Author’s response to reviews

Title: Early and late mortality after malaria in young children in Papua, Indonesia

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Author’s response to reviews:

BMC Infectious Diseases
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Re: Early and late mortality after malaria in young children in Papua, Indonesia
Manuscript Reference Number: INFD-D-18-00771R2

29th July 2019

Dear Dr. Hetzel,

Thank you for your email of the 20th June, regarding our manuscript resubmitted on the 15th February 2019. We note that you have taken over the role as editor of this paper since one of the original reviewers was unable to complete a second review. The response of Reviewer #2 supports the revised manuscript with a few minor typological corrections that we have now addressed below.
We note that you have additional queries regarding the manuscript and we have now addressed these as well. Our detailed response is provided below and in the revised manuscript.

We sincerely hope that the manuscript is now acceptable for publication. We would like to point out the extraordinary delays in processing this paper which was originally submitted in the April 2018 (16 months ago), taking almost 9 months for the first set of reviewers’ comments and almost another 6 months following our submission of the revised manuscript. Whilst we appreciate the importance of scientific rigor, the delays in processing the manuscript have been detrimental to what we regard as a useful contribution to the literature. We would now appreciate timely review to either accept or decline so that, if necessary, we can consider resubmission to another journal.

Yours sincerely,

Dr. Jeanne Rini Poespoprodjo
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Response to reviewers’ comments
INFD-D-18-00771R2
Title: Early and late mortality after malaria in young children in Papua, Indonesia

Editor Comments (Manuel W Hetzel):

The authors have analysed a substantial hospital dataset with the aim to investigate differential risk of death over a 12-month period in patients presenting with P. falciparum or P. vivax malaria.

1. Previous publications have found that treatment of fevers at public facilities was 46% in 2005 and 67% in 2013 (Karyana et al. Malar J. 2016 Nov 8;15(1):536; Devine et al. Am. J. Trop. Med. Hyg., 98(2), 2018, pp. 543–550.) On what do the authors base the assumption that the single hospital captures all episodes?

The numbers referred to in Karyana et al and Devine et al refer to the general population and to presentations to an entire community network rather than to the RSMM hospital per se. Until 2010 the RSMM hospital was the only inpatient healthcare facility in the region, and thereafter it still captured 80% of all inpatient malaria. RSMM is funded by a local mine and offers free services for the local population, hence for the majority of patients (93% are of lowland or highland Papuan ethnicity) it is the preferred source of medical care, for inpatient, outpatient and antenatal encounters.

Our retrospective analysis of this environment provides unique insights into health outcomes in this otherwise poorly resourced community. The passive follow up ensures an unprecedented large dataset for analysis, however we acknowledge that some episodes of illness will have been treated in the community and will have been missed from our analysis. In view of this potential attrition bias we
have deliberately focused our analysis on the comparative morbidity and mortality between P. falciparum (Pf) and P. vivax (Pv), rather than comparing with all patients presenting with non-malarial disease. This decision was taken in conjunction with extensive review by our statistical team in order to account for the biases (also raised by the reviewer). Importantly we assume that the attrition bias between patients with species is similar – and we believe that this is justified. Patients with uncomplicated malaria are generally unaware of the species of infection since the initial febrile illness is very similar between Pf and Pv. As with previous analyses/publications from this dataset we controlled for baseline differences in patients populations, particularly age, sex, ethnicity and hospital inpatient status, which may differ between species and be associated with differing attrition bias. Our focus on the comparative morbidity and mortality is of particular public health relevance since historically Pf has been considered a severe malaria whereas Pv is associated with a benign illness. Our analysis suggests that this paradigm neglects the indirect burden of Pv, and we hypothesise that this is attributable to P. vivax’s propensity to recur.

We have revised our text to clarify this:

In the methods we have included these details (lines 76-84).

In the discussion we acknowledge that our results represent only a selection of the local population who attend RSMM (line 431-435).

2. Is there any data on where deaths happen? In many places, e.g. in neighbouring PNG, many deaths occur in a village and not at a hospital. Acknowledging the difference in settings, it remains crucial to support the calculations with some evidence of the proportion of deaths expected to happen at the hospital.

Since the RSMM is the primary source of medical care and is free, most people (particularly lowland and highland Papuans who make up 93% of the hospital attendees) attend this facility when they are severely ill. In a community household survey of treatment seeking behavior in 2005 and 2013, 82% (9/11) children under 5 who died in the preceding year had done so at the hospital. Hence whilst our estimates of mortality will indeed miss some cases of patients who die at home, this proportion is relatively small. Furthermore it’s important to recognize that this attrition bias makes our estimates of mortality conservative. The stand-alone conservative risk of late mortality following P. vivax suggests that 1 in 100 children with P. vivax die within a year – approximately 3 fold higher than the background mortality risk in under 5s. The magnitude of the risk in this vulnerable population presenting with P. vivax warrants further investigation and the development of tailored interventions to improve life expectancy.

