Reviewer’s report

Title: Impact of Vitamin A and zinc supplementation on malaria morbidity in Ghana

Version: 1 Date: 26 July 2013

Reviewer: Gloria Folson

Reviewer’s report:

1. Is the question posed by the authors new and well defined?

   Yes. Although this study sought to ‘replicate’ the findings by Zeba et al (2008), where the benefit of both Vitamin A and zinc administered together compared to placebo were shown, there was some novelty here in that this study was designed to investigate the impact on malaria morbidity of both Vitamin A and zinc administered together compared to Vitamin A together with placebo. Hence the word ‘replicate’ could be replaced with ‘further elucidate’. (Minor essential)

2. Are the methods appropriate and well described, and are sufficient details provided to replicate the work?

   Study design; Participants and study intervention

   Mention is made that children were identified from 12 ‘selected’ communities using listings generated from the KHDSS and a screening form. Details of methodology of how selection of communities as well as 200 eligible children was done should be provided. Also, explain how randomization was done. (Major Compulsory)

   Study design; Study Procedure

   The quantity of blood sampled under ‘Study procedure’ on pg 6 should be specified as well as how it was collected (venous?). (Major Compulsory)

   Morbidity and follow-up

   Reference is made to ‘the dried blood spots’ kept for future anti malarial drug resistance analysis using genotyping. If these were blood spots taken in addition to those taken for PCR to detect the presence of malaria parasites, this should be clarified. (Minor essential)

   Was malaria detected using slides prepared by field workers, PCR using blood spots on filter paper or both? Reference is made to all 200 children giving blood spots for malaria parasite assessment at baseline. Clarify the procedure used for this assessment (ie PCR?). Were slides then prepared by field workers only when a child was reported to have had a fever? So what were the blood spots obtained during follow up for (future genotyping)? (Minor essential)

   How was blood obtained for the HemoCue readings? Finger prick (capillary blood) or blood draws (venous blood)? Was it obtained separately from blood for
Vitamin A and Zn analyses? (Minor essential)

7. Were morbidity forms completed at the end of each week as suggested by the second sentence under this section ‘Morbidity forms were completed by field workers at the end of each week to collect information on signs and symptoms of illnesses occurring during that week’ or once every two weeks (fortnightly) as suggested by the first sentence under the ‘Morbidity assessments and malaria parasitaemia’ section under the ‘Results section: ‘A number of childhood morbidities were assessed during two weekly visits from the start of supplementation until the completion of the study which was at the 22-week visit’? The phrase ‘two weekly’ should be once every fortnight, fortnightly or once every two weeks. (Major Compulsory)

Sample size

8. The sentence ‘This was based on the assumption that there will be a reduction of malaria of at least 20% among the children who were supplemented with combined vitamin A and zinc compared with those supplemented with vitamin A alone.’ The main outcome should be clarified (eg. malaria incidence/malaria episodes/malaria prevalence). As it stands, ‘malaria’ is not clear. (Minor essential)

9. The sentence ‘The significance was p = 0.05 and 80% power allowing for 10% lost to follow-up’ should read ‘The significance level was set at p = 0.05 and the power was 80%. Allowing for 10% loss to follow-up, the project required a sample size of 200 children (100 per arm). (Minor essential)

Sample analyses

10. This section would be more appropriately named ‘Laboratory analyses’ or ‘Laboratory analyses of samples’, or ‘Blood sample analyses’. (Minor essential)

11. This section should include Zn analyses (Major Compulsory)

Are the data sound and well controlled?

Results

12. Baseline comparability (Table 1) is useful. However, for mean age, total number of subjects for baseline and end line are not the same for both groups and these need to be shown in the table. (Major Compulsory)

13. Alignment of text within the Table 1 needs to be checked. Under ‘Occupation’, the figures for ‘Farmer/labourer’ and ‘Professional’ are not in line with their respective categories. The same problem pertains to the figures for ‘Highest education level’. (Minor essential)

14. In Table 2 also, total number of subjects at end line need to be fixed into the table above each set of data for ‘end line anthro.’, and ‘Final anthro.’. (Major Compulsory)

15. Please also present standard deviations for mean weights, heights and Haem in Table 2. (Major Compulsory)

16. Less malaria morbidity in the intervention group should give rise to improved
nutritional status. Strangely, the control group gained more height than the intervention group during the study period. Check data analyses and ensure that the two groups have not been switched around for all of Table 2. (Major Compulsory)

17. Same comment as above for Heam, Aneamia(%), Low Vit A status. Control group seems to have done better. Check data again to see if groups were switched. (Major Compulsory)

18. Additional analyses comparing changes (difference of means) between baseline and end line for the intervention and control groups respectively might be interesting. For example was there a y greater change (significant or not, was there a trend?) in weight, height, HAZ, WAZ and WHZ in the intervention group than in the control group? (Major Compulsory)

19. The suggestion in 13 above might be enhanced by comparing food intake for the control and intervention groups. It was mentioned that dietary intake was assessed weekly, (in the last sentence of the ‘Participants and study interventions’ section but this was not mentioned anywhere in the results/analyses. Controlling for dietary intake, if different between the two intervention groups, could also enhance the analyses suggested in 13. If data is not available, then it should not be mentioned. (Minor essential)

20. Very importantly, compliance to the intervention is not taken into account at all in the analyses although visits were made to check compliance. (Major Compulsory)

21. What units are results for serum Zn recorded in? Needs to be mentioned under ‘Sample analyses’ and in Table 2. (Minor essential)

22. The study definition of malaria has not been stated anywhere in the paper, but has been referred to in the ‘results’ section, under ‘Clinical malaria’: ‘Using the study definition(s), the number of children who were diagnosed with uncomplicated malaria in the intervention group was 27%, which was significantly lower than the children in the control group p = 0.03.’ (Minor essential)

23. Label on Table 4 should read ‘Impact of supplementation on malaria and general morbidity. (Minor essential)

Does the manuscript adhere to the relevant standards for reporting and data deposition?

