Author’s response to reviews

Title: Imported Pediatric Malaria at the Hospital for Sick Children, Toronto Canada: A 16 Year Review

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Author’s response to reviews: see over
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Dear Editor:

Thank you for the thorough review and the reviewers’ helpful suggestions. We have revised the manuscript accordingly and attached the revised version. We have also maintained our original position on a few suggestions and explained our reasons for doing so. Please see below an itemized response to the reviewers’ comments.

Sincerely,

Andrea Evans MD, MSc

Reviewer 1
1) There are numerous reports (including from Canada) of malaria detected in asymptomatic siblings of symptomatic cases (with detection rates as high as 23% - see attached articles for examples). Some therefore advocate for screening well siblings as hyperparasitemia cases have been described in this group. The authors do not report any cases fitting this category. If siblings are generally not screened then I would at least explain this practice. Also perhaps mention if any cases were known siblings.

Thank you for your comment. We have revisited our data and have added the number of siblings (2 pairs) that were in our study. There is no institutional policy within our hospital to screen siblings. However, when there is a family history of travel and the patient is very ill siblings are generally evaluated to make a decision on performing a thin smear – this is done at the discretion of the ordering physician.

Revision line 168-169
The median age of infected children was 6.7 years (IQR 2.8 – 11.7) and 69 (64%) were boys (Table 1). There were 2 pairs of siblings in our study.

Revision line 326-329
Furthermore, there is no institutional policy within our hospital to screen siblings. However, when there is a family history of travel and the patient is very ill siblings are generally evaluated to make a decision on performing a thin smear at the discretion of the ordering physician.

2) Line 249 - what proportion of children had blood cultures collected? Essentially all the countries listed are typhoid endemic and given that all the patients had at least a history of fever, blood culture should likely have been collected in most cases. If not, I would mention this in discussion.
Thank you for this discussion point. There is no institutional policy on performing routine blood cultures for a patient returning from travel with a fever. However, the majority of patients will get blood cultures when there is clinical indication at the discretion of the physician. It is out of the scope of this retrospective review to comment on laboratory testing practices for typhoid. All of the patients admitted had blood cultures drawn. We have mentioned this in our discussion.

Revision line 258
“Blood cultures were routinely collected for patients being admitted to hospital.

Reviewer 2:
Major compulsory revisions:
1) Lines 87-90: “Children account for 15-20% of imported malaria cases and present distinctly from adults with malaria. (8, 12) Importantly, children have different clinical presentations, are more likely to be non-immune, and as a result are at higher risk of developing severe disease and have an increased likelihood of death compared to adults.” Neither children nor adults who have lived all their lives, or even for the past several years, in a non-endemic area will have appreciable immunity to malaria.

Thank you for this important comment. We have changed our introduction accordingly.

Revision line 88-89
“Importantly, children have different clinical presentations, are at higher risk of developing severe disease, and have an increased likelihood of death compared to adults.”

2) Appropriate prophylaxis for the region of travel was prescribed in 6 (27%) of cases, only in one case was it documented the child adhered to the medication as directed. Was adherence not documented in the other cases (meaning that they might have been adherent) or was it documented that they were non-adherent (as suggested by the table)? This is not very clear although it is mentioned multiple times in the paper, and the authors should clarify in how many case it was documented that the adherence was not complete.

Thank you for this helpful comment. We have revised the results to clarify that adherence to prophylaxis was commented in 5 out of 6 cases where appropriate prophylaxis was prescribed, of which only one commented on proper adherence. In addition, please note that the limitations of our data on prophylaxis is in the discussion (Line 323 to 325).

Revision line 187 to 190
Appropriate prophylaxis for the region of travel was prescribed in 6 (27%) of cases, all but one of these cases recorded adherence to medication, however only in one case documented adherence to the medication was as directed.

3) Figure 1- how can there be so many weeks from departure to arrival? I don’t find this graphic particularly helpful- what point are you trying to emphasize?
We have clarified the meaning of ‘departure’ in this context, as departure was from Canada, for patients leaving from Canada to another country where there was exposure to malaria. This graphic illustration was to illustrate the differences and similarities between travelling patterns, and delay in diagnosis, between \textit{P. vivax} and \textit{P. falciparum}.

\textbf{Revision: Figure subheading.}  
Figure 1: Timeline of events leading to presentation and treatment of malaria a) \textit{P. falciparum} b) \textit{P. vivax}. Data represents median and interquartile range (IQR). Departure is defined as departure from Canada for subjects leaving Canada to another country. Arrival is defined as the approximate time of arrival in Canada for all subjects. Presentation is defined as the first day of presentation to any physician.

4) Please explicitly provide the sensitivity and specificity of BINAX now in your test population. In addition, as you have comparative microscopy data, it would be interesting to make some comparisons of the BINAX positive vs negative tests, which would be informative for clinicians.

Thank you for your comment. We have data from 2006 to 2013 on Binax T1 and T2 for smears positive for malaria by microscopy only, thus our data is not complete for all subjects.

\textbf{Revision: Lines 217 to 220}  
Binax T1 Sensitivity for \textit{P. falciparum} 91.3\%. Binax T2 sensitivity for \textit{P. falciparum} 69.6\%. Binax T1 is not sensitive for the detection of \textit{P. vivax} whereas Binax T2 has a sensitivity of 75\% for \textit{P. vivax}. Our data is limited to patients who had positive microscopy for malaria, thus specificity cannot be calculated.

\textbf{Revision line 313 to 314}  
Our data on BinaxNow is limited by the fact that this test was used only between 2006 and 2013, not report false positive results.

5) In your discussion you seem to make an argument for routine screening of immigrants/ refugees for malaria. Although 2/3 of your cases occurred in refugees/ immigrants, as you have no data on the denominator of refugees/ immigrants you can make no statement about what proportion of refugees/ immigrants develop malaria shortly after arrival. There is no recommended test for “screening” of an asymptomatic person; even if an immigrant had a negative blood smear on arrival, this would not rule out the later development/ appearance of malaria.

Thank you for your observations. In lines 319 to 325 in our discussion we comment on the issue of malaria in refugees/immigrants. However we do not advocate for routine screening of malaria in this population, but rather, advocate that “there must be a high index of suspicion for malaria with any systemic illness” (line 312) due to the fact that screening is not recommended routinely.
6) Although you have 16 years’ worth of data, other than noting a difference in treatment regimen prior to and after 2001, you have not made any attempt to describe whether there have been improvements (or not) in diagnosis and management of malaria, which would hopefully occur as physicians become aware of the need to investigate for malaria. In addition, there is no attempt to describe whether the cases have been spread out roughly evenly over the years, or whether there has been an increase/decrease in annual cases.

Thank you for your important comment. The number of cases have been spread out evenly over the 16 years of our study. We have added a sentence summarizing this in our results.

Revision line 165 to 166
There was a median of 6.5 (interquartile range (IQR) 4 - 10) cases per year with no appreciable trend over the 16 years.

7) While the data on country of acquisition is interesting, it may be that this reflects the areas where Torontans are travelling more than the actual risk of acquiring malaria in these particular areas. For example, the risk of acquiring malaria in Guyana is quite low, particularly compared to sub-saharan Africa, however, there were 3 cases from Guyana and 3 each from Tanzania, Cameroon, and DRC. It would be helpful if any background on the population could be given which would help put this in perspective (ie, if for example there is a huge population from Guyana so many more people travelling there).

Thank you for your commenting on an additional limitation to our study. The country of origin of immigrants and permanent residents of Canada fluctuates greatly on a year to year basis, including the sixteen years in this study. We have attempted to comment on the origin of newcomers to Canada during the years included in our study without being exhaustive as that would be out of the scope of this paper.

Revision line 299-306
In general, the top source country for newcomers in Canada are China, India, Pakistan. Source countries (between the year 2000 and 2013) with high risk of malaria are in order: Nigeria, Afghanistan, Cameroon, Democratic republic of Congo, Guyana, Ghana, Rwanda, Uganda, Honduras. In general, countries with English or French as a predominant language such as Guyana and Honduras, may be choice countries for Canadians to travel for tourism or education and as such may be overrepresented in our data set even though the risk of acquisition of malaria is by comparison low in these countries.

8) Although 25% of patient presented with severe malaria, there is no real attempt to determine if this was a result of longer delays to seek treatment, or other risk factors for severe disease which might be instructive to clinicians.

Thank you for your comment. There were 19 cases in total, or 25% of the *P. falciparum* cases, which met the WHO criteria for severe malaria. All but three of the cases met this criteria based on level of parasitemia alone (WHO criteria of parasitemia >2% or >5% in semi-immune
population). Therefore, the association between variables such as time to presentation, treatment delay or hospital stay and severe malaria in our study correlates with hyperparasitemia. Unfortunately there was no significant correlation between severe anemia and these variables in our study.

Revision Line 208-210
There were no significant differences in time away from Canada, time to presentation, delay in treatment, hospital stay between patients with non-severe and severe malaria.

9) You note: “Our chart review includes 17 additional cases to those reported as being seen by SickKids in the Canadian Institute for Health Information (CIHI) database.” Does this mean that the hospital failed to report 17 cases? Please clarify what is the purpose of this statement.

Thank you for this comment. We have removed this sentence from the revision of our manuscript as it is not relevant to an international audience.

10) The discussion notes “According to the CIHI database, between 2002-2012 there were 242 cases of pediatric malaria in the province of Ontario (61% of all Canadian cases), of which 23% were seen at our institution.” This would make more sense in the intro/background than as part of the discussion.

We have inserted this comment into the introduction.

Revision line 97-98
According to the Canadian Institute for Health Information (CIHI) database, between 2002-2012 there were 242 cases of pediatric malaria in the province of Ontario (61% of all Canadian cases), of which 23% were seen at our institution.

Minor essential revisions

11) No child had anemia (hct <15%, hgb < 50 mg/dL) in the WHO criteria for severe malaria. This degree of anemia is severe, any anemia is considered Hb <11. This must be made clear/corrected.

Thank you for your important comment. We have reworded the above sentence as it was to report on the number of children meeting the severe anemia criteria as established by the WHO. As consistent with most cases of malaria due to the pathophysiology of the disease, all children within the third interquartile quartile range had a hemoglobin < 11 and this is clearly reported in Table 3.

Revision line 223-224
“No child had severe anemia as defined by the WHO criteria for severe anemia (hct <15%, hgb < 50 mg/dL).”
Discretionary revisions

12) This might be better documented graphically: “Forty-six (43%) cases had parasitemia of $\leq 0.1\%$. Of those with parasitemia $>0.1\%$, the median parasitemia was 1% (IQR 0.4 – 5).”

Thank you for your suggestion. The curve of percent parasitemia is particularly challenging to graph due to the x-axis being predominantly <0.1% to 1% and there being relatively few subject points beyond the 1%. Thus limiting the yield of graphically representing this data. We have chosen to represent this data in written rather than graphic form.

13) Lines 131 to 140 include a long list of definitions of different status of patients, however, these are mostly not used subsequently and are therefore not needed. This could be shortened to only what is subsequently used.

Thank you for your comment. The use of these definitions of immigrant of ‘recent’ or ‘previous’ arrival is used in the results section, and is as well particularly relevant for Table 4. We have chosen to leave this paragraph in the revision of our article.