PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Preventive zinc supplementation for children, and the effect of additional iron: A systematic review and meta-analysis
AUTHORS	Mayo-Wilson, Evan; Imdad, Aamer; Junior, Jean; Dean, Sohni; Bhutta, Zulfiqar

VERSION 1 - REVIEW

REVIEWER	Olga García Universidad Autonoma de Querétaro Mexico
REVIEW RETURNED	19-Feb-2014

GENERAL COMMENTS	**General comments:** This review describes the evidence available regarding the effect of zinc supplementation alone or with iron on different outcome variables, such as growth, morbidity, mortality and zinc status. Overall, the manuscript is well written, analysis of the data is appropriate and well described, and also gives important conclusions regarding the use of preventive zinc supplementation in terms of public health policies. Minor details are suggested: **Introduction:** Page 3 line 12. The main objective of the review is not clearly stated. It should include the main variables studied, including the outcome variables. This will give the reader an idea of what the methods and results section will contain. **Study characteristics:** Include in the text how many studies were made in zinc deficient population. Several papers have argued that the effect of zinc supplementation is greater in zinc deficient populations. Also, include in the text the most common use of zinc supplements according to their chemical form (ie: zinc sulphate or others) and their formulations (ie. Powder, pills, solution, etc). The information of formulations is in the tables, but should be stated in the text as well. **Effect of zinc supplementation** In this whole section, specify what the authors mean of “high or low

	quality”. Page 4 Line 47. Clarify what “other measures” are. Page 4 Line 57. “evidence of medium effect of zinc supplementation”. Suggest adding “on zinc concentration”. Page 4 Line 58. Clarify what “favoured zinc” means. Page 5 Line 7. Specify what “either group” is referring to. Supplement vs non-supplemented? **Effects of zinc plus iron compared with zinc alone** Page 5 Line 33. Specify what “other outcomes” are.

REVIEWER	Wieringa, Frank UMR-204 Prevention of Malnutrition Institut de Recherche pour le Développement Montpellier France
REVIEW RETURNED	03-Mar-2014

GENERAL COMMENTS	Abstract line 22. Please change to: there was no effect on all-cause mortality. With such a large group of participants (>200.000), and risk ratio of 0.95 with CI including 1.00, one cannot say there was 'a small but non-significant' effect. line 25. A '-' is missing for the 0.09, or the '-' before the 0.13 and 0.06 are incorrect. Please change to 'a small but negative / positive effect on linear growth' for clarity lines 33-35. I am surprised by the conclusions of the authors. They report only a reduction in all-cause diarrhoea risk (a 13% reduction), yet commend preventive zinc supplementation. Given the large sample size, and given the lack of clear benefits, a more modest conclusion is warranted. Page 5, line 36. See above. No effect instead of 'small effect' Lines 36 - 38. Please change all to: there was no evidence for an effect on mortality due to diarrhoea, LRTI, or malaria.... Line 50. It is interesting to see that the author describe a RR of 1.04 as 'no effect' whereas an RR of 0.95 is 'a small but non-significant effect. All non-significant RR's should be held as evidence of no effect, regardless of the direction of the effect. Page 7, Discussion. line 21. Again, the authors should report their findings. That is, the review did not find a significant impact of preventive zinc supplementation on all-cause mortality page 8, lines 8-14. I see no evidence in this review that zinc supplementation could reduce mortality by 15%. Please re-write the last paragraph. Figure 5 Height

	Can the authors clarify whether the large study in India reporting height and zinc supplementation (paper Taneja, J Nutr 2010, reference 65) was included in the analysis or not? It is a bit confusion on whether this falls under Bhandari 2002 or not. The paragraph in the discussion lines 52-57 discusses iron-zinc co-administration, but although maybe only 4 have reported mortality outcomes, many more have reported effects on growth or hemoglobin concentrations or ferritin concentrations. For example, authors have excluded the studies in SE Asia by Berger/Dijkhuizen/Wieringa/Winichagoon, as the age of recruitment was between 4 and 6 months of age, but these and other studies looking into iron - zinc interactions should be taken more into account in the discussion. Page 20. In Table 2, I see that zinc supplementation resulted in a significant increase in the prevalence of LRTI. Is this something which needs more attention?

VERSION 1 – AUTHOR RESPONSE

Reviewer 1	**Response**
This review describes the evidence available regarding the effect of zinc supplementation alone or with iron on different outcome variables, such as growth, morbidity, mortality and zinc status. Overall, the manuscript is well written, analysis of the data is appropriate and well described, and also gives important conclusions regarding the use of preventive zinc supplementation in terms of public health policies.	Thank you very much for the positive feedback.
Introduction: Page 3 line 12. The main objective of the review is not clearly stated. It should include the main variables studied, including the outcome variables. This will give the reader an idea of what the methods and results section will contain.	We have revised to include the outcomes as follows: 'To evaluate the effects of zinc with or without iron on illness and mortality, as well as growth, we analysed direct comparisons (i.e. zinc plus iron versus zinc alone) as well as subgroups within an overall analysis.'
Study characteristics: Include in the text how many studies were made in zinc deficient population. Several papers have argued that the effect of zinc supplementation is greater in zinc deficient populations. Also, include in the text the most common use of zinc supplements according to their chemical form (ie: zinc sulphate or others) and their formulations (ie. Powder, pills, solution, etc). The information of formulations is in the tables, but should be stated in the text as well.	It is only possible to describe zinc deficiency for studies including serum measures and reporting deficiency status. Deficiency was not consistently reported, and many large studies did not include serum measures. To address the reviewer's point, we have added a summary of the serum levels as reported in studies that : "Forty-six studies reported the mean baseline plasma or serum zinc concentration of their participants; the median of these mean concentrations was 72.5 µg/dL."

	We have also added details about formulation: "Studies reporting the chemical compound of their zinc supplements provided zinc as sulfate (45), gluconate (12), acetate (six), and other compounds (8)."
Effect of zinc supplementation In this whole section, specify what the authors mean of "high or low quality".	We appreciate the reviewer's comment and expect that the details of the GRADE system may be unfamiliar to come readers. We have added a paragraph to the "Methods" section to explain how we judged "Quality of the evidence".
Page 4 Line 47. Clarify what "other measures" are.	Thank you. We have revised to clarify "Results for prevalence".
Page 4 Line 57. "evidence of medium effect of zinc supplementation". Suggest adding "on zinc concentration".	We have added this as suggested.
Page 4 Line 58. Clarify what "favoured zinc" means.	We have added "rather than no-intervention" to clarify.
Page 5 Line 7. Specify what "either group" is referring to. Supplement vs non-supplemented?	Thank you. We have clarified by adding "(i.e. supplemented or non-supplemented)".
Effects of zinc plus iron compared with zinc alone Page 5 Line 33. Specify what "other outcomes" are.	The other outcomes are listed in Table 3, as referenced in the text. We would be happy to list all of them here if the editors prefer, but we think this would be redundant.
Reviewer 2	**Response**
I have reviewed the manuscript on preventive zinc supplementation for children. Although the paper is well-written, I have one major concern with the current manuscript, and that is that the authors tend to be biased towards a positive effect of zinc supplementation. Hence, a non-significant RR of 0.95 is regarded as 'a small non-significant benefit', whereas a RR of 1.05 is regarded as non-significant. Both values should be treated similar however, that is, no evidence for benefit or harm. In my review for the authors, I have tried to point this out each time it occurred, but I am convinced I missed a few.	We understand and appreciate the reviewer's point, and the interpretation of these results is something the team discussed carefully and with colleagues from the Cochrane Collaboration. To the discussion, we have added "In interpreting these results, we considered that the results of this meta-analysis are drawn from 13 trials including almost 140,000 participants. The results of those studies are statistically consistent, the overall confidence intervals are relatively small, and the balance of probability favours zinc supplementation rather than placebo. Small reductions in cause-specific mortality were consistent with effects on illness and cause-specific mortality, and the results were biologically plausible. Benefits in any specific are may be related to level of deficiency;

