| **Article details: 2015-0115** | |
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| Title | Malaria in travellers returning or migrating to Canada: surveillance report from CanTravNet surveillance data, 2004—2014 |
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| **Reviewer 1** | Dr. Marek Smieja |
| Institution | McMaster University, Pathology & Molecular Medicine, Hamilton, Ont. |
| General comments (author response in bold) | First, this represents only about 11% of all the malaria recorded in Canada between 2004-2014. If the intent is to inform physicians throughout Canada about malaria, it must be first shown that these 11% are reasonably representative. For example, do we know what percent of all of the malaria cases were P. falciparum overall in Canada? Severity? Mortality? If the cases summarized here are non-representative, their publication could be highly misleading in guiding Canadian physicians regarding malaria in Canada.<br>**RESPONSE: We thank Dr. Smieja for raising this point. From the national notifiable disease statistics, the breakdown of malaria by causative species is not provided. However, at least for the province of Ontario, I can say that P. falciparum comprises 58% to 60% of imported cases of malaria annually. For many years now across all provinces, P. falciparum has been the predominant imported species, however, national-level data on those precise numbers are lacking. Extrapolating from the Ontario provincial data, we can say that CanTravNet data are reasonably representative in terms of species. As indicated in our tables, approximately 6% of cases seen at CanTravNet sites were severe or complicated. By using data on severe and complicated malaria in Canada provided in reference #4 as a national annual numerator, and total imported cases provided by the notifiable disease statistics online per year as the annual denominator, we see that at a national level, severe and complicated cases constitute anywhere from 3.3% to 10% of cases, with a 10-year average of 6.7%, suggesting that CanTravNet data are reasonably representative. As for mortality, since less than 1 Canadian dies every year of malaria, the numbers are too small to draw any conclusions around representativeness. Reference number 4, which is an analysis of Canadian Malaria Network data, cites only 3 deaths in Canada over a 12-year period.**<br><br>Second, I assume that more clinical information could be given that would help physicians appreciate the presentation and outcomes of malaria in Canada. Thus, clinical details such as time between travel and clinical presentation, and clinical outcome (days hospitalized, need for ICU, deaths) are missing. This should be done separately for P. falciparum and other species.<br>**RESPONSE: We thank Dr. Smieja for this insightful comment, and agree that these data would be most informative. Unfortunately, due to the epidemiologic surveillance nature of the database and limited data collection instrument, we lack clinical details beyond presenting symptom, final diagnosis, management setting, and interval to presentation.**<br><br>The tables are busy and could be simplified. The figure serves no real purpose; as few as 4 cases as summarized per year. I would eliminate this altogether.<br><br>**RESPONSE: We thank Dr. Smieja for these suggestions and have eliminated the Figure as suggested. We have tried to simplify the tables as well.**<br><br>The STROBE statement guidelines for observational studies are mostly adhered to, although the reader is not informed whether any of the analyses were pre-specified, or what power the study had for the various analyses. Given the number of potential analyses, P-values are not likely meaningful. But the key point is one of generalizabity, as addressed above.<br><br>**RESPONSE: We thank Dr. Smieja for this comment, and as our analysis is largely descriptive, we only compared the rate of severe malaria in non-immigrant/non-VFR travelers to those whose travel purpose was VFR or immigration, as the over-representation of severe cases among travelers not born and raised in malaria-endemic areas has been noted by others in the past. This particular comparison was not prespecified, but, rather, performed after observing the possible over-representation as noted. We will defer to Dr. Smieja around inclusion of that particular p-value if desired.** |

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| **Reviewer 2** | Dr. Sandra Steiner |
| Institution | Centers for Disease Control and Prevention, OPHPR, Atlanta, Ga. |
| General comments (author response in bold) | 1. Please spell out Plasmodium in the abstract.<br><br>**RESPONSE: We thank Dr. Steiner for noting this error, which has been corrected.**<br><br>2. Is it 16. 9% or 16.2 % for the business travelers? The abstract and page 9 numbers do not match.<br><br>**RESPONSE: We thank Dr. Steiner for noting this discrepancy and have corrected the abstract.**<br><br>3. Please remove the N= after 341 in the abstract. RESPONSE: We have corrected this.<br><br>4. In the conclusions in the abstract and in page 12, the words "preventive measures and surveillance associated with" should be added to the sentence: It confirms the overwhelming importance of…. To read: It confirms the overwhelming importance of preventive measures and surveillance associated with travel to SSA and India, particularly by VFRs.<br><br>**RESPONSE: We thank Dr. Steiner for this suggested wording and have amended the statement accordingly.**<br><br>5. In page 7. Can the authors clarify if the final diagnoses are made by attending physicians at the tropical center clinics or by their personal physicians? If the later, how is the information communicated to the GeoSentinel network? If the former, how are the travelers referred to the surveillance clinics?<br><br>**RESPONSE: We thank Dr. Steiner for this query. Final diagnoses are assigned by the attending physician at the GeoSentinel network site. Final diagnoses along with other collected variables are communicated to the centralized database through a secure, online data entry portal. This has been clarified in the manuscript.**<br><br>6. The GeoSentinel website cites 59 centers, the authors list 57. Please reconcile this number.<br><br>**RESPONSE: We have reconciled the numbers. At the time of writing there were 57 sites, however, now there are 60.**<br><br>7. Was the immigrant status given regardless of Canadian citizenship status and based only on country of origin and travel patterns? RESPONSE: We thank Dr. Steiner for this query. Ill returned travelers were classified as "Immigrants" if their diagnosis or complaint was related to Immigration travel. For instance, although a traveler may have been a Canadian citizen at the time of presentation, if they manifested P. vivax infection having immigrated from Pakistan and having no other relevant travel, their malaria would be attributed to Immigration travel.<br><br>8. While the network is well established, it is not clear how are traveler identified to be referred to the clinics. Is the referral pending demonstration of symptoms? What is the rate of compliance? RESPONSE: We thank Dr. Steiner for this query. Ill returned travelers are referred to CanTravNet sites via primary care offices, emergency departments, walk-in clinics, and other specialists. Our sites are referral based clinics only, and thus, we rely on front line clinicians who initially assess ill patients to refer on to our centres if the patient has traveled. There is no mandate to send ill travelers to our clinics, nor is there systematic enrolment of patients prior to the referral stage.<br><br>9. In table 1. The age range is so wide: 1 to 82 years. Can the authors add row with the numbers of those under 18 years to separate children and teens from adults?<br><br>**RESPONSE: We thank Dr. Steiner for this suggestion and have added Ns for the pediatric travelers accordingly.**<br><br>10. In table 1 all the percentages can be given in parenthesis |

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| | instead of listing them in a separate column. This will help with the visualization of the data.<br><br>**RESPONSE: We thank Dr. Steiner for this suggestion. As most journals request that each data metric be represented in its own field, we have left Ns and % in separate cells. However, the visualization will be improved by typesetting at the production stage (when grid lines will be removed, presumably).**<br><br>11. In table 2, please rearrange the % and associate them with current column 3, then list the numbers in parenthesis after the total numbers listed in current column 3. The way the table is given is confusing. The new table 2 should only have two columns.<br>**RESPONSE: Again, as above, individual data points, whether Ns or percentages, are usually represented in their own cell by request of the journal. Since we have a numerator (number of cases with malaria presenting with fever), a denominator (total number of cases of malaria), and a percentage (numerator/denominator), there are 3 represented data points, and we require 3 columns. We have amended to try to improve the clarity of the table.**<br><br>12. In tables 2 and 4, the listing of severe cases is given as a separate data entry should it be qualified in the footnotes as being P. falciparum severe cases? Similar comment for Figure 1.