We have revised the text to add these data into the methods (lines 74-84) and also in the discussion (lines 390-400). Again, we have acknowledged this limitation in line 432-455 of the manuscript.

3. Assuming one subsequent malaria episode has an adverse health effect, it would be plausible that several subsequent episodes have an even bigger impact. Why was the number of subsequent episodes per patient not included in the models?

We agree. Multiple events are likely to be more detrimental than a single event.

However the prospective analysis of multiple events and associated mortality raises significant statistical issues due to immortal time bias.
The current paper is a descriptive analysis of early and late mortality. A formal analysis of the impact of multiple events will require sophisticated multistate modelling which is beyond the scope of the current paper - we propose to undertake this approach in a complementary analysis for a subsequent paper.

The current paper therefore focuses on the overall risk of early and late mortality of Pv and Pf, as taken from the moment of the first encounter. It is not designed to determine the effect of multiple events or indeed the role of other comorbidities (Comments #4 below). This simplified approach still has merit since it provides the first documentation of the late mortality associated with Pv.

To clarify this we have toned down the text regarding attributing the late mortality of multiple Pv episodes, and acknowledge that at this stage, although potentially very important, this is speculative.

4. I also agree with the previous reviewer that not including non-malarial re-attendances is a significant shortcoming, particularly since the diagnoses at death point to many non-malarial causes. It would hence be important to consider the frequency of any re-attendance in the assessment of risk factors for mortality. As it stands, there may be a focus on malaria only that is not entirely justified by the disease burden. It is difficult to understand why the authors would consider co-morbidity diagnoses not sufficiently reliable for first and subsequent attendances but sufficiently reliable to present the data for the time of death.

As mentioned in comment #3, we acknowledge that comorbidities with malaria illness particularly sepsis, are important. Indeed we have published on this previously from the same location. Whilst clinical diagnoses are recorded in patient encounters these are less reliable than the documentation of malaria which relied on objective blood film examination for all febrile patients attending the RSMM.

We have given careful consideration to including non-malarial illness, but feel strongly that the focus of the current analysis is a simple descriptive comparison of the early and late mortality in patients with Pf and Pv and the risk factors associated with these. We do not attempt to define causality, merely to present data that although Pf has a higher early mortality Pv is associated with a higher late mortality. This could indeed be incidental to young children being at greater risk of Pv as well as other comorbidities and it’s the latter that kill, or (as other studies suggest) recurrent Pv may make the patient more vulnerable to anaemia and sepsis. Understanding this causal pathway will be crucial in designing suitable interventions, but is beyond the scope of the current study.

Irrespective of the cause of death it is important to realize that, after controlling for age difference, patients with Pv are at subsequent risk of mortality that stretches beyond the initial acute episode. This has very important public health implications, since these children should be a focus of additional healthcare including nutritional supplementation, malaria prevention and close follow up.

We have revised the limitations section of the discussion (lines 420-430).

5. The risk factor analyses for are limited to few specific covariates but other important ones are missing. E.g. co-morbidity or severity of illness at first presentation. It is also not clear how children who died were treated in the analysis of re-attendance risk factors. Some risk factors for death appear to be protective factors for re-attendance which may be a consequence of dead children not being able to re-attend the hospital.

We acknowledge this limitation of the study. In view of the retrospective nature of the analysis the available covariates are limited, although we believe sufficient to control for our primary objectives. Severity of disease was not recorded, although it is reflected by whether children were admitted to hospital and whether they were treated with intravenous therapy. Since March 2006 all patients with
malaria (irrespective of species) are treated similarly: DHP for uncomplicated malaria and intravenous Artesunate plus DHP for severe malaria. Again it’s important to stress that the focus on the analysis is the comparative mortality between these two species. Whilst the acute management of blood stage malaria maybe reflected in acute mortality it will have no influence on the associated late mortality, which is the primary focus of the paper.

In the risk factors for re-attendance with malaria, all children were censored from the analysis at the time of death, or the end of the study 31/12/13. It is indeed possible that early death would preclude subsequent re-presentation with malaria.

We have acknowledged the issues of criteria for severe malaria in lines 349-356.

We have stated the process for censoring data in the survival analyses on lines 160-163.

6. In the response letter, the authors point out that the primary focus of the analyses is comparative mortality between Pf and Pv. It would require more explanation why the authors on the one hand stress differences in pathophysiology and clinical presentation of Pf and Pv malaria (lines 362f, lines 383ff) but then assume that attrition (I would consider of relevance: treatment seeking as a result of severity and frequency and distance, etc.) does not differ between cases with Pf and Pv malaria.

Whilst the pathobiology of these two species varies, in uncomplicated malaria the acute clinical manifestations are indistinguishable – a febrile illness with malaise and prostration. In the early stages P. vivax causes as much prostration and incapacity a P. falciparum. We have analysed this extensively in two large treatment seeking behaviour surveys (Karyana et al and Devine et al) – in both cases the tendencies and locations that patients and the carers seek treatment are very similar. However once they have presented to hospital it is likely that patients with Pf are more likely to be admitted, hence this covariate (inpatient status) is included in all of our risk models.

