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Research

Risk of malaria associated with travel to malaria-endemic areas to visit friends and relatives: a population-based case–control study

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Abstract

Background: Reports relying on population-based data and using epidemiologic methodologies such as case–control study designs for malaria in travellers and multivariable regression analysis of risk factors are rare. The aim of this study was to investigate the epidemiologic characteristics of travellers who tested positive for malaria after visiting friends and relatives in malaria-endemic areas to determine the risk of malaria associated with such travel.

Methods: Using routinely collected data from a population-based laboratory database, we conducted a case–control study of symptomatic people returning from travel to malaria-endemic areas who presented for malaria testing in Calgary from 2013 to 2017. We used a multivariable logistic regression to analyze the association between the presence of malaria and other risk factors.

Results: There were 251 confirmed malaria cases during the study period, of which 219 were matched to 1129 returning travellers without malaria. Based on the multivariable regression, the odds of a traveller who visited friends and relatives in malaria-endemic areas being diagnosed with malaria was 2.82 (95% confidence interval [CI] 1.42–5.92) times greater than that of other travellers to these regions. Adults (odds ratio [OR] 3.62, 95% CI 1.66–8.84), males (OR 2.70, 95% CI 1.56–4.80), travellers to Africa (OR 11.52, 95% CI 6.33–22.05) and those who did not seek pretravel advice (OR 0.38, 95% CI 0.20–0.70) were more likely to be diagnosed with malaria. Although those travelling to visit friends and relatives tended to stay longer in endemic areas than other travellers, visit duration was not associated with an increased likelihood of malaria in the model. The annual incidence of malaria was highest (13.34 per 100 000) in metropolitan wards associated with lower socioeconomic status and immigrant communities.

Interpretation: Travellers who visited friends and relatives in malaria-endemic areas were less likely than other travellers to these regions to seek pretravel advice, take prophylaxis and have a visit duration less than 2 weeks; travelling to Africa and being male increased the odds of being diagnosed with malaria, independent of other factors. These data suggest that targeted strategies to provide pretravel care to travellers who visit friends and relatives in malaria-endemic areas may aid in reducing the burden of malaria in this population.

In 2017, there were 219 million malaria cases and 435 000 deaths from the disease worldwide, with US$3.1 billion allocated globally for malaria eradication and management.[1] In Canada, there were about 490 imported malaria cases annually in 2010–2014.[2]

In the Calgary metropolitan area, 4.3% and 27.9% of the population self-identified as belonging to an African or Asian ethnic origin, respectively.[3] In addition, 37.5% of all Canadian children currently are first- or second-generation immigrants.[4] Although not all immigrants necessarily return to their country of origin, immigrants contribute to the population of people who travel to visit friends and relatives. Moreover, other Canadians may be married to immigrants and travel to malaria-endemic regions to visit in-laws, with the same risk as the spouse. Therefore, understanding the effects of travel to visit friends and relatives in malaria-endemic regions on being diagnosed with malaria is necessary to provide appropriate preventive and clinical care for this population.

Travellers visiting friends and relatives are known to be at higher risk for travel-related illnesses in general.[5–7]

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They are likely to make travel plans at short notice, travel with dependent children and stay in rustic family settings.[8] The unique travel characteristics of this group put them at increased risk for malaria compared to other traveller groups. Travellers visiting friends and relatives are more likely than other travellers to visit malaria-endemic areas, make regular visits to same regions and have long stays.[5–9] Within malaria-endemic regions, travellers visiting friends and relatives are more likely to visit areas within countries defined by the World Health Organization as high risk for malaria, such as rural remote locations.[10] Local family accommodations are often more basic than those used by tourists, including less likelihood of air conditioning and indoor residual spraying.[9,10] Travellers visiting friends and relatives are less likely to use personal protection such as long-sleeved clothing, mosquito nets and insect repellant.[9] Finally, some travellers visiting friends and relatives may downgrade their perceived risk owing to a faulty belief in ongoing protection from past exposure to malaria before emigrating. This may be a reason for some to avoid taking effective antimalarial prophylaxis.[5–11]

Children of first- and second-generation immigrants are also at a higher risk for travel-related illnesses than those of other traveller groups.[8,12] Canadian children of immigrants visiting friends and relatives are exposed to the same hazards as their parents but are naive to many travel-related illnesses foreign to Canada. This places them at higher risk than recent immigrants, and they develop severe malaria with increased morbidity and mortality.[8] They are also more likely than adults to have delays in treatment owing to greater likelihood of initial misdiagnosis, as well as higher parasitemia.[13–16] As a result, many epidemiologic factors affect the incidence of imported malaria among travellers visiting friends and relatives and other traveller populations in Calgary and in Canada.

