Reviewer’s report

Title: Temporal changes in haematocrit following artemisinin-based combination treatments of uncomplicated falciparum malaria in children

Version: 2 Date: 10 March 2015

Reviewer: Prabin Dahal

Reviewer's report:

This is an important report as little is known about the full scope of changes in haematocrit levels over the course of ACT treatment. The authors have done a comprehensive analysis to examine different possible patterns of haematocrit changes following AL and ASAQ treatment and to evaluate the clinical determinants associated with a haematocrit fall >=5 units. The report documents a general trend that the level of haematocrit declines post ACT treatment and reaches a local minimum on day3. After this some patient experience haematological recovery (patterns 2 and 6) and some exhibit further decline (patterns 1 and 3).

My main comment is with regards to results presented in Page 9: Lines 18-22 (Also presented in Table 5). The results show three variables (baseline parasitaemia, artesunate dose and baseline haematocrit) are significantly related to a haematocrit fall # 5 units. All of them have been evaluated on univariable analysis. Some of the variables might be correlated with each other and hence the effect observed in univariable analysis may have been confounded. Hence, in order to understand the independent determinants, I suggest evaluating the effect of these variables using multivariable logistic regression using all those covariates significant in univariable analysis (p<0.05). These results can be added and referred as a supplemental file. It doesn’t have to be an elaborate analysis. Just a line or two stating which of the variables still remained significant in the multivariable analysis will be sufficient, and the interested reader may be pointed to the supplementary file.

Also, any limitation of the analysis has to be clearly declared. For example, the results from patterns 3, 5 and 7 aren’t conclusive enough as there are only very few patients with these patterns.

Minor essential revisions:

I have some very minor comments, mostly on the consistency of the presentation.

Methods (Patients)

1) Were both treatments given under supervision? Was AL given with or without fatty meal?

2) Was any form of quality control (internal or external) performed on microscopy procedures?
3) I suggest adding reference or link for “Turbo Ken” program.

Methods (Kinetics of disposition of deficit in haematocrit from 30%)
4) I suggest adding reference for the relationship between haemoglobin and haematocrit.

Results
5) Paragraph 2: “Children who were anaemic at presentation (Pattern 6), were younger, weighed significantly less, had longer duration of illness and a higher proportion of children who were hyperpyrexial compared to children without anaemia (Patterns 1 and 2) (Table 2a)”.

Children with pattern 6 actually weigh higher on average than those from those who had pattern 2 as shown in Table 2a.

6) Paragraph 3: “A late fall in haematocrit occurring between 21 and 28 days after treatment began was seen in Patterns 1, 3 & 7 (Figure 2)”.

In patterns 1 and 3, the fall is actually from day 14. After day 28, the haematocrit levels begin to rise. For pattern 7, the fall is correctly mentioned after day 28.

7) Paragraph 3: “On the whole, virtually all of these children were anaemic for a period of approximately 14 days”

I will suggest quoting an exact answer rather than approximate figures. I suggest given mean duration (and 95% confidence interval) together with the range for which the children remained anaemic.

8) Paragraph 6: “Overall, in all children, mean AUC of deficit in haematocrit versus time was 74.2%.day (95% CI 59.32 – 89.1, range 0.66 – 286.2)…”

I suggest being consistent with decimal places. 89.1 should be quoted as 89.10 for being consistent with remaining texts.

9) Paragraph 8:

In some places, it is given to 1 dp whereas in other, results have been given to 2 dp. Again I suggest being consistent with decimal places throughout the manuscript.

Discussion
10) Paragraph 1:

There is a typo here. Pattern has been spelt as patten.

11) Paragraph 4:

#5 units is being written differently. Sometimes it is written with spaces and sometimes without. For consistency, I suggest using one or either.

12) Paragraph 4:
Again, I will suggest making a quick comments on which of these variables stayed significant in multivariable model.

13) Paragraph 5:
A Full stop is missing at the end of the last sentence of the paragraph.

Level of interest: An article of importance 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 declare that I have no competing interests.