Reviewer's report

Title: Invasive bacterial infection complicating malaria in African children: a systematic review

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Reviewer: Jacqueline Deen

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This is an interesting review but disorganized and difficult to follow.

Major compulsory revisions:

1. I think the title (and throughout the text) should qualify that this is on falciparum malaria in sub-Saharan African children.

2. Abstract-
   a. I believe that the line (in the abstract) “however the data supporting such an association remains fragmented” is misleading. The line seems to indicate that by doing this review, the authors aim to show the association between falciparum malaria and bacteraemia? Perhaps it would be more appropriate to state clearly that falciparum malaria has been shown to increase the risk for bacteraemia followed by the objectives of the review.
   
   b. The conclusions (in the abstract) should be consistent with those in the discussion section (i.e. focus on the major findings and end with the therapeutic implications).

3. Background - There has been a previous paper describing concomitant bacteremia in falciparum malaria mentioned by the authors as follows: “A sub-analysis within a comprehensive systematic review of blood stream infections in Africa indicated 6.5% of 11,814 malaria infections had concomitant bacteremia[32].” It would be good to transfer this line to the background section followed by an explanation of what makes this current review different (i.e. the additional information provided).

4. Methods –
   a. Suggest that the authors provide additional details on how they observed the principles of a systematic review. For example, how was the screening of the reference lists of selected articles done? Was an effort made to contact experts in the field to identify unpublished datasets? Was a standard form used to extract the data and was this form piloted? How was the extracted data validated? Were any studies excluded because of the quality of the methods or of the reporting? How were studies including children and adults handled?
   
   b. Definitions - “Prevalence” seems to be used interchangeably with “rates” in the
results section? Based on the types of studies included in the review, perhaps the term “case-fraction (of malaria with concomitant bacteraemia)” is more appropriate than rather than prevalence or rate. Describe what was used as the numerator and the denominator in the calculations. What was considered acceptable as “malaria” and “severe malaria” cases (RDT or blood film positive? Adherence to WHO criteria for severe malaria?) How were the C.I. calculated?

c. Describe how studies reporting the proportion of bacteraemia cases with malaria (instead of the other way around) were handled in the review?

5. Results-

a. I think the second and last paragraphs under “Risk factors for malaria associated IBI” (page 7-8) do not describe risk factors but associated clinical manifestations/criteria.

b. Table 1 – the citation for the Mtove papers are reversed.

6. The discussion is disorganized and needs editing. It would be good to state clearly in the first lines what are the big findings of the review, in relation to the objectives stated in the introduction. Instead, the authors discuss the evidence for increased risk for bacteraemia in falciparum malaria, which really only comes from one paper (not the findings from the review as a whole) and the underlying pathophysiology of the association. It might be good to organize the discussion as follows:

- Case fraction of bacteremia in severe malaria and in malaria? How much of the severe manifestations can be attributed to bacteraemia/sepsis rather than malaria?
- Risk factors and level of association (perhaps with a box)?
- The impact on case fatality
- Therapeutic implications
- Limitations of the review
- Further studies needed

Similarly, I think the conclusions should reflect the main findings based on the objectives that were set out at the beginning.

Minor essential revisions

1. Table 1 is quite data dense. It would be most useful if the authors add a line introducing the reader to the table before the results are described. For example: “We tabulated studies of concomitant bacteraemia in severe malaria and malaria by location, study period, study type… etc (Table 1)” (last paragraph, page 5).

2. Table 2 repeats the data from Table 1 and is confusing. The only new information is the C.I.? perhaps Table 2 could be merged with Table 1?

3. The lines describing the history (from references 18 and 79?) is scattered
around the manuscript and contributes to the lack of organization of the material:

- “Since 1987, when Mabey and colleagues made the initial observation of an association between invasive NTS infections and the malaria season[18], there has been a plethora of studies from across Africa supporting an association between NTS bacteraemia and malaria, particularly in those with severe anaemia[41], acute severe[21] and recent[23] malaria” (page 7)

- “The clinical association (of what?) was first suggested in the 1920s in Guyana by Giglioli who observed both increased prevalence and virulence of paratyphoid fever during malaria seasons with a co-infection rate of 29%[58]. In 1975 Duggan postulated that the rise in typhoid fever in Nigerian children during the rainy season might be linked to the increased incidence of malaria[59]. The first description of a relationship between the incidence of NTS infection and malaria seasonality in The Gambia[18] demonstrated that whilst stool carriage rate of NTS remained constant throughout the year, rises in invasive NTS infections occurred in parallel to the annual rise in malaria cases.”

4. The lines “In a Rwandan study, 27% of children with community-acquired bacteremia had concomitant parasitemia[33]. Malawian children with NTS bacteremia were significantly more likely to have coincident malaria and anaemia than children infected with other organisms[34]” should probably be in a separate paragraph with its own heading? (See above on studies reporting the proportion of bacteraemia cases with malaria.)

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests