Reviewer's report

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

Version: 4 Date: 9 September 2010

Reviewer: Marcus Lacerda

Reviewer's report:

The study is of interest, especially for those seeing patients in Africa, where severe falciparum malaria is still frequent and quinine is still the drug of choice in many countries. However the study is essentially ecological in its design, considering that the authors compare data from two distinct periods of time, where other factors not clear for us may have impacted the endpoint of interest (hypoglycaemia post-admission), such as the best access to the diagnosis or to the treatment.

Minor essential revisions

1. In the introduction of the manuscript, the authors state that hypoglycaemia is probably related to depletion of glucose stores, parasite utilisation of glucose, cytokine-influence and hyperinsulinemia, this last restricted to adults. The references cited point to the absence of hyperinsulinemia triggered by quinine in children, therefore, it is highly expected that no dose-dependent effect on the glucose level would be seen anyway. The authors should clarify their hypothesis in the introductory section.

2. Apparently only those with cerebral and/or pulmonary malaria were enrolled, but the authors do not mention if children exclusively with hypoglycaemia pre-treatment were also analysed and if there was any. From what they present, we conclude that hypoglycaemia presenting during the hospitalization was much more a prolonged effect of hypoglycaemia pre-treatment therefore not related to quinine itself.

3. The higher dose of quinine should clear parasitemia faster, and therefore, lead to less hypoglycaemia post-treatment if parasite consumption of glucose is actually a relevant mechanism for hypoglycaemia. The authors do not discuss this point of view. In the multivariate analysis, parasitemia should be added because the inhibitory effect of a higher dose of quinine on hypoglycemia could be masked by the statistically significant higher parasitemia in the second group (from 2006 to 2009). The authors also neglect to analyse if parasitemia was an independent factor associated to hypoglycaemia on admission.

4. In table 2, authors do not analyse the level of hypoglycaemia (pre and post-treatment) with fatality, which is discussed in the discussion section, but not based on the analysed data.

5. In table 3, I do not agree that the second column is an univariate analysis, because age was also used to correct the OR. Maybe it would became more
clear if they present in each column which variables were considered for that model.

Discretionary revisions

1. It should be emphasized that the dosage of glucose during the admission and every 4 hours thereafter is a routine in the service and how many patients were excluded due to the lack of this information in the retrospective analysis, which is a weak point of the manuscript, despite of being useful for the literature.

2. The authors do not mention if the drug used during the two periods are from the same source or any attempt to let us believe that quinine suppliers did not change over time.

3. It is not described how the nutritional status was assessed in the children in the methods section, since this is a major characterization for the discussion of hypoglycaemia. In table 3, only visible wasting is used for the statistical analysis.

4. Time of disease and the time between diagnosis and treatment were not presented. Peripheral parasitemia could somehow estimate these variables, but that would also be dependent on the immune status of children, which was not discussed.

5. It is referred that oral treatment was used, but no clear criteria for its use is presented for those not familiar with the antimalarial policy in Kenya.

**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.