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Title	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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Reviewer 1	Ms. Jennifer Geduld
Institution	Controlled Substances and Cannabis Branch, Health Canada, Ottawa, Ont.
General comments (author response in bold)	1. The introduction outlines a good amount of the literature with the current knowledge in this field and available data on Canadian travellers which can be limited. However, it is unfortunate that more up to date data were not sought from the Public Health Agency of Canada after 2014 as data are currently available on the Notifiable Disease Online website up to 2016 showing higher number of cases in 2015 and 2016 at 552 and 612 cases respectively (https://diseases.canada.ca/ndis/charts-list). Similarly, a better description of trends in cases diagnosed either in the province of Alberta or Calgary would have been appropriate especially as these data are not available to PHAC. Also, when it is stated that the number of imported malaria cases has steadily risen since 2000, it sounds as if there is autochthonous transmission which is not the case in Canada. Perhaps this can be re-worded to be clearer. **Reworded to "In Canada, the number of malaria cases imported from endemic areas has steadily risen since 2000". Page 5 line 104.** 2. It is not clear how malaria-endemic region was defined except from the Malaria History form where it shows a link to PHAC's website although a malaria endemic region is perhaps not all countries where there is autochthonous transmission. There is a good description of the risks of VFR traveller as compared to other types of travellers. The reason for the study as well as the design and methods were well described. The results were interesting but based on available literature it is certainly not surprising and seem in line with other studies on VFR travellers and malaria. **We thank the reviewer for the comments and confirm endemic area is linked to the PHAC definition.** 3. There is a good interpretation of the results however the relevance to the Canadian context is unclear. As this was analysis on one city in Canada it is not necessarily generalizable to all cities in Canada. There also does not seem to be a good description of how or whether this can be applicable to other areas in Canada. A description of how data from Calgary may compare to other cities in Canada may be interesting. A comparison nationally or with other cities would be useful or at least the recommendation that this type of analysis may be useful if it was done more broadly with involvement of data from other jurisdictions **We thank the reviewer for this comment. We are the only large metropolitan centre in Canada that has a single testing site making this study unique but informative to other sites.** 4. Important limitations are outlined in this paper. The lack of national level data as a comparison is unfortunate as no data on reason for travel, age, gender or species are available from PHAC. Mentioning this limitation may be work considering. **Mentioned in the MS. Thank you. (Page 13 lines 289-290)**

	5. The results were not surprising; research shows that VFR travellers are less likely seek pre-travel advice, take prophylaxis and travel for longer durations, and travel to Africa. A reasonable description of the recommended strategies to reduce the risks associated with this type of travel has been outlined. However, a focus on how to reach this group of travellers through methods other than through routine health care and pre-travel clinics would be of interest in this paper. **We believe that is the next step. Namely, we hope to assess the fiscal impact of VFR who return with malaria on the heath system and build a business case for an intervention most like at the primary care clinic level.** 6. Note: the spelling of traveller is inconsistent – sometimes traveller sometimes traveler. **Adjusted to be consisted throughout the MS** 7. Line 159 – there is a typo 'ued' should be used **Adjusted.** 8. Line 182 – typo 'as oppose to' should be 'as opposed to' **Adjusted.** 9. Line 202: I believe you are missing 'as a' in this sentence: the effect of exposure status 'as a' VFR. **Adjusted.** 10. Line203: Perhaps you can avoid starting with 47% unless this is mistaken. **Rearranged the sentence.**
Reviewer 2	Dr. Michael Hawkes
Institution	Medicine, University of Alberta, Edmonton, Alta.
General comments (author response in bold)	The authors are to be congratulated on an interesting report of imported malaria among travellers in Calgary, based on a laboratory database. The findings are not entirely new or surprising, but these data from a Canadian centre are of local interest and likely generalizable to other Canadian settings. There are remediable methodologic issues and the writing needs considerable attention, but the findings would ultimately merit publication. 1. MAJOR REVISION (ESSENTIAL BEFORE MANUSCRIPT IS PUBLISHED. I WOULD NOT RECOMMEND PUBLICATION UNLESS THIS ANALYSIS IS PERFORMED AND REPORTED). Because of the matched design, conditional logistic regression is the appropriate analytic technique to account for matching. There is no mention of this, rather the authors used "multivariate logistic regression." Each case needs to be analyzed with its ~5 controls. This is easily performed in R. **Controls were "matched" to cases based on the year only and not by age and gender, for example. Each negative individual for a given year was given a study number. Using a random number generator in R, these study numbers were selected such that the total number of controls would match to five controls per case for a given year. These study numbers were then linked to accession numbers in order to collect information from the MHFs and CLS database. Controls were not matched by age and gender as the effect of each on likelihood of acquiring malaria was sought from the**

	multivariable analysis. Thus a conditional analysis was not performed for this reason. We believe the multivariable analysis is informative and unmasks associations such as age and gender with VFR risk of acquiring malaria. We have clarified the nature of how negative controls were selected so there is no confusion on this point. We hope the reviewer will be satisfied with this approach. (Page 7, line 147-154) 2. It would be helpful to have a list of inclusion and exclusion criteria in the methods section. For example, only patients who presented for care and for whom a malaria test was ordered in Calgary and referring labs are included (seems obvious, but important for interpreting findings – e.g., male is risk factor for test positivity). Patients who catch malaria and get tested elsewhere (e.g, country of travel), who self-treat fever (common in African patients), or who self-cure without therapy (semi-immunes expected in African VFRs) would not be included. Exclusions (visitor, new immigrant) should be described early on; these are eventually presented as exclusion criteria, but the organization could be improved for clarity. The repeated claim of "population-based" data may not be warranted/accurate since this is already a selected group, based on their health seeking behaviour. Systematic prospective sampling for malaria in returned travellers would be needed for a "population-based" study. **Inclusion and exclusion criteria are explained in more detail in the manuscript now.** **A note is added with the following limitation: "Only patients seeking health care are included and does not include individuals who are asymptomatic and may have malaria." (Page 5 line 121 – 126. Page 13 lines 283 – 285.)** 3. Case definition. Important details are lacking here. a. First, a wording issue: "clinical diagnosis of malaria." (page 6, line 126). However, cases were based on microbiological diagnosis (Giemsa-stained peripheral blood film using light-microscopy, RDT and/or PCR). "Clinical diagnosis" implies clinical criteria (fever) without laboratory confirmation. b. Although a standard malaria diagnostic algorithm is described, it is not obvious to me whether all patients received all tests. The possible diagnostic testing consisted of microscopy (up to 3 tests per patient), RDT, and PCR. The number of each test (percent of patients with 0, 1, 2 or 3 microscopy results), percent with RDT results, and percent with PCR result could be reported (I suspect this information is available; laboratory database review). The agreement between the tests could be reported. The definition of a "positive case" could then be better described (e.g., any positive test of the multiple tests performed? positive microscopy or RDT needed to be confirmed by PCR?). c. False positives (24) are shown in Figure 1, suggesting there was some interpretation applied to discordant results, which should be explicitly described. I'd suggest that these patients not be analysed as controls, as suggested by the cross-over in the Figure but excluded from further analysis. d. Also confusing are 5 "Negatives" among the cases. Not clear how they were initially classified as cases but were then "Negative". **a. Added the confirmation through laboratory testing to the MS** **b. This information is available but not the focus of this work. We have reported on diagnostic accuracy of various tests as have others. We followed the standard clinical testing algorithm here.** **c. As these were false positives ie negative for malaria we used them as controls. We think they belong in the control group.**

	d. These were classified as cases in the original database and were selected as cases. But through the review of MHFs and other material that were done after the original selection, these 4 never tested positive through laboratory testing and re-classified accordingly. 4. Selection of controls is appropriate (random selection of ~5 patients in the same year who tested negative); however, the description of the random number generation to select the controls (Supplemental) is not clearly written. I think that, for each case, the authors randomly chose 5 accession numbers from all tests that were negative in the same year. A more concise description is needed. **Each negative individual for a given year was given a study number. Using a random number generator in R, these study numbers were selected randomly such that the total number of controls would match to roughly five controls per case for a given year. These study numbers were then re-matched with accession numbers to collect information from MHFs and CLS database. (Updated in Supplementary Material)** 5. Needs extensive editing for language. This substantially interferes with readability/clarity. Examples of incorrect grammar include: “Canada is not considered as an endemic malaria region” (p3 line 12) “there are an approximately 488 imported malaria cases a year” (p3 line 13), “accommodations are often more basic than that used by tourists” (p4 line 86) “protection from past exposure to malaria exposure prior to coming to Canada” (p4 line 90) (many more examples) **Done.** 6. Confusing statement: “Prophylaxis was removed due to its collinearity with pre-travel advice (and p value less than 0.05 suggesting prophylaxis intake does not differ between two malaria groups)” (p7 line 155) Usually $p<0.05$ on univariate analysis suggests the variable does differ between groups and should be included in multivariable analysis. **Prophylaxis was removed due to its collinearity with pre-travel advise. Not because it had a p-value less than 0.05. This sentence was removed from the MS.** 7. Supplementary materials: “Hospital controls were selected from the CLS database”. The use of the term “hospital controls” is confusing. I think the controls came from the CLS database and could include outpatients or inpatients. Why are they called hospital controls? **The phrase “hospital controls” is commonly used in case control studies as a contrast to community controls (including those who does not present to a care facility but might have engaged in travel to a malaria endemic area). However, due to the confusion, word hospital was removed and adjusted in the supplementary materials and in MS.** 8. The description of “effect modifiers” is confusing and the manuscript would probably be improved by simplifying the description. I think the authors examined the two-way interaction terms in the multi-variable model. The reporting of the statistics and rationale/justification tend to be pedantic - would be clearer if more concise. Nonetheless, it is worth exploring interaction terms and I agree with this approach. **We have tried to clarify this better.**