Reviewer's report

Title: Major reduction of malaria morbidity with combined vitamin A and zinc supplementation in young children in Burkina Faso: A randomized double blind trial

Version: 1 **Date:** 4 June 2007

Reviewer: Amy Webb

Reviewer's report:

General
General Comments: This is an interesting examination of the effects of micronutrient supplementation on malaria moribidity in young children. I commend the authors on a well-designed placebo controlled study that investigates the role of micronutrient nutrition in malaria morbidity in children. To date few controlled studies have tackled the questions addressed in this manuscript. In general the background, methods, and results sections are presented in a straight forward and concise manner. I have a concern regarding the final calculated RRs and some concerns regarding the conclusions and arguments put forth in the discussion section which I will address in the following sections.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)
1. With respect to the statistical analyses, given that the prevalence of anemia differed at baseline, were the results in Table 2 (ie, the means and the RRs) adjusted for the presence/absence of anemia? It is possible that vitamin A + zinc helped correct a severely anemic condition and it is this and not any additional immunomodulating effects of vitamin A and zinc that may have contributed to reductions in malaria morbidity. Potential effect modification by severe anemia may also be considered for investigation.
2. My greatest concern for the discussion is the manner in which the authors conclude that a synergistic relationship must exist and attempt to attribute specific actions of morbidity reduction to specific nutrients, when this study was not designed in such a way as to test these assumptions. While the authors are correct to attempt to explain their findings relative to the findings of other studies and to form hypothesese regarding potential mechanisms, they must be ever mindful of the limitations of their research design. In order to say that for example, the prolongation of time to first episode was due to zinc or that a synergistic effect existed, single nutrient supplementation groups would be necessary. Given the design of the current study, it is not possible to distinguish to what extent either nutrient was responsible for the reduction in malaria morbidity and /or whether the effects of the nutrients were additive (not suggestive of synergism) or multiplicative (suggestive of synergism). In my opinion the discussion needs to include the limitations of the study, of which the aforementioned concerns can be addressed.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
Please review for grammatical errors. There were several instances where subject-verb agreement was violated, words were misspelled, of linking words were used inappropriately.

Discretionary Revisions (which the author can choose to ignore)
The closing statements in the discussion feel rushed and lacking the clarity found in the rest of the manuscript. Maybe the authors would consider reworking it a bit or potentially expanding it somewhat to better clarify potential policy implications or "next steps".

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article of outstanding merit and interest in its field

Quality of written English: Acceptable

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