Author's response to reviews

Title: Micronutrient Fortification of Food and its Impact on Woman and Child Health: A Systematic Review

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Author's response to reviews: see over
Reviewer's report
Title: Micronutrient Fortification of Food and its Impact on Woman and Child Health: A Systematic Review
Version: 2
Date: 9 March 2013
Reviewer: Kenneth Brown
Reviewer's report:

Overview of study
This paper describes the results of a suite of meta-analyses of the effects of food fortification with one or more micronutrients (MNs) on biochemical and functional responses among young children and women of different age groups. The comprehensive bibliographic searches represent a valuable resource for individuals working in this field, and the analyses conform to standard statistical procedures for meta-analyses. However, as described in more detail below, the analytical techniques have been applied rather mechanically, without due consideration of the underlying nutritional physiology or study designs, so the results are not very helpful for decision-making on the usefulness of specific types of MN fortification of particular food vehicles for different target groups. Rather than presenting multiple analyses of different MNs in a single, somewhat superficial, summary manuscript, the authors should consider reporting more thorough analyses of single MNs (or combinations of MNs), which could then be used for assisting with decisions on which vehicles to fortify, with which chemical forms and amounts of the nutrient(s), and in which populations. The current paper is not very helpful in guiding these decisions.

Major compulsory revisions
The results of randomized, controlled efficacy trials and of effectiveness studies that examine the impact of fortification program (using pre- and post- study designs or simultaneous comparison groups) may yield different outcomes and should not be combined in a single analysis. Depending on the specific MN, biochemical responses to interventions often differ according to the underlying nutritional conditions of the individuals or populations. For example, it is possible to detect increases in hemoglobin concentration only if there is anemia initially or if anemia emerges in the comparison group. Similarly, serum retinol concentration is homeostatically controlled, so it is possible to detect an impact of an intervention only if there is underlying vitamin A deficiency. By contrast, urinary iodine and serum zinc concentration may change regardless of the underlying status. For the former nutrients, it is essential to provide some information on the prevailing status of the study population and analyse results separately according to these conditions. Generally, functional responses, like physical growth, are detectable only when there is a deficit initially. Certain analytes, like serum thyroxin, are tightly controlled and unlikely to respond to nutritional interventions. It is well known that MN absorption varies according to the chemical form of the nutrient and the food matrix in which it is provided. Thus, it does not seem sensible to include studies of elemental iron, ferrous sulphate, NaFeEDTA and heme iron in a single meta-analysis, nor is it reasonable to include formula milks, processed and unprocessed cereals, and other foods in a single analysis, as
mineral absorption from these foods is likely to differ substantially and the results of these analyses are likely to lead to erroneous conclusions. It is surprising that no information was provided on vitamin A fortification of processed vegetable oil, since that is the most commonly used food vehicle in vitamin A fortification programs.

Response to fortification is likely to vary by the amount of fortificant added to the food vehicle and the amount of the vehicle consumed, but the authors do not seem to have considered these issues in the analyses.

Response: Thanks for reviewing our manuscript and for these really important comments. We totally agree to what the reviewer has suggested and had also attempted to do the same. We also acknowledge that fortification is a complex process and results vary according to the food vehicle used, compound chosen, target population and the duration of intervention. For this purpose, we had done an extensive sub group analysis based on these variations and reported separate estimates for the various compounds, foods, age, duration and baseline nutritional status. The overall estimates are just to give a general impression to evaluate if this strategy works, while the more specific sub group estimates on the above mentioned parameters are to guide future decision and policy making. We now have highlighted these differences in the results and consolidated our discussion based on this feedback. The tables provide more specific estimates and also show the number of studies and participants for that particular estimate; so not only quantify the estimate but also to assess the strength of a single estimate.

We also have done separate meta analysis of RCTs and before/after trials and have reported evidence from before/after studies ONLY if there was no RCTS present for a particular micronutrient and now cleared this in the methodology and results section. We also now have provided forest plots for all the outcomes as an additional file.

Minor essential revisions
The authors misuse the term “functional impact,” which usually refers to some physiological response, like immune function or psychomotor development, not to biochemical indictors of MN status, such as the concentrations of nutrients in biological fluids or concentrations of specific transport or storage proteins associated with those nutrients.

Response; Thanks for pointing this, we have now corrected this error.

The authors consistently refer to “serum hemoglobin,” but I presume the papers they reviewed did not measure hemoglobin in serum, but in whole blood.

Response: Corrected

The authors should define what is meant by “deficiency” or “asymptomatic deficiency” for each of the nutrients for which these analyses were completed.

Response: All the outcomes have been defined now in the revised manuscript.
The authors refer to effects on “overall morbidity,” but do not define the term. How many studies actually assessed the incidence of urinary tract infections? Is it possible to draw a definitive conclusion on this issue? How many studies assessed bone resorption markers?

Response: We have now defined ‘overall morbidity’ and also shown separate estimates and the number of studies included for each.

The discussion does not deal with the main issues of the analyses, but wanders into a discussion of a variety of programmatic issues concerning food fortification that are not actually covered by the results of the studies that were analyzed.

Response: In the revised draft, we have consolidated our discussion based on these comments.

Level of interest: An article of importance in its field
Quality of written English: Needs some language corrections before being published
Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.
Reviewer's report
Title: Micronutrient Fortification of Food and its Impact on Woman and Child Health: A Systematic Review
Version: 2
Date: 5 February 2013
Reviewer: Alexander Tsertsvadze

Reviewer's report:
1. Methods section needs to be broken down into the following sub-sections:
   • Search sources/strategies
   • Inclusion/exclusion criteria (PICO elements)
   • Study selection process
   • Data extraction
   • Risk of bias assessment
   • Data/evidence synthesis
   • Overall quality of evidence (GRADE)

   Note that there is no mention of how risk of bias of individual studies was assessed. I could not find the data on risk of bias assessment. Likewise, data extraction process needs to be described. Inclusion exclusion criteria needs more detail. More detail needed for how the studies were pooled, specifically what were the rules for pooling/not pooling.
2. Did the authors attempt to assess publication bias? If not, the authors need to state why?
3. Any results from grey literature? How they are different from those of published evidence?
4. Provision of forest plots of pooled analyses would be very informative.
5. In Results section, Children sub-section, sometimes it’s not clear whether the results pertain to children or infants. Perhaps, results of children and infants need to be separated in the text.
6. In Discussion section, the authors are encouraged to present only the bottom line of the results without numerical data (looks like the repetition of Results section), as it is already in the Results section and the tables.

Response: Thanks for these suggestions. We now in the revised draft have broken the methodology in the sub sections as proposed and also strengthened these as suggested. Forest plots are also now provided as an additional file. We have now mentioned separate results for infants and various age groups in children where possible. We have also removed the RRs from the discussion section and strengthened the discussion. From grey literature, we did not find any studies that could be pooled but have taken contextual factors from program implementation (as mentioned in the methods section. For publication bias- according to Cochrane, there should be at least ten studies pooled under one outcome, we have very few outcomes which have that many studies.
Reviewer's report
Title: Micronutrient Fortification of Food and its Impact on Woman and Child Health: A Systematic Review
Version: 2
Date: 10 March 2013
Reviewer: Simon Wieser
Reviewer's report: see uploaded file
Level of interest: An article of importance in its field
Quality of written English: Acceptable
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

Reviewer's report
General comment
The paper by Das and co-authors makes a big effort to give a broad overview of the impact of food fortification interventions for women and child health. This broad overview may be an important contribution to the design and selection of appropriate interventions. The paper should however be improved by clarifying a number of methodological issues and by a more comprehensive discussion of the results. My general impression is that the range of studies included may be too broad and that more restrictive exclusion criteria would have made the interpretation of the results easier.

Major Compulsory Revisions
• Page 5 last paragraph: The authors state that “Existing evidence on fortification has not been sufficiently and consistently analyzed to assess its overall effectiveness.” There have however been a number of previous systematic reviews of food fortification interventions, including some carried out by the authors of the paper under review. It would be important to inform the reader of these findings of these previous systematic reviews and how the research question of this paper differs.

Response: We have now referenced previous reviews in this area and their conclusions.

• Page 7 first paragraph: “The control groups in the included trials either received no intervention, unfortified foods or regular diets.” The inclusion of control groups with no intervention or regular diets makes it hard to interpret the results as the effects may be due not only to the additional micronutrients but also to the additional macronutrients. It would be very important how understand how the results of these intervention strategies differ und how.

Response: We have now clarified what the control groups were.

