Author's response to reviews

Title: False positive malaria rapid diagnostic test in returning traveler with typhoid fever

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Version: 3 Date: 23 May 2014

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

Please find attached the revised version of the manuscript entitled “False positive malaria rapid diagnostic test in returning traveler with typhoid fever”. We have addressed all the questions raised by the reviewers in the following pages. We have also inserted the lot numbers in question of the RDT as per your request. We hope you find the manuscript now in good order.

Sincerely,

Dylan R. Pillai MD, PhD, FRCP(C)
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Dear Editor:

Please find the responses in bold italics to each item raised by referees.

Response to reviewers:
Referee 1
Reviewer's report
Title: False positive malaria rapid diagnostic test in returning traveler with typhoid fever
Version: 2 Date: 17 April 2014
Reviewer: Hugh Kingston
Reviewer's report:
• Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)
  1. Line 67 – is in present tense, whereas the others are past tense (‘He is otherwise healthy…’) This has been changed.
  2. If a HIV test was done it would be interesting to include the result of this. HIV is commonly associated with false positive serological tests, although there is no evidence that this is associated with false positive HRP2 (antigen) tests. An HIV test was not done as there we no risk factors. However, HBV and HCV testing was negative.
  3. The authors might consider citing Bell et al, who discuss causes of ‘false’ positive RDT.; Am J Trop Med Hyg. 2005 Jul;73(1):199-203. False-positive results of a Plasmodium falciparum histidine-rich protein 2-detecting malaria rapid diagnostic test due to high sensitivity in a community with fluctuating low parasite density. Bell DR1, Wilson DW, Martin LB. This reference we feel is not particularly relevant because PCR was done on this patient and also failed to detect malaria. PCR has exquisite sensitivity and if the issue was sub-microscopic infection, it should have been picked up.
• Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
  1. Are references 2,3,4 cited in line with the journal’s recommended format? It might be nice to include ‘accessed on’ for the internet references. Also the publisher for ref 2. This has been changed.
  2. In the background (line 56) the authors state that ‘diagnosis of malaria relies both on rapid diagnostic tests followed by thick and thin film microscopy for confirmation’. This is just one diagnostic approach. Isolated use of blood film and
rapid tests are frequently used approaches too. The text could be changed to state this. **This has been changed.**

3. The sentences (starting line 145) about the patient also having a dengue IgM and IgG positive rapid test/PCR negative should be in the case presentation as opposed to the conclusion. **This has been changed (line 98).**

- **Major Compulsory Revisions (which the author must respond to before a decision on publication can be reached)**
  1. Please state explicitly if the patient took drugs with antimalarial activity in the 1 to 2 months preceding day 0 of laboratory testing, or that this is not known. **This has been changed (line 67).**
  2. Line 149 – it is stated that interfering antibodies ‘reside within the buffy coat’. Surely they are in the serum/plasma, not the buffy coat? Perhaps they can provide a reference for this statement. There should also be a comma after ‘performed’. **This has been changed.**
  3. Line 150 – the authors mention that S.typhi strains inoculated directly do not cause RDT positivity. It is not clear if they did these experiments or someone else has? This should be in the results/case presentation section if they did. **This has been changed (line 101).**
  4. Figure 2 does not add much to the case – the test is designed to be read by eye. If the authors want to include it then they should include densiometry for the whole strip – the t2 region as well (currently this is not shown). **We disagree as the photo shows the RDT both T1 and T2 position in Figure 1. Figure 2 focuses on T1 in question here and adds an objective if not quantitative element beyond the naked eye.**

**Referee 2**

**Review:**
This case report describes an interesting and useful observation.

**Major Compulsory Revisions**
None

**Minor Essential Revisions**
1. It is not clear on which day the blood culture became positive (e.g. in relation to the malaria treatment). **The blood cultures was drawn of day 7 of illness, day 0 of presentation/laboratory testing, and first day of antimalarial therapy (line 81).**
2. The antimicrobial susceptibility pattern is interesting. What method was used to assess susceptibility e.g. disc diffusion versus E test? Was nalidixic acid susceptibility assessed? **Ciprofloxacin by E test, whereas ampicillin and TSX by Vitek 2. We directly test ciprofloxacin by E test rather than infer from nalidixic acid disc diffusion. Now clarified in the text (line 82-3)**
3. Do the authors have any thoughts as to why this patient relapsed following the first treatment—was treatment adherence assessed? *IV ceftriaxone was stopped prematurely and oral septra not ideal.*

4. Why was the patient seen on day 20? *Because of unusual test results and serological testing that was pending (eg. Dengue serology).*

5. Line 100 Please specify the ‘pan malaria antigen’ e.g. aldolase? *This has been changed.*

6. It would be useful if it was stated in the text how the manufacturer suggests discordance between the T1 and T2 bands should be interpreted and any biological explanation for such a discordant observation. *The T2 band is for non-falciparum species and would be expected to be negative with P. falciparum. Now clarified in text (line 102).*

7. The Tanzanian study findings (reference 9) should probably be interpreted a bit more cautiously taking into account the prevalence of sub-microscopic malaria infection in the study population. *Thank you for this. This has been changed. (line 132-3).*

8. Table 1- please indicate which Binax band was positive each time (e.g. just T1 or T1+T2) *This has been changed.*

Spelling, grammar, style suggestions (not for publication)

1. Line 67 change to past tense *This has been changed.*

2. Line 77 were not was *This has been changed.*

3. The correct term for this organism currently is Salmonella Typhi (short form of Salmonella enterica serotype Typhi) *This has been changed.*

4. Line 155 spelling bacteraemia *This has been changed.*

5. Line 163 ‘of’ missing *This has been changed.*

Discretionary Revisions

1. Can anymore be added about how likely it could have been that the patient had acquired falciparum malaria in India and then cleared the infection—was it malaria season? Was his travel to a falciparum-endemic area? *The area is hypo-endemic for malaria and travel was mostly urban therefore low risk.*

2. NMFI Suggest drop this abbreviation *This has been changed.*