Whilst we acknowledge potential biases we believe that in a comparative analysis of the two species this is justified and doesn’t undermine our conclusions.

We have added in further text to the limitations section of the discussion (lines 437-444)

7. While for some aspects, further clarification may be sufficient, I think additional analyses are required to draw an adequate picture if the situation and draw conclusions supported by the data.

I suggest that the presentation of incidence rates and rates of recurrent malaria should be less prominent and better contextualised unless authors have a compelling argument why the numbers they present are unbiased.

As stated above, whilst we acknowledge attrition bias, we believe that the comparative analysis between species remains valid. The only reference to incidence rates is in table 6, which we believe remains important - if anything these estimates are conservative. We have now revised the text considerably to highlight the limitations of the study.

8. The manuscript and some responses to the previous reviewers suggest that the study setting provides a perfect and 100% compliant quality of care. Guidelines are sometimes assumed to be implemented always correctly. I am unsure whether this assumption is correct and would suggest more careful wording. E.g. in Devine et al. 2018 it is reported that a blood test was reported by 76% of patients attending public facilities in 2005 (and 94% in 2013) while in this manuscript it is assumed that microscopy is always conducted in case of a fever.
The DeVine et al study was from a community survey of public and private healthcare centres, and not specifically the well equipped RSMM hospital. The policy at RSMM is that all people with a febrile illness are tested for malaria. We have published previously on this and our quality control demonstrates that the microscopy service is very well maintained. We do not assume 100% adherence with hospital policy, although informal assessment suggests it is high. However we believe that it is likely that application of diagnostic processes in patients presenting with febrile illness will be similar between species (after stratifying by IP and OP care). Any bias will therefore affect the detection of patients with Pf and Pv similarly.

We have added a statement to the methods to clarify this (lines 109-113).

9. The study area is not very well and consistently described. Do the population numbers refer to Timika town, the district or a wider area?

The population number is for the Mimika district, of which 90% of the population living in Timika town and surrounding villages.

We have revised the methods to clarify this (lines 63-66).

10. What population does the hospital serve? Only its own district or a wider population? Were also patients from without a certain catchment area considered for this study and might the distance have biased re-attendance as well as exposure?

The majority of hospital attendance is from the district (99%) with the remaining referrals from the neighboring districts.

11. The description of recommended first-line treatment pre-2006 in this manuscript (lines 106ff; oral quinine + 14 days of PQ for Pv) contradicts what was previously published in Karyana et al. Malar J 2016, where it is chloroquine +SP for Pf and chloroquine + PQ for Pv. Which one is correct? Please provide a clarification and a reference.

We apologize for the confusion. Whilst the local district policy included CQ+SP for uncomplicated malaria, prior to March 2006, most patients at the RSMM hospital were treated with oral quinine.

We have revised the methods to clarify this (lines 113-118).

12. In the discussion, lines 406f, it is stated that “Our findings highlight the significant risks of not providing effective antirelapse therapy.” However, this was not investigated and cannot be concluded from the data as a comparative mortality analysis of Pv patients with and without PQ-treatment would have been required. (Maybe this can be done?)

We agree that our attribution of the late mortality of Pv to multiple relapses and thus amenable to radical cure is speculative and is not specifically addressed by our current analysis. Nonetheless this remains an important plausible explanation which we hope will prompt further studies of this extremely important relationship.

We have revised the discussion to soften the conclusions, although still raising this is a potential intervention (lines 400-404).
13. In general, I find the term “representation” (for: “presenting again”) very confusing, as this word is more often used to mean “display” or “depiction”, etc. I suggest using “re-attendance” instead, or at the very least introduce a hyphen (“re-presentation”).

The word representation has dual meaning in English and can refer to either presenting again, or to the presentation as depiction.

To clarify for the reviewer we have hyphenated the word representation throughout the manuscript to “re-presentation”.

Reviewer 2 Comments:

GENERAL COMMENTS: The paper has been substantially improved and now addresses most of my concerns. My remaining concerns are mainly typos and some grammatical errors and not technical issues.

Thank you.

ADDITIONAL REQUESTS/SUGGESTIONS:

1. The most important of these is that species names should be spelled in full at first mention, thereafter all the names are to be abbreviated, i.e. Plasmodium falciparum, (first mention)….changes to P. falciparum throughout the manuscript.

We have revised the text accordingly at the start of the abstract and main text.

2. Figure 1 to be improved. The information presented in the boxes are blurred. Also, rework figure 2A, particularly if you could improve on values on the axis to ensure clarity for lower values.

We have revised Figure 1 and 2a for clarity. Fig 2a now has an isent to highlight the columns at the right end of the X axis.

3. "Figure 2" is spelled incorrectly as "Figure2".

We have revised the text accordingly.

4. Moreover, the authors must check all references because in some the journal names are abbreviated, while in others the names are written in full.

We have reviewed the references and revised accordingly.