• The population of age group “children” unclear and should be clearly defined in inclusion criteria.
Response: Age group defined.

• Page 7 second paragraph: The interpretation of “standard mean difference” is not clear. Do the authors mean the “mean difference” calculated by weighting the single studies by sample size or standard deviation? In this case the mean difference should have a dimension attached, e.g. Hb (g/dl). Or the authors mean the “mean standardized effect size” used to standardize different dimension on a single scale?

Response: ‘standard mean differences’ mean ‘mean differences’ calculated by pooling the individual study means and SDs.

• Page 7 second paragraph: “We performed separate meta-analysis for randomized/quasi and pre-post studies to maintain the quality of evidence”. I cannot find the results of this separate analysis in the tables with the results.

Response: We ONLY reported results of before/after studies if there was no evidence from RCTs for a particular micronutrient.

• Tables with results: It would very important to understand which single studies were considered in the single sub-analysis. This information is missing.

Response: We have now provided all forest plots as an additional file.

• Page 16 discussion: “There are a large number of reviews on the effectiveness of micronutrient supplementation but relatively few on fortification. None of the previous reviews on fortification have attempted to quantify impacts for policy.” As noted above a number of previous systematic reviews of fortification interventions exist. The novelty of the new review in comparison with these previous reviews should be discussed by the authors.

Response: These have now been discussed.

• Page 19 last paragraph: The discussion of the limitations of the study should go deeper into the limits of the study.

Response: We have highlighted the broad limitations pertaining to these specific studies as we also have to adjust to the word count.

• An assessment of risk of bias according to PRISMA statement is missing but would be essential to evaluate the validity of the results.

Response: We have evaluated all the evidence according to the GRADE criteria and tables report the quality of evidence for each outcome.
• The conclusion that “fortification seems to be a potentially effective strategy...” is too weak. The results presented in the paper show that fortification is effective for a number of micronutrients/food vehicles/populations.

Response: Statement corrected. Thanks for this suggestion.

Minor Essential Revisions
• Method section page 6: Example of search strategy is missing. Search period and language not stated. Did the search include previous systematic reviews?

Response: Search is now more comprehensively explained in the methods section.

• The numbering of figures should be checked.

Response: Checked and corrected. Thanks

• Page 9 2nd paragraph: Definition of anemia is missing.

Response: Definition added.

• It would be helpful to see the forest plots of the single sub-analysis, especially of those with many studies.

Response: Forest plots added as additional file.

• Page 11: Definition of Vitamin A deficiency is missing.

Response: Definition added.

• Tables on study characteristics: Please check all the tables for inconsistencies. There are so many that we cannot report them all here. Some examples:
  – Use of abbreviations for study design varies much between the tables (e.g. pre-post, Before After Design, Pre-post, Pre and Post). As a consequence of this imprecision the reader is not certain whether DBRCT is different from RCT. “Quasi” is also used as an equivalent of RCT. Please use consistent terms and abbreviations.
  – Definition of target population is not consistent. In table 1 please just give age range of children included. In some lines the age range is incomplete or missing. Information on nutritional and health status is sometimes given and sometimes not – please give complete information. “Male and female” can be omitted.
  – Same point for “Fortification compound and carrier” column: In some lines the compound is missing, sometimes the number of d/w is given and sometimes not.
  – Some fields in the tables are empty and it’s not clear if this is an omission or a “non applicable” or a “non mentioned” (e.g. column 6 in table 1). Please complete the tables.
It should be considered that some studies most probably evaluate the same interventions. This is for example the case for folate fortification of cereals in Canada or the US. Regarding these mass fortification interventions in a specific country one would also expect the same information on fortification compound, carrier, amount used etc.

The header of the column “Duration of intervention” might be specified as “duration of intervention period evaluated” as in the case of folate fortification in Canada it is most probably the same intervention evaluated in different time windows.

Response: Thanks for the detailed look; we have corrected the tables according to the suggestions

Discretionary Revisions
• Discuss whether effects are not only statistically significant but also substantial from a public health perspective.

Response: Discussion has been strengthened along these lines in the revised draft.

• The discussion should be deeper into the results and attempt a more fair reaching interpretation of the results. Are there for example any food vehicles or types of fortificant better suited for the populations most in need? What are the differences between low-income and high income countries?

Response: Discussion revised and strengthened.

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 importance in its field
Quality of written English Acceptable
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