Reviewer's report

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

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Reviewer: Kenneth Brown

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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.

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 indicators of MN status, such as the concentrations of nutrients in biological fluids or concentrations of specific transport or storage proteins associated with those nutrients.

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

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

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?

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.

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.
Declaration of competing interests:

I declare that I have no competing interests.