In Canada, the number of malaria cases imported from endemic areas has risen steadily since 2000.[11,17] Our previous study of returning travellers in Calgary showed that the majority belonged to the group of travellers visiting friends and relatives.[11] Therefore, the primary objective of the present study was to examine the epidemiologic characteristics of travellers who tested positive for malaria after visiting friends and relatives in malaria-endemic areas to investigate the impact of this type of travel on testing positive for malaria. Given previous findings,[11] we hypothesized that travellers and their children who had visited friends and relatives in malaria-endemic areas might be at increased risk for the disease.

Methods

Study design and setting

We conducted a case–control study of symptomatic people who presented for malaria testing in Calgary after having travelled to visit friends and relatives in malaria-endemic areas to compare the epidemiologic risk factors between those who tested positive for malaria and those who did not. Traditionally, people who travel to visit friends and relatives have been classified according to ethnic origin or immigration status.[18] However, following the recommendations of Barnett and colleagues,[18] we defined them as the population of returning travellers who had recently visited a malaria-endemic region for the purpose of visiting friends and relatives. As such, this definition also captured those who had connections to the local population but did not qualify as a traveller visiting friends and relatives under traditional definition based on ethnic origin and immigration status. In doing so, we hoped to increase the generalizability of the study findings.

Calgary is a city of 1.4 million people with a growing immigrant population.[19] This study captured those who were tested for malaria between 2013 and 2017.

Data sources

Data collection and analysis took place between May and August 2018. Malaria testing is handled by the centralized Calgary Laboratory Services. When a malaria test is ordered, a malaria history form is required according to Calgary Laboratory Services protocol to allow for collection of data on epidemiologic risk factors. The Calgary Laboratory Services database contained a record of all malaria diagnostic tests requested during the study period in the metropolitan centre of Calgary.

All recorded malaria tests for patients who presented to a care facility in the Calgary area during the study period were eligible for the study. Those who were tested for malaria elsewhere or who self-treated were not captured in the study population. During the analysis stage of the study, tests conducted for other reasons such as screening owing to being a visitor or a new immigrant were excluded, as were people who were not symptomatic and underwent testing for alternative reasons (e.g., visa requirement).

Patients in the Calgary Laboratory Services database were linked to the malaria history form by means of the laboratory accession number. Observers who recorded information on the malaria history forms were inherently blinded to the patient's outcome, as the forms were completed before the diagnostic test was conducted; however, the investigators conducting the analysis were not blinded. For the purposes of this study, we defined "symptomatic" as having presented to a physician with symptoms related to malaria, as recorded in the malaria history form.

Selection of cases

A case was defined as a clinical diagnosis of malaria confirmed as per standard operating procedure for malaria testing at the time, with 3 Giemsa-stained thick and thin peripheral blood smears at least 6–8 hours apart and rapid diagnostic tests (BinaxNOW). Malaria species were identified by microscopy. In-house polymerase chain reaction assays were performed in cases in which further confirmation was required. People who underwent repeated malaria tests within a 3-month period were included only once.

Selection of controls

The Calgary Laboratory Services database also contains information regarding people who present with malaria-like symptoms to a medical facility but who test negative for malaria. We used these people as control subjects. Each person with a negative malaria test result for a given year was assigned a study number, and these study numbers were selected via a random number generator in R (R Foundation for Statistical Computing) such that 5 control subjects were matched to each case for a given year. The study numbers were then linked to accession numbers to collect information from the malaria history forms and the Calgary Laboratory Services database. Control subjects were not matched by age and gender; we examined the effect of these 2 variables on the likelihood of acquiring malaria in multivariable analysis. The main purpose of omitting matching for age and gender was to explore the impact of age and gender on acquiring malaria in travellers who visited friends and relatives versus other travellers. Further information regarding the randomization process and selection of control subjects is available in Appendix 1 (available at www.cmajopen.ca/content/8/1/E60/suppl/DC1).

Risk factors

Epidemiologic data were collected prospectively by the testing clinician on paper files as malaria history forms (Appendix 2, Supplementary Figure S1, available at www.cmajopen.ca/content/8/1/E60/suppl/DC1) and stored in Calgary Laboratory Services testing facilities. We performed electronic data entry for the study retrospectively via review of the malaria history forms. Information from the original malaria history form was complemented with information from repeated forms and the Calgary Laboratory Services database to reduce recall bias.

Variables analyzed included age, gender, reason for travel, continent visited, whether pretravel advice was sought, whether malarial prophylaxis was taken and duration of stay. We included these factors in the study given their availability in the malaria history forms and their relevance to the objective of the study, determined with a directed acyclic graph. Symptoms of case and control subjects were also recorded. Further information on the epidemiologic risk factors and their definitions can be found in Appendix 1.

Statistical analysis

We conducted an initial descriptive analysis to compare confounding variables and other characteristics of the study population based on outcome (positive or negative for malaria). We used a multivariable logistic regression to investigate the association between travel purpose and malaria, controlling for age, gender, location visited, pretravel advice and duration of stay. We chose these confounding variables based on results from the descriptive analysis and information from the literature.[11] We removed prophylaxis owing to its collinearity with pretravel advice. Symptoms were not included in the multivariable analysis since this is a descendent of our outcome (malaria). Only those who travelled for the purpose of visiting friends and relatives, tourism or business were included in the multivariable logistic regression.

We used the χ^2 test to investigate differences in pre- and posttravel factors such as obtaining pretravel advice, taking prophylaxis and duration of travel between those who travelled to visit friends and relatives and other travellers. We determined the study sample size based on the number of cases during the study period. A sample size calculation that indicates the number of cases needed to support effect sizes with 80% power is given in Appendix 1. We carried out a sensitivity analysis using the multiple imputation method in R (MICE package) (R Foundation for Statistical Computing) to determine the impact of missing data.

Ethics approval

Ethical approval was obtained from the Conjoint Health Research Ethics Board of the University of Calgary.

Results

There were 251 confirmed malaria cases during the study period, of which 219 were matched to 1129 control subjects (Figure 1). Basic demographic and clinical characteristics of the study population stratified by malaria status are given in Table 1. Of the 219, 48 were children (age ≤ 16 yr). Thirteen (7.8%) of the 167 children who travelled to visit friends and relatives were diagnosed with malaria, as opposed to 0 (0%) of the 48 other pediatric travellers.

Plasmodium falciparum was the most commonly detected malaria species (144 [65.8%]), followed by *P. vivax* (54 [24.7%]). The proportion of males in the malaria-positive group was significantly higher than that in the control group (64.8% v. 51.3%, $p < 0.001$). There was no difference in the most common age at travel between the case and control groups (33 yr v. 35 yr, $p = 0.1$).

Visiting friends and relatives was the most common reason for travel in both groups (49.7% and 46.6%, respectively). Among those who tested positive for malaria, Africa was the most common travel destination (145 [79.7%]), whereas Asia was the most common destination among those who tested negative for malaria (469 [48.7%]). Significantly more people who tested negative for malaria than who tested positive for malaria sought pretravel advice (278 [35.9%] v. 29 [19.6%], $p < 0.001$). The proportion who took prophylaxis was not significantly different between the 2 groups ($p = 0.3$).

The proportion of travellers who reported headache as a symptom was significantly higher in the case group than the control group (117 [64.6%] v. 492 [51.0%], $p = 0.001$), whereas the reverse was true for sore throat (243 [25.2%] v. 22 [12.2%], $p < 0.001$). The proportions of travellers with other symptoms such as fever, cough and diarrhea are presented in Table 1.

The mean duration of travel was significantly higher for those who tested positive for malaria than for those who tested negative (239 d v. 49 d, $p < 0.001$).

The average annual incidence of malaria was highest in municipal Ward 5 (13.34 per 100 000), followed by Ward 9

