Reviewer’s report

Title: Hypoglycaemia in severe malaria, clinical associations and relationship to quinine dosage

Version: 4 Date: 25 August 2010

Reviewer: Merlin L. Willcox

Reviewer’s report:

Overall I think this is an interesting paper which merits publication. It reassures clinicians that a higher loading dose of quinine is not related to a greater incidence of hypoglycaemia.

- Major Compulsory Revisions

1. Table 1: Please add a row to show the proportion of children with severe hypoglycaemia (<2.2mmol/l) in both groups.

2. Table 2: Please add rows to show deaths in those with / without hypoglycaemia AT admission (as well as the data already shown for hypoglycaemia AFTER admission). Presumably post admission means “post treatment” – please confirm this is the case.

- Minor Essential Revisions

1. Methods 2nd paragraph: “three different definition thresholds; <2.2 mmol/l (severe hypoglycaemia), <2.5 mmol/l (moderate hypoglycaemia), and <=3 mmol/l (any hypoglycaemia)” – it only becomes apparent in the penultimate paragraph of the discussion why these cut-offs were chosen. It would be better to give the explanation with references here in the methods section.

2. Results line 1: a total OF; THE old regimen

3. Line 3: bracket needs to appear before “median age” or after “28 months” otherwise it doesn’t make sense

4. 2nd para: insert “the” before “2002-2006 cohort” and “2006-2009 cohort” (on all occasions)

5. Line 4 : insert “cohort” after 2002-6

6. Timing and distribution of hypoglycaemia episodes: Delete the 2nd and 3rd sentences of this paragraph which simply reiterate data which is clearer to see in table 2. Refer to table 2 instead.

7. Predictors of hypoglycaemia: please explain what is meant by “temperature gradient” and how this was calculated (either here or in the methods section).
8. Discussion para 3: “These observations concur with our earlier studies indicating that whilst glucose production is increased in severe malaria gluconeogenesis fails to compensate, in the presence of decreased glycogen flux to glucose (glycogenolysis), putting children at risk of developing hypoglycemia [27].” – this sentence is difficult to read and comprehend. Please re-word and re-punctuate to improve clarity.

9. Discussion para 4: “careful monitoring is recommended to facilitate early diagnosis and prevent poor outcome and neurological sequelae [31-33].” – do the authors have any data on the prevalence of neurological sequelae in the patients in their two cohorts? If so it would be useful to include this in table 2.

10. “The WHO guidelines, on the other hand, recommends <2.5 mmol/l threshold for treatment of hypoglycaemia in children with severe malaria.” – please quote reference. The guidelines I have recommend <2.2 as the threshold.

11. “Another recent study conducted in Mali by Willcox and colleagues demonstrated that low glycaemia (2.2-4.4mmol/l) was significantly associated with odds of mortality in children with a clinical diagnosis of severe malaria [38]. The authors concluded that an optimum threshold of 6.1mmol/l for intervention which is much higher than currently recommended.” The first of these sentences is accurate but the second is not. I suggest rewording as follows: “The authors concluded that the optimum threshold is 6.1mmol/l for predicting mortality which is much higher than current definitions.” We were not able to comment on the effect of intervention but instead concluded that “There is a need to conduct a randomized controlled trial to assess whether treatment with intravenous glucose or sublingual sugar is beneficial to those with low glycaemia, above the current treatment threshold.”

12. Discussion para 5: “patientS with moderate to severe anaemia”

- Discretionary Revisions

1. Results:

“42% (78/187) of episodes occurred during a blood transfusion or a period of inadequate glucose supply” – can you separate out the transfusions from the other interruptions? If so it would be useful to quote these separately so that the reader can judge which is likely to be the bigger problem.

2. Discussion: “We found a coincidence of hypoglycaemic episodes during transfusions or periods of disruption of intravenous glucose infusion”.

What implications does this have for treatment? Would the authors suggest that i-v glucose or sublingual sugar is given simultaneously with blood transfusions to prevent these episodes of hypoglycaemia?

**Level of interest:** An article whose findings are important to those with closely
related research interests

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests