Reviewer’s report

Title: A Randomized Trial of Multivitamin Supplementation in Children with Tuberculosis in Tanzania

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Reviewer: Christian Wejse

Reviewer’s report:

Overall
This study reports the finding of a randomised clinical trial testing the effect of multivitamin vs placebo in 255 children with presumed TB in Tanzania. The paper deals with a very important subject and the study provides important new information. The research question is novel and well defined, there is limited knowledge in the field and this type of trial is difficult to recruit patients for and to undertake in a resource limited setting. The randomised trial appears to be well conducted although more detailed information about the trial is needed in order to be able to replicate the work. It is not clear if the manuscript adheres to the relevant RCT standards, and a CONSORT statement would be helpful. The conclusion is sound and based on the presented data, but needs further clarification and more data should be presented.

Major comments
1. A secondary outcomes at the time of trial registration was clearance of chest x-ray which is not reported. Standard TB outcomes (cure, completed treatment, default, relapse, transfer, death) should be reported.

2. The authors study a large number of outcomes with no adjustment for multiple outcome assessment which should be done (Bonferroni). The question whether some of the findings are chance findings resulting from the large number of analyses conducted should be discussed more thoroughly. It is also critical to know whether the authors were testing a priori hypotheses or generating hypotheses.

3. The authors state the results of a subgroup analysis of weight gain in the youngest age group as their main finding, but this analysis was not stated in the protocol as a pre-specified analysis and the result should be interpreted as such and may only be hypothesis-generating.

4. It is not clear from the introduction that the aim was to study HIV-infected as well as HIV-uninfected individuals. Both groups are mentioned in the trial registration, but they may not be comparable, and the evidence on this matter should be referred to as well as discussed further.

5. What were the considerations on choice of content of micronutrients as well as dose? The authors only state why zinc and iron were not added, but more details on the choice of interventions should be provided. Why was vitamin D not
included? There is a long history of vitamin D treatment for TB and recent epidemiological and laboratory data suggest an effect on MTB infection.

6. How many of the children had microbiologically confirmed TB?

7. What is the reason for the skewed distribution of HIV infected and did this have any effect on outcomes?

8. The estimated sample size was not met, the authors should state what difference in the primary outcome would be possible to show with the sample reached.

9. In the trial profile or in the text please add more information on how many patients participated in all follow-up visits, and how many were missing one or more visits/information on primary outcomes. How did you deal with missing information?

10. In the conclusion it should be stated specifically that there was no effect on weight, or that the study was not able to assess the primary outcome sufficiently.

Minor comments:

1. It is not clear whether “HIV infection” covers only HIV-1 (supposedly since in TZ) or HIV1 and/or 2. Were there any dual infected patients?

2. There is available evidence from adults which should be described, eg. the recently published major similar (and larger) trial in adults from Malawi (INT J TUBERC LUNG DIS 11(8):854–859)

3. It would be relevant to add information about the prevalence of micronutrient deficiencies in the study area.

4. Was the success of the blinding evaluated? If not done already, we recommend that the authors fill in the CONSORT check list.

5. Did the authors conduct the analyses by sex? There are important sex-differences with regard to TB and HIV – and in the response to micronutrients – therefore the main outcomes should be analysed by sex. It should be stated in the results section that all analyses were done separately for each sex, and important findings should also be presented.

6. The number of tables is high and they all report multiple outcomes. Table 4 might be omitted and the results mentioned in the text.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I declare that I have no competing interests