24.

Are the discussion and conclusions well balanced and adequately supported by the data?

25. The limitations of the study and how these may have impacted on the results have not been discussed at all. (Major Compulsory)

- The intervention was ‘self-administered’ by mothers/care givers
- Weekly/fortnightly visits may not have captured compliance fully.
- Also the study was not powered to detect the effect of supplementation on other
indices. The main outcome on which sample size was based was incidence of malaria.

26. Results for malaria parasite densities were not discussed. Reasons for categorizing densities in the given ranges and why the effects of supplementation differed for various ranges should be discussed. (Major Compulsory)

27. To make for easier reading, this should be followed directly by a discussion of findings for other morbidities before discussion of anthropometry results and other indices. (Minor essential)

28. Findings for anthropometry (but not other indices such as hemoglobin, anemia, low Vitamin A status, etc....) were stated in the discussion section, but no explanations offered. (Major Compulsory)

Do the title and abstract accurately convey what has been found?

29. Modification of the title to read ‘Impact of Vitamin A with zinc supplementation on malaria morbidity in Ghana’ more accurately conveys findings. (Minor essential)

30. The objectives in the abstract are as follows: ‘The primary objective was to determine the effect of vitamin A alone vs. vitamin A and zinc supplements on the incidence of clinical malaria. It also sought to assess the effects on the incidence of anaemia, diarrhoea and pneumonia’. However under the ‘Introduction’ section, the first sentence on pg 4 reads: ‘The primary objective of this study determined the effect of vitamin A alone vs. vitamin A and zinc supplements on the incidence of clinical malaria. In addition, we determined the effects of vitamin A alone vs. vitamin A and zinc supplements on changes in anthropometric measurements, such as weight and length/height, as well as assessing the effect of the study interventions on the incidence of anemia, diarrhea and pneumonia. The tolerability of the supplements was also assessed’. The abstract needs to mention anthropometry also. . (Minor essential)

31. The results in the abstract should also mention anthropometry findings. . (Minor essential)

Is the writing acceptable?

Generally the ‘Methods’ section did not flow well and was hard to follow.

32. In the Introduction section, the third paragraph refers to the study by Zeba et al (2008) and reads ‘The authors hypothesized that children up to 3 years of age receiving combined vitamin A and zinc supplements will have a lower incidence of symptomatic malaria than similar children receiving vitamin A supplements alone.’ The study by Zeba et al looked at children aged from 6-72 months ie 6 months to 6 years, and not 3 years. . (Minor essential)

33. The first paragraph on pg 4 reads ‘Our study sought to investigate whether the findings from Zeba et al (2008) using the combination of vitamin A and zinc
supplements could be replicated in younger children between the ages of 6 and 24 months, who are mostly fed weaning foods, to demonstrate if there will be an impact on overall morbidity and/or anthropometric indices’. The reference to weaning foods seems irrelevant and may be omitted. (Minor essential)

34. The following sentence: The primary objective of this study determined the effect of vitamin A alone vs. vitamin A and zinc supplements on the incidence of clinical malaria. Will read better as ‘The primary objective of this study was to determine the effect of vitamin A alone vs. vitamin A and zinc supplements on the incidence of clinical malaria. (Minor essential)

35. The study procedure is mixed up in different sections of the paper, and makes reading difficult. To make for better reading, the ‘Participants and study intervention’ section should be followed by the ‘Eligibility’ section. The ‘Study procedure’ section should follow with what was done in clear chronological order. Measurements and data collected should be clearly detailed under the ‘Study procedure’ section. The ‘Enrolment section’ as it is now is repetitive and redundant and may be scraped. (Major Compulsory)

36. Under the ‘Morbidity and follow-up’ section, the sentence ‘Information was also collected if the child had any other acute illness such as diarrhea, fast breathing or cough’ gives the reader the impression that information was only collected if the child had any other sickness. However, if the relevant questions were posed to all participants, then the sentence will read better as ‘Information was also collected on any other acute illness such as diarrhea, fast breathing or cough in which case the child was then immediately referred to the study clinic. ……(Major Compulsory)

37. Under ‘Morbidity assessments and malaria parasitaemia’ of the ‘Results’ section, the first sentence ‘A number of childhood morbidities were assessed during two weekly visits from the start of supplementation until the completion of the study which was at the 22-week visit.’ Should read ‘A number of childhood morbidities were assessed during two weekly visits from the start of supplementation until the completion of the study which was at the 22nd -week visit or week 22 visit. (Minor essential)

**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:**

No
No
No
No
No

I declare that I have no competing interests.