Reviewer's report

Title: Plasmodium vivax associated severe malaria complications among children in some malaria endemic regions of Ethiopia

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Reviewer: John Kevin Baird

Reviewer's report:

The authors provide a concise, well-written, and very timely report of an analysis of severe morbidity associated with a diagnosis of acute P. vivax from Ethiopia. This is a very welcome addition to this literature on a neglected parasite from a continent where most consider it an insignificant public health issue. The report is an important contribution to the growing body of evidence that P. vivax is not benign but pernicious.

The authors may not yet be aware of the recent review of this topic by this reviewer appearing in Clinical Microbiological Reviews last month “Evidence and implications of mortality associated with acute Plasmodium vivax malaria”. A copy of this article has been uploaded with this review. The authors may find it helpful in providing broader context and emphasizing greater importance of their work.

A few suggestions are made here to improve the manuscript, and perhaps subsequent study of this important problem. Each is labeled compulsory or discretionary per the Editor’s instructions to reviewers.

1) Study of adult patients would also be very interesting for future studies, but in this report can the authors say a bit about their perception of P. vivax as a problem in adults at these study sites? DISCRETIONARY

2) The exclusion of the patients with P. falciparum is unfortunate but certainly does not disqualify the report as publishable. The relative risk of severe disease in patients with either diagnosis is an important consideration. It also somewhat addresses the issue of co-morbidities, i.e., risk of those being presumably equally distributed across these patients. This is offered for the sake of future studies of this problem. In this report the authors could perhaps mention the issue of co-morbidities, as this is the primary default for those malarologists who remain dismissive of pernicious P. vivax. COMPULSORY

3) The authors open the Introduction with a statement of dogma which their study serves to refute. They could perhaps add “is widely perceived as causing...”. COMPULSORY

4) Were RDTs used at all diagnosis? If so, negativity for P. falciparum would do much to dampen the criticism of mixed infections missed in microscopy. And that is a real issue. The authors ought to address it. COMPULSORY
5) In reporting key indicators of severe disease, like hemoglobin, glucose, and parasite densities, the authors should include ranges with the reported means, and consider the value of median values in that context. COMPULSORY

6) The authors should acknowledge that the criteria for severe disease were “borrowed” from those established for P. falciparum. This is important because for P. falciparum those indicators have been statistically linked to risk of a fatal outcome. The same has not been done for P. vivax and this needs to be acknowledged, while at the same time not dismissing these criteria as being real severe illness, regardless of statistical linkage to death as an outcome. COMPULSORY

7) The authors close be describing “emergence” of severe P. vivax. They ought to be clear that this is either an emergence of this kind of illness, or the emergence of awareness of it (as they hint earlier in the paper). DISCRETIONARY

8) Figure 1 could be greatly improved simply by visiting the Malaria Atlas Project website and downloading a map of P. vivax risk for Ethiopia, and indicating on it where the sites were located. MAP welcomes this sort of use and no permission from them is required to publish (just credit the source). If you cannot find such a map, contact them. They will happily provide it (your reviewer heads the MAP Asia-Pacific effort). DISCRETIONARY

9) Figure 2 does not seem to show “prevalence” but numbers of cases. The Y-axis needs a specific label to clear this confusion. COMPULSORY

10) The X- and Y-axes of Figure 3 are not labeled and unclear as to what is being shown. This needs to made much clearer, and perhaps with a less complex presentation. COMPULSORY

The findings of the authors actually agree quite well with studies elsewhere. The risk of being classified as having severe illness is almost precisely the same as elsewhere (with few exceptions elsewhere of even much higher risks). The syndromes are also largely similar. Greater emphasis on this agreement would highlight what appears to be a global phenomenon – pernicious vivax malaria presenting essentially similar risk and consequences from South America, Africa, and Asia. Of course there will be differences in such clinical presentations, but it is the similarities that are most compelling. DISCRETIONARY

Congratulations on an important and timely contribution. I do hope you find these remarks useful in improving this report, and guiding subsequent investigations. Well done.

Level of interest: An article of outstanding merit and interest in its field

Quality of written English: Acceptable
**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I have no competing interests to declare.