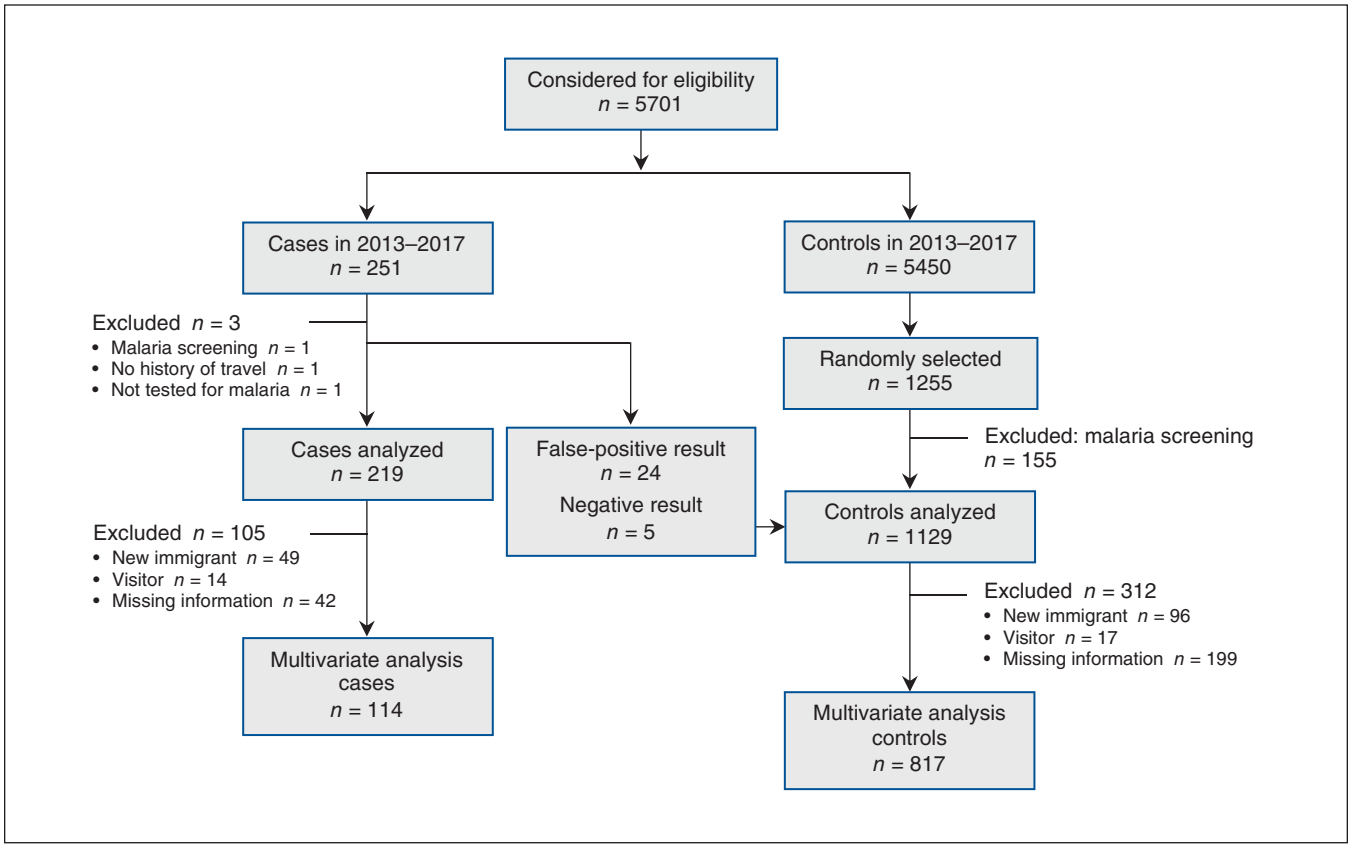

Figure 1: Flow diagram showing selection of case and control subjects. Only those who travelled to malaria-endemic areas to visit friends and relatives, for tourism or for business were included in the multivariable analysis; those who were excluded because of missing information did not have the purpose of travel specified in their malaria history form. False-positive cases were discrepant cases that were confirmed by negative results on polymerase chain reaction testing.

(6.31) and Ward 10 (5.44), which corresponded to the northeast and southeast quadrants in Calgary (Figure 2; Appendix 2, Supplementary Table S1).

Multivariable analysis

Travellers visiting friends and relatives were less likely to seek pretravel advice ($p < 0.001$) and to take prophylaxis ($p = 0.002$), and more likely to stay longer than 2 weeks ($p < 0.001$) compared to other travellers (Figure 3). After we controlled for other factors, being an adult compared to being a child (odds ratio [OR] 3.62, 95% confidence interval [CI] 1.66–8.84), being a male compared to being a female (OR 2.70, 95% CI 1.56–4.80), travelling to visit friends and relatives compared to being a tourist (OR 2.82, 95% CI 1.42–5.92) and travelling to Africa compared to travelling to other continents (OR 11.52, 95% CI 6.33–22.05) were all significantly associated with testing positive for malaria (Table 2).

Seeking pretravel advice was associated with testing negative for malaria (OR 0.38, 95% CI 0.20–0.70). There was no significant evidence to suggest that travel duration had an impact on malaria status (OR 1.40, 95% CI 0.60–3.67). Even after a sensitivity analysis (data not shown), we found no evidence to suggest that either gender or travel destination increased the risk of malaria in those who travelled to visit friends and relatives (Appendix 2, Supplementary Tables S2 and S3).

Interpretation

The odds of being diagnosed with malaria were higher for people who travelled to visit friends and relatives in malaria-endemic areas than for other travellers. The former were also less likely to seek pretravel advice, take prophylaxis and have a visit duration less than 2 weeks. These factors have been hypothesized to put people who travel to visit friends and relatives at high risk for malaria during their travels.[6,11] Even after we controlled for these and other factors, people who travelled to visit friends and relatives in malaria-endemic areas were still more likely than other travellers to these regions to be diagnosed with malaria. Travelling to Africa and being male also increased the odds of being diagnosed with malaria, independent of other factors.

Our findings are consistent with those previously published from other industrialized countries.[5–7,11,17,20] Currently, Sub-Saharan Africa has the highest malaria burden among World Health Organization regions, with 95% of malaria cases in 2016 originating from this region.[1] In addition, previous studies showed that those who travel to Africa carry the highest burden of imported malaria.[12,21,22] Our observation that those who travelled to Africa carried higher odds of being diagnosed with malaria is in keeping with these findings.

Table 1: Characteristics of travellers returning to Calgary from malaria-endemic areas stratified by malaria status, 2013–2017

Characteristic	Malaria; no. (%) of travellers*		
	No (controls) *n* = 1129	Yes (cases) *n* = 219	*p* value†
Male gender	579 (51.3)	142 (64.8)	< 0.001
Age, yr, mean ± SD	34.80 ± 21.05	32.59 ± 18.01	0.1
Reason for travel‡			
Business	59 (6.3)	10 (5.6)	< 0.001
New immigrant	96 (10.3)	49 (27.7)	< 0.001
Tourism	325 (34.9)	16 (9.0)	< 0.001
Visiting friends and relatives	433 (46.6)	88 (49.7)	< 0.001
Visitor	17 (1.8)	14 (7.9)	0.6
Missing	199/1129 (17.6)	42/219 (19.2)	–
Continent visited‡			
Africa	313 (32.5)	145 (79.7)	< 0.001
North/South America	175 (18.2)	5 (2.7)	< 0.001
Asia	469 (48.7)	31 (17.0)	< 0.001
Europe	2 (0.2)	0 (0.0)	0.2
Oceania	4 (0.4)	1 (0.5)	0.2
Missing	166/1129 (14.7)	37/219 (16.9)	–
Obtained pretravel advice‡			< 0.001
Yes	278 (35.9)	29 (19.6)	
No	496 (64.1)	119 (80.4)	
Missing	355/1129 (31.4)	71/219 (32.4)	–
Took prophylaxis‡			0.3
Yes	54 (25.2)	15 (18.3)	
No	160 (74.8)	67 (81.7)	
Missing	915/1129 (81.0)	137/219 (62.6)	–
Symptom(s)‡			
Fever	829 (86.0)	166 (91.7)	0.05
Night sweats	336 (34.8)	65 (35.9)	0.8
Headache	492 (51.0)	117 (64.6)	0.001
Sore throat	243 (25.2)	22 (12.2)	< 0.001
Cough	323 (33.5)	44 (24.3)	0.02
Arthralgia/myalgia	342 (35.5)	77 (42.5)	0.08
Diarrhea	257 (26.7)	34 (18.8)	0.03
Splenomegaly	21 (2.2)	7 (3.9)	0.3
Missing	165/1129 (14.6)	38/219 (17.4)	–
Duration of stay,§ d, mean ± SD	48.98 ± 77.74	239.00 ± 665.62	< 0.001
Plasmodium species			
P. falciparum	–	144 (65.8)	–
P. vivax	–	54 (24.7)	–
P. ovale	–	17 (7.8)	–
P. malariae	–	4 (1.8)	–

Note: SD = standard deviation.
*Except where noted otherwise.
†Categorical variables: χ^2 test with continuity correction; continuous variables: analysis of variance with equal-variance assumption.
‡Missing values were excluded from the *p* value and proportion analysis.
§In malaria-endemic area.

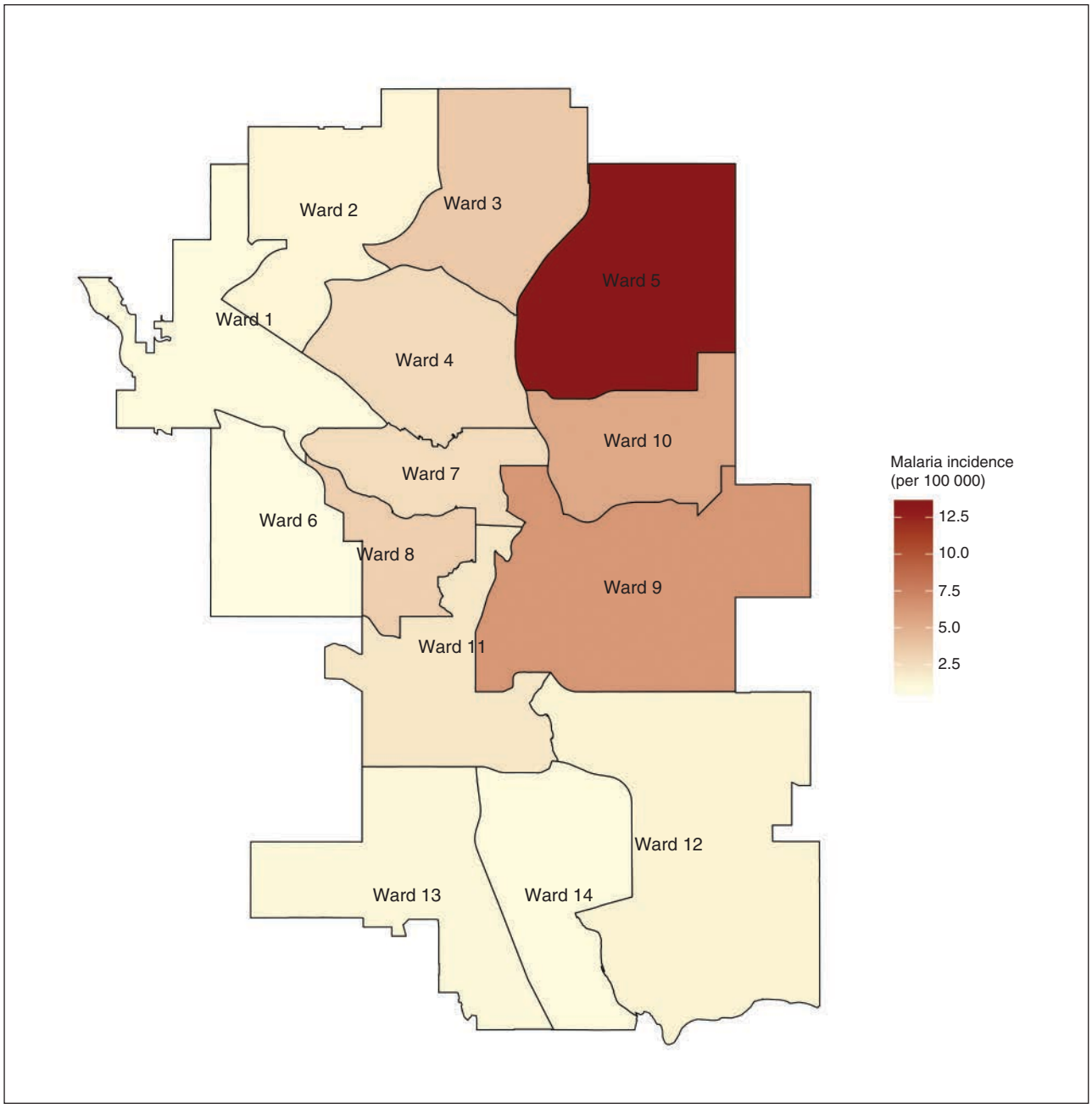

Figure 2: Average annual incidence of malaria in the Calgary area from 2013 to 2017 by municipal ward boundaries based on the 2016 Canadian census.[3] The locations for ward boundaries and population information were obtained from the City of Calgary (Open Calgary, open data source). Most immigrants from malaria-endemic countries reside in the northeast of the city.

Males were more likely than females to be diagnosed with malaria in this study population. Possible explanations are that they may travel disproportionately to the highest-risk malaria areas (e.g., rural and remote, and repetitive travel) and may take fewer personal protective measures (e.g., bed nets, repellant use).[23,24] Therefore, the disparities we found between men and women in malaria diagnosis indicate that men may need greater outreach regarding pretravel clinical prevention than women.

We were also interested in investigating children who travelled to visit friends and relatives in malaria-endemic areas and who tested positive for malaria. We found that children were less likely than adults to be diagnosed with malaria after we controlled for traveller status and other confounders. However, 7.8% of children who travelled to visit friends and relatives were diagnosed with malaria, as opposed to 0% of other pediatric travellers. Regardless of the type of travel, parents are more likely to seek medical care for children presenting with febrile symptoms than for themselves.[25–27] Therefore, it is likely that our study population contains a higher proportion of children with nonmalaria causes for their febrile illnesses compared to adults. This is likely to have produced bias in the effect measure and to suggest erroneously that children

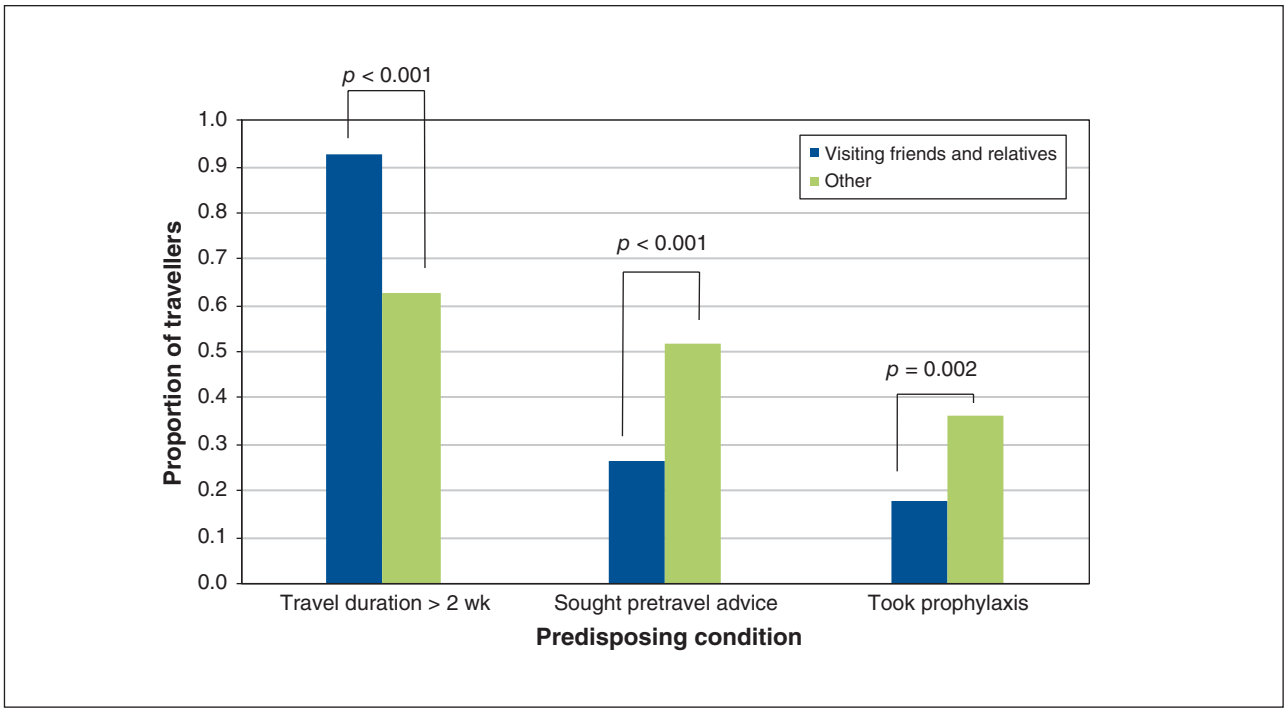

Figure 3: Proportions within the 2 traveller groups with travel duration longer than 2 weeks who sought pretravel advice and who took prophylaxis. *p* values for difference between the 2 traveller groups (χ^2 test).

are at disproportionately lower risk for malaria than adults. Owing to the lack of a sufficient sample of children travelling for reasons other than to visit friends and relatives in our study, we could not establish evidence to support effect measure modification between being a child and travelling to visit friends and relatives.

Even with published evidence to suggest that pretravel clinical prevention in general helps to reduce commonly encountered health risks such as malaria,[9,20,21] little has been done to create programs or interventions tailored to the specific needs of travellers visiting friends and relatives regarding low-cost vaccination and chemoprophylaxis, especially for vulnerable dependent children. Instead, this population is often treated by health policy decision-makers as having the same needs and ability to pay as tourists.[28] By creating financial and structural barriers to pretravel clinical prevention for groups at high risk, an unnecessary burden may be placed on the health care system in that expensive posttravel medical interventions may be needed for preventable conditions. Previous studies suggest that financial support is a more effective strategy than education and awareness in dealing with the health risks of travelling to visit friends and relatives.[29–32] Currently in Canada, pretravel clinical prevention has been defunded or delisted from publicly funded provincial health care services. Travellers visiting friends and relatives must pay out of pocket for pretravel health services, as well as most, if not all, travel-related vaccinations and prophylaxis, with or without public or private prescription drug benefit plans. In addition, few private health organizations have access to publicly funded language services to assist in reducing iatrogenic mistakes with travellers for whom English is a second language. Finally, many travellers

Table 2: Odds ratios and corresponding 95% confidence intervals for multivariable regression analysis of case and control subjects for various exposure measures (*n* = 931*)

Variable	OR (95% CI)
Gender	
Female	1.00
Male	2.70 (1.56–4.80)
Age group	
Children	1.00
Adults	3.62 (1.66–8.84)
Reason for travel	
Tourism	1.00
Business	1.12 (0.35–3.26)
Visiting friends and relatives	2.82 (1.42–5.92)
Continent visited	
Other	1.00
Africa	11.52 (6.33–22.05)
Obtained pretravel advice	
No	1.00
Yes	0.38 (0.20–0.70)
Travel duration > 2 wk	
No	1.00
Yes	1.40 (0.60–3.67)

Note: CI = confidence interval, OR = odds ratio.
*After exclusions (see Figure 1).

visiting friends and relatives are of moderate socioeconomic status,[11] with limited funds even for the cost of airfare.

Until access to good-quality, appropriate travel health services is improved for those travelling to visit friends and relatives, we cannot assume that all cases of malaria in this high-risk population are due solely to lack of awareness or lack of concern. The incidence of malaria in the Calgary area during the study period was highest along the border of the northeast and southeast quadrants, where most new Canadians and people of lower socioeconomic status reside. These incidence rates appear higher than those documented in 2011.[11] Travelling populations living in this area of the city should be the focus of further study to determine community-based needs to reduce the prevalence of malaria. Further investigation regarding social factors such as risk perception, socioeconomic status and ability to pay, and language barriers should be conducted to determine their impact on timely access to appropriate pretravel clinical prevention.

Limitations

A major limitation of this study was that we had information only for people who presented with malaria-like symptoms to a care facility and the consequent use of some of them as control subjects. This likely introduced selection bias, which would have exaggerated the effect measure. In addition, travellers visiting friends and relatives were not distinguished according to first- or second-generation immigration status. It would have been valuable to make this distinction, because perception of risk 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 nonendemic areas.

There is also a potential for information bias in this study. Only people who sought health care were included, and the study population did not include those who were asymptomatic but may have had malaria. Malaria history forms are completed by the referring clinician with the information provided by the patient. The reliability of these forms is limited owing to the self-reported nature of the data. Therefore, the information collected is subject to limitations in ability to recall and language barriers. Information regarding the validity of the Calgary Laboratory Services database and malaria history forms is not available for this study.

This study adds to the growing body of knowledge regarding the travel-related health burden among travellers visiting friends and relatives and the need for better access to pretravel clinical prevention that suits the specific needs of various traveller populations. It was population-based, covering the entire Calgary metropolitan area, and the findings could be compared with those for other major metropolitan areas in Canada that have similar immigrant population demographic characteristics. However, since we studied people from only 1 city and only those who presented to a care facility with malaria-like symptoms, the results are not necessarily generalizable to the entire Canadian population. Population-based analysis looking at similar trends in other major metropolitan cities in Canada is warranted.

Conclusion

Travellers visiting friends and relatives in malaria-endemic areas represented a distinct epidemiologic risk group with a higher risk of malaria. They were less likely than other travellers to such areas to seek pretravel advice and take prophylaxis, and more likely to have a longer stay in a malaria-endemic area. Men travelling to Africa who did not seek pretravel advice had the highest odds of contracting malaria. We highlight the need for targeted pretravel health care services for those who travel to visit friends and relatives.

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