	countries with very high levels of deficiency could expect the largest reductions in mortality as a result of supplementation."
Also, I wonder what the benefit is of reporting for example in Table 3 results on all cause mortality or hospitalisation, if only 1 study has reported this.	The purpose of a systematic review is to present a complete and transparent account of the state of evidence. These are important outcomes, and we have presented the available data for them.
Abstract line 22. Please change to: there was no effect on all-cause mortality. With such a large group of participants (>200.000), and risk ratio of 0.95 with CI including 1.00, one cannot say there was 'a small but non-significant' effect.	If the risk ratio were 1, we would agree that there is evidence of no effect, but the risk ratio is less than 1 and the balance of probability favours zinc supplementation. The reviewer's suggestion that "there was no effect" is neither consistent with this analysis nor with the overall results. Attending solely to statistical significance is not a rigorous way to interpret the results of clinical studies and meta-analyses. Following best practices, we have used the GRADE system (described above), which considers imprecision (e.g. confidence intervals) as one of several factors that affect the quality of evidence. The reviewer notes the size of the review and this analysis: With such a large group of participants, we think the evidence indicates that there is probably a small effect and that our interpretation is appropriately cautious. More importantly, we present the results transparently so readers may reach their own conclusions about the data.
line 25. A '-' is missing for the 0.09, or the '-' before the 0.13 and 0.06 are incorrect. Please change to 'a small but negative / positive effect on linear growth' for clarity	Thank you – we have revised here and in the text. The correct result is SMD=0.09 (0.06 to 0.13).
lines 33-35. I am surprised by the conclusions of the authors. They report only a reduction in all-cause diarrhoea risk (a 13% reduction), yet commend preventive zinc supplementation. Given the large sample size, and given the lack of clear benefits, a more modest conclusion is warranted.	Our conclusion already reflects our interpretation that the benefits of zinc supplementation are probably small, and that zinc supplementation is most likely to be beneficial for children who are most deficient: "Benefits of preventive zinc supplementation may outweigh any potential adverse effects in areas where risk of zinc deficiency is high" In critiquing our interpretation, the reviewer appears to be attending to the confidence intervals for specific results without considering the totality of the findings. We have added the text above to address this point, and we believe that our recommendation is very qualified and

	supported by the data presented. As noted above, the data are presented completely and transparently, and we would be happy to respond publicly if readers who disagree with our interpretation wish to comment on the published paper. We note that our review is quite negative compared with previous reviews on the subject, and we expect it will be interpreted this way by experts in the field.
Page 5, line 36. See above. No effect instead of 'small effect'	Our description of the magnitude of the difference is consistent with the GRADE system, which is endorsed by the Cochrane Collaboration and by NICE. We have followed best practices for systematic reviews and meta-analyses. It is incorrect to interpret any result that is not significant as evidence of "no effect."
Lines 36 - 38. Please change all to: there was no evidence for an effect on mortality due to diarrhoea, LRTI, or malaria....	See above.
Line 50. It is interesting to see that the author describe a RR of 1.04 as 'no effect' whereas an RR of 0.95 is 'a small but non-significant effect. All non-significant RR's should be held as evidence of no effect, regardless of the direction of the effect.	As above, the reviewer appears to be commenting based on the confidence interval for one analysis without considering biological plausibility, the quality of the evidence, and results for related analyses. We did not find other evidence to suggest that there is an effect on malaria and there's no reason to think zinc would be harmful, so we interpreted this as a negative result. On the other hand, there is much better evidence for mortality, and that evidence is consistent with evidence of benefits for the most likely pathways. For example, zinc supplementation reduces diarrhoea, which is a leading cause of death in malnourished children. In attending only to the confidence intervals, the reviewer draws a false analogy. However, we have revised to say "that would be consistent with no effect or a harmful effect on malaria incidence".
Page 7, Discussion. line 21. Again, the authors should report their findings. That is, the review did not find a significant impact of preventive zinc supplementation on all-cause mortality	We have responded above.

page 8, lines 8-14. I see no evidence in this review that zinc supplementation could reduce mortality by 15%. Please re-write the last paragraph.	This point in the final paragraph refers to another paper, which is cited.
Figure 5 Height Can the authors clarify whether the large study in India reporting height and zinc supplementation (paper Taneja, J Nutr 2010, reference 65) was included in the analysis or not? It is a bit confusion on whether this falls under Bhandari 2002 or not.	Ths reference is one of several reports about the same study; as indicated in appendix 4.
The paragraph in the discussion lines 52-57 discusses iron-zinc co-administration, but although maybe only 4 have reported mortality outcomes, many more have reported effects on growth or hemoglobin concentrations or ferritin concentrations. For example, authors have excluded the studies in SE Asia by Berger/Dijkhuizen/Wieringa/Winichagoon, as the age of recruitment was between 4 and 6 months of age, but these and other studies looking into iron - zinc interactions should be taken more into account in the discussion.	We did not review studies of children under 6 months of age, for whom exclusive breastfