Reviewer’s report

Title: The risk of morbidity and mortality following recurrent malaria in Papua, Indonesia: a retrospective cohort study

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Reviewer: Quique Bassat

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Manuscript Number: BMED-D-19-01549
Full Title: The risk of morbidity and mortality following recurrent malaria in Papua, Indonesia: a retrospective cohort study

This is an interesting retrospective analysis looking at an impressive cohort of over 68,000 patients and their subsequent risk of morbidity and mortality (measured by passive case detection) after an initial malaria episode (irrespective of species). The manuscript is well written, but sometimes rather confusing, probably as a result of the complexity of the models built (which are good, but may require more clarity). I have lots of comments that I believe could contribute to improve its clarity and the message that its authors are attempting to convey.

* The abstract is not clear about the remaining [68,361-(37,168+22,209)=8984] patients (13.1%) that are not included in the analysis. I understand these correspond to Pf or Pv monoinfections, but it should cleared in the abstract
* "Within 12 months of the first four malaria episodes": this is mentioned in the abstract and is not easy to understand. Why after four (specifically) episodes? The reader should be clear when seeing this in the abstract (in the text it is clearer)
* The conclusions about late mortality and association to the initial episodes are difficult to sustain without proper cause of death data. From an epidemiological point of view, these associations may be statistically significant, but attribution of causality is challenging. It may be interesting to compare long term mortality (i.e post 12 months) in a cohort of non-malaria patients, if you have the data
* The rate of early death presented after multiple recurrences has a CI that includes 1, so may be good to tone down the strength of your statement
* Background: lines 58-63: this paragraph seems to be only focused on vivax, I would make it more general to all species. I would also include the immediate risks of morbidity posed by both species at initial presentation, and specify that they both can cause severe disease, although the majority of episodes are uncomplicated. But the recurrence of many episodes, either because of high intensity of transmission, or because of multiple relapses, can lead to cumulative morbidity and eventually lead to mortality
* Please add a paragraph stating the current challenges for telling apart a reinfection from a recurrence from a relapse
* Are there any data on compliance rates in the region for 14 day long unsupervised PQ courses? These are presumably low
* Did you have a secondary endpoint of admissions due to malaria? (beyond all cause admission?)
* Data come from the period 2004-2013, and are now a bit old. Are there more recent estimates (than those from 2013) of the "point prevalence of parasitaemia by microscopy for the different
species? Is there any indication that this may have changed in the last 6 years?

* I see that mixed infections were also analysed and that data are presented in figures and tables, but little is said in the results/discussion sections of the text. This is a missed opportunity to discuss whether patients which originally present with a mixed infection have a higher (or not) risk of cumulative recurrences than those with Pf or Pv monoinfection. I would encourage you to add more info on this particularly interesting and relevant group, at least in the results/discussion section

* I may have misunderstood, but did the time at risk for patient follow up was always ONLY 12 months, or did it extend 12 months beyond each recurrent episode (totaling to over 12 months?). In other words were all patients (irrespective of the number of recurrences) followed for a maximum of 12 months after their "baseline" initial episode?

* Rate of representation according to age. How did this take into account the presume difference in the median age in your population regarding different species? I understand vivax infections probably peak at a younger age in comparison to falciparum ones, isn't it?

* How did you account for multiple admissions? Or did you only take into consideration risk to first admission?

* The results about late mortality and association to the initial episodes are interesting. From an epidemiological point of view, these associations may be statistically significant, but attribution of causality is challenging, particularly if all-cause mortality is to be considered (rather than specific malaria mortality). It may be interesting to compare long term mortality in a cohort of non-malaria patients, if you have the data

* Authors seem to put a great weight on anemia as the potential explanation for the high morbidity and mortality associated to recurrent vivax. While I would agree with them that is very likely, it may also be interesting to assess the contribution to severe malnutrition. Do authors have any data in that direction? Do authors have any supporting data also on anemia prevalence at recurrence, according to species?

* Can the authors differentiate risk of short- and long-term morbidity/mortality according to severity of the initial episode (for both species)?

* Line 296: "the data used in this work is" change to "are"

* Table 1: add age unit (years) for the median

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
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Not applicable

Are the conclusions drawn adequately supported by the data shown?
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