<br><br>**RESPONSE: We thank Dr. Steiner for this suggestion, however, we cannot say that all severe cases were P. falciparum. Although we could assume that most were, we have avoided making this assumption as we simply do not know as a final diagnosis of severe or cerebral malaria does not have a species ID embedded in that final diagnosis code.**<br><br>13. In Figure 1. There is a clear difference in the surveillance data from 2004 and 2005 compared to later years. How do the authors explain the difference in other types of malaria diagnosed during the earlier years of surveillance? Is this because of the few surveillance sites in earlier years?<br><br>**RESPONSE: We thank Dr. Steiner for this observation. Indeed, we attribute this difference to the smaller number of centres early on, with increasing numbers over time due to accrual of sites.**<br><br>14. Figure 1 would be more informative if the total N is listed a top each stacked bar. This reviewer suggests modifying this figure.<br><br>**RESPONSE: We thank Dr. Steiner for this suggestion, however, we have been asked to remove this figure and have done so. We will leave it to the editor's discretion whether to include with N's listed at the top of each stacked bar (which we are happy to do), or to eliminate as we have done in accordance with Reviewer 1's suggestion.**<br><br>15. Does the surveillance network track how many of the cases diagnosed were successfully resolved and how many died due to malaria infection? Adding overall mortality numbers would be informative.<br><br>**RESPONSE: We thank Dr. Steiner for this query. Due to the travel surveillance nature of the database, limited data collection tool, and lack of clinical linkage, we do not have access to these data.** |
| **Reviewer 3** | Dr. Mark Riddle |
| Institution | Naval Medical Research Center, Silver Spring, MD |
| General comments (author response in bold) | 1.The use of 'N' vs. 'n' : from a strict statistical methods stand point, a capital letter N represents the entire population or sample that one is working with, while the 'n' represents the number of individuals in a subgroup in which you are describing some statistical estimate. Recommend using standard nomenclature or justify use of "N" throughout.<br><br>**RESPONSE: We thank Dr. Riddle for noting this error. We have amended throughout accordingly.**<br><br>2. Table 3 has a number of acronyms that need to be spelled out in a legend.<br><br>**RESPONSE: We thank Dr. Riddle for noting this oversight and have corrected.** |

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| | 3. Figure 2 appears misleading. While it states that the colors are based solely on numerators, it has the appearance of higher 'risk' areas. However, as stated by the authors, without denominators it is not true risk. Recommend removing this map to avoid confusion with the 'heat' map.<br>**RESPONSE: We thank Dr. Riddle for this suggestion, and have removed the map accordingly**<br><br>4. It would be interesting to have information that details the time between end of travel and time of visit/diagnosis to CTN. Such information could be helpful for the clinician to know the anticipated durations of illness that might be occurring before seeking care, AND could be useful to know so that travelers could be appropriately counseled.<br><br>**RESPONSE: We thank Dr. Riddle for this suggestion and agree that duration of symptoms prior to care-seeking would be informative. Unfortunately, we do not have those data, and using the "Interval to Presentation" by subtracting the Trip End Date from the Initial Visit Date would be an inaccurate corollary due to the highly variable "Trip Duration", as well as more prolonged known incubation periods for vivax and ovale. For instance, we routinely see travelers presenting with vivax and ovale many months (even out to a year) post-travel, however, they have almost always only been ill for a couple of weeks at most. Also, we do not know how many travelers on longer itineraries actually became sick while traveling. So using a 1-year "interval to presentation", for example, might tell us a bit more about probable incubation period, it doesn't really answer the question that we would like to answer, which is symptom duration and delayed care-seeking. We are most happy to add "Interval to Presentation" if you feel that it would be informative for reasons other than approximating symptom duration.**<br><br>5. Conclusion - the lack of pre-travel counseling should be highlighted in the discussion. This would appear to be a root cause.<br><br>**RESPONSE: We thank Dr. Riddle for this suggestion, and have added some text accordingly. We also mention this issue at length in the VFR section of the discussion.** |