Author’s response to reviews

Title: Evaluating the Cost-Effectiveness of Preventative Zinc Supplementation

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Version: 2 Date: 2 July 2014

Author’s response to reviews: see over
To Dr. Basu  
BMC Public Health

June 26\textsuperscript{th} 2014

**Evaluating the Cost-Effectiveness of Preventive Zinc Supplementation**

Dear Dr. Basu,

Please find attached – as new submission - our revised manuscript titled "Evaluating the Cost-Effectiveness of Preventive Zinc Supplementation". Following your (and reviewer # 1’s) suggestion we have consulted with nutritionist colleagues in Boston and Switzerland to make sure our evidence summary reflects the latest knowledge in the field.

With their input we feel we were able to address all comments and concerns raised by the reviewers. Please see below for a detailed reply to each reviewer comment.

With best wishes,

Jesse Heitner  
On behalf of the authors
“The authors’ responses did not address my main concerns. Most importantly, the authors fail to distinguish between the evidence of zinc supplementation trials where zinc was given in form of syrup and tablets and zinc fortification, where zinc was added to food. As the authors correctly summarize, several meta-analyses find a significant beneficial impact of preventive zinc supplementation on morbidity outcomes and growth. So instead of arguing that phytate and micronutrient interactions are not considered in the model, I would recommend that the authors state clearly that they are basing the cost-effectiveness calculations of all 3 delivery forms on preventive zinc supplementation trials, even though the present evidence only supports zinc given in tablet or syrup form. For any future revision of this manuscript, I strongly suggest that the authors collaborate with a nutrition and zinc expert who can interpret the nutrition evidence. While the cost-effectiveness calculations seem well done, the background and rationale of the nutrition aspects need revision throughout the manuscript. The manuscript may be suitable for publication in BMC Public Health after major revisions by a nutritionist. As the manuscript is written now, however, I cannot recommend it for publication.”

Our sincere apologies – we clearly did not interpret the previous comment made correctly. Following your suggestion we have reached out to several colleagues working directly on supplementation trials, and also brought a nutrition expert (Dr. Wafaie Fawzi) on board for the revised version of the paper. Your main point is of course well taken – the evidence on the health impact of delivery forms other than zinc supplementation is limited and weak, and we have tried to make this very clear in the revised version of the manuscript where we write on pages 12 and 13:

“Health effect parameters were modeled to be equal across zinc delivery modes. Virtually all existing evidence on the health effects of preventive zinc are based on zinc supplementation trials, and we assume that the health benefits documented for supplementation trials can be achieved by all other delivery modes considered. This might not be the case as zinc is differentially absorbed across modes. In practice, absorption may be difficult in the presence of phytate, which is a known inhibitor of zinc absorption found in grains [1]. Iron can also act as an inhibitor of zinc absorption, though in lower doses [2] or when incorporated into meals [1-3] this effect is greatly dampened. More generally, the potentially deleterious interactions between simultaneous zinc and iron delivery should be carefully considered when delivery modes are developed [4-7].

Evidence on the effectiveness of other modes of zinc delivery is very limited. A recent meta-analysis on micronutrient powders (MNP) including zinc neither finds no effect of MNP on zinc deficiency or child health [8]. A recent systematic review on food (formula, milk or porridge) fortification interventions suggests a positive impact of these interventions on serum zinc concentration, positive weight gains for zinc-deficient school age children, and positive height gains for infants with very low birth weight, but also highlights the “[.]dearth of evidence for the impact of fortification strategies on morbidity and mortality outcomes in women and children”[9]. For aqueously dissolved zinc, high rates of absorption seem feasible. Tran et al.[10] found that the fractional absorption of zinc ranged from 0.62 to 0.73 for

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aqueous zinc sulfate doses of 2mg to 15mg, with declining fractional absorption for 20 and 30mg dosing. Solomons et al. [11] compare the absorption of aqueous zinc sulfate with the absorption of NutriSet tablets, and find that aqueous zinc administration doubles the bioavailability of zinc compared to the NutriSet tabs. To date, no evidence on the health impact of aqueous zinc is available.”

We pick this point up again in the Discussion, where we write [additions in bold font]:

“Several modeling assumptions limit the generalizability of the results, and are worth highlighting. First, all of our the cost-effectiveness calculations are based on the evidence from trials administering zinc in the form of tablets or syrup. Zinc absorption and the resulting health impact may differ across delivery modes, which would clearly affect the cost-effectiveness results presented in this paper. Second, while a large number of studies have analyzed the health benefits of zinc for children under 5, very little evidence is available for older children and adults. In the absence of better evidence, we assumed the health benefits to be zero outside of this age range. In the (rather likely) case that older populations also benefit from supplementation, the cost-effectiveness numbers reported here would clearly underestimate the true effectiveness of zinc interventions in general, and of water filtration systems in particular, where older household members are naturally exposed to zinc due to the household-based nature of the intervention. Third our model is calibrated to a representative household in a developing country. To the extent that a specific country has higher dependency ratios or higher rates of stunting, the average numbers used in this analysis will clearly be an underestimate of the health impact achievable and the actual cost-effectiveness of the respective programs. We also assumed that adherence to each treatment was perfect, which is unlikely to hold in general, and with pill supplementation in particular. While both zinc supplementation through pills and multi-nutrient biscuits have been successfully implemented in controlled trials, limited evidence is available to date regarding the scalability and adherence to such interventions over time. Last, we only considered technologies currently available; new technologies to deliver zinc such as genetically modified crops are likely to improve the cost-effectiveness numbers substantially.”
Most of my comments have been addressed, but a couple remain:

"Main results Tables 4 and 5 are still not in accordance with the recommendations of Gold. A main results table should normally include the following information for each intervention being compared: Total cost, total effectiveness, Incremental cost, Incremental effectiveness and Incremental cost-effectiveness. Tables 4 and 5 in the manuscript provide only the latter of these."

We agree – as outlined in Gold [12], it is important to understand both incremental and total cost-effectiveness when evaluating various intervention packages. Most typically, cost-effectiveness studies will compare various scenarios, under which increasing proportions of the target populations would be reached through various combinations of interventions. The study presented differs a bit from the usual approach with respect to the underlying scenarios. Even though we agree that it would be possible in principle to combine the interventions analyzed (e.g. provide supplements to kids coming to health check-ups, and use water treatment to cover everyone else), it seems more likely that governments would focus on one strategy only to reach the entire target population. Accordingly, all of our cost-effectiveness estimates were done under the assumption that it would either be status quo, or the specific intervention only – which means that average (total) and incremental cost-effectiveness are the same. We have tried to make this clearer in the revised manuscript, where we write on page 8:

"Dividing the estimated cost of delivery by the incremental reduction in DALYS from providing each intervention yielded the incremental cost-effectiveness of providing each intervention to 100 synthetic households given current disease trends. For all cost-effectiveness calculations the assumed counterfactual was no intervention at all, i.e. that none of the other interventions considered would be implemented, which means that incremental cost-effectiveness estimates equal mean cost-effectiveness estimates."

"The authors have included a Tornado chart, which is much appreciated. However, only the lump-parameters "efficacy" and "cost" are illustrated. I would like to see disaggregated information, both for the different cost parameters and for the different parameters determining the efficiency of the interventions being compared."

Thank you for this suggestion – we have expanded the charts to now show disaggregated information for diarrhea, ALRI and mortality in the new Figures 1a and 1b; we also considered showing further costing details, but for most interventions the cost estimates provided in the literature do unfortunately not provide the necessary detail (cost split) to conduct more disaggregated analysis.
References