Reviewer’s report

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

Version: 1 Date: 02 Nov 2018

Reviewer: Sharon Cox

Reviewer's report:

This manuscript reports an interesting analysis of a rare dataset from an area of high malaria transmission for both P. falciparum and vivax and high child mortality in Indonesian Papua. I congratulate the researchers on collecting and analysing this large important dataset in a challenging environment. However, although the analyses appear to be largely appropriate the description of the methodology is currently insufficient. The reporting of the results is sometimes repetitive and a little hard to follow, whilst the reasons for conducting some analyses or presentations of results and their interpretation is not always very clear. I suggest that some of the tables and figures could be moved to supplementary material or removed.

Major comments

A significant omission of the methods is that it is not made clear how survival status of the children was determined over the course of the observation period. No mention is made of any surveillance outside of the hospital. Therefore I am left to surmise that unless children re-presented to the hospital, they are assumed to be alive at month 12? Similarly, how were deaths detected? Was this limited to those that died during an admission?

Although hospital data occurring within a 30 day period of a presentation were recoded as a single event (was this only done for the first presenting malaria episode, or for all presentations/episodes?), should children have been censored from the survival analysis (analysis of re-presentation) for a period after completion of treatment/admission to accurately assess PYO?

Consider if including date of birth as the point of origin in the survival analysis might improve estimates of age stratified rates of recurrence and mortality. I believe this is called the Cnaan and Ryan approach?

The methods text also does not make it clear if all re-presentations at the hospital were included in the recurrent episodes analysis or ONLY re-presentations that were defined as malaria (which appears to be the case). The case definition of a presentation for malaria (first or subsequent cases) is also not clearly defined. Was this the presence of any parasites? Or was this based on the ICD-10 diagnosis of malaria (final, proximal or any recorded diagnosis).

Minor comments

Abstract - line 25: typo? Should it be "…before either 30 days or within 30 to 365 days…"

Study site, p5: Can more information be provided to indicate the likely proportion of cases with active symptoms who were likely to present for care at the study hospital compared to primary health care clinics in the area?
Methods p6 - were there any hospital guidelines/criteria for admission. Was blood transfusion available for severe anemia - is BT history available in the dataset?

Methods - describe that both inpatient and outpatient presentations were included, earlier in the text.

Methods/results - malnutrition. It says this was assessed by the attending physician, yet complete data is presented for a composite score of severe acute malnutrition (weight for height/length zscore<-3) or stunting (height for age z-score <-3). This seems very unlikely that physicians assessed weight and height in every admission?? Or, was the absence of recorded malnutrition assumed to be "normal? Finally, I would separate out severe acute malnutrition from stunting, as they are likely to have quite different associations with risk of death between the short and longer term.

Statistical methods: More details should be provided of how multivariable models were developed and models compared. Was effect modification assessed (please see later comment). Description of the calculation of PAF is not included.

Results.

Figure 1: could be improved - formatting and consistent inclusion of percentages.

Table 1:
Suggest re-naming to include "…. Under 5 years old at first presentation…"  
Include denominators for inpatient/outpatient for those with hgb data

Proportions of children in the first column for Hgb<7g/dl or <5 g/dL are incorrect. It is correct in the text on p9

Results in the text are too repetitive of those presented in the table.

P9-10 - description of pharmacy records for first presentations - consider describing by inpatient/outpatient status, which is probably your best indication of disease severity.

Risk factors for recurrent malaria?

P10 lines 174 - 181. Please specify if referring to Fig 2A or 2B. line 176-177 - it is not entirely clear if this means that 63.9% of all re-presentations (regardless of species at first presentation) were due to P.vivax in infants … and 50.4% in young children.

Fig 2A is this excluding first presentations on the x-axis?

Fig 2B is not referred to in the text?

Table 2: consider including inpatient/outpatient as columns as well as rows?

Table 3: What number of children/events are included in the multivariable analyses - as presumably this is much reduced due to the smaller numbers of data points for hgb. Consider reporting sensitivity analyses in supp material - to determine if the other risk factors look different in multivar analysis not limited to those with Hgb data, However, at least for this table - the HRs don't appear to be altered very much between the univariable and multivariable models, so in this case it is probably not an issue.

Odd footnote text - typo?
P14 lines 226 - 232: to help the reader, I suggest explaining what question you are asking in relation to the results being presented. Lines 226-232 appear to be reporting results within subgroups ..., why? Were you trying to assess if the effect of parasite species differed by malnutrition - in which case report the stratified analysis (as supplementary info if no indication it differed) - - also note that investigating effect modification is not described in the statistical methods.

P17 lines 250-251: Risk of later mortality greater in infants than young children. This is touched on in the discussion - that this may be that older children at first presentation represent a survivor cohort.

Table 5: footnote erroneously relates to multivariable analyses

Results: consider including analysis of all-cause risk of re-presentations?

Results: I expect if the data were available you would have included them?- parasite density; Blood transfusion during admission; co-morbidities at first/subsequent presentations? However, the latter is reported for diagnosis at time of death - and so the presence of co-morbid pneumonia or diarrhea is presumably available?

Results: Are you able to assess if there is any indication that when low dose primaquine was included in anti-malarial treatment (pre 2006?) if it was effective in reducing recurrence of P.vivax? the way it is written in the methods it appears that once DHP became the first line treatment, low dose primaquine was no longer included, even if was known P.vivax. Is this correct?

Discussion

Any comments on the opposite effects observed for ethnicity in recurrent malaria vs death analyses?

I don't think the inherent limitations of the data and are adequately acknowledged and discussed- and potential effects on bias.

Conclusions - line 408. I don't think that inclusion of sepsis (or the later comments about broad spectrum antibiotics) in the conclusions are warranted - given that no data is presented concerning the incidence of sepsis.

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?

If not, please specify which controls are required in your comments to the authors.

Unable to assess

Are the conclusions drawn adequately supported by the data shown?

If not, please explain in your comments to the authors.

Yes
Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

Not relevant to this manuscript

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Please indicate the quality of language in the manuscript:

Needs some language corrections before being published

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