from Clinic/physician: ☐ Yes ☐ No

Reason for travel:

Tourism ☐ Visiting friends / relatives ☐
Business ☐ Visitor to Canada ☐
New Immigrant ☐

Countries with malaria visited: For affected countries refer to: Malaria Risk - Public Health Agency of Canada

Country:	Departure Date:

Date of arrival in Canada ____ / ____ / ____ (YYYY / MMM / DD)

CLINICAL HISTORY

Onset of Symptoms ____ / ____ / ____ (YYYY / MMM / DD)

Symptoms and Signs:
(Check all that are present)

Fever / Chills / Rigors ☐
Night Sweats ☐
Headache ☐
Sore Throat ☐
Cough ☐
Arthralgia / Myalgia ☐
Diarrhea ☐
Splenomegaly ☐

Malaria Prophylaxis taken?
Indicate below:

None ☐
Chloroquine ☐
Mefloquine ☐
Doxycycline ☐
Malarone ☐
Other (list): ☐

On Malaria Treatment: ☐ No ☐ Yes

Questions? Call the Laboratory Information Centre at 403-770-3600

References

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4. Hendel-Paterson B, Swanson SJ. Pediatric travelers visiting friends and relatives (VFR) abroad: illnesses, barriers and pre-travel recommendations. Travel Med Infect Dis. 2011;9(4):192-203.
5. Ward Boundaries [Internet]. 2018 [cited August 2018]. Available from: https://data.calgary.ca/Government/Ward-Boundaries/r9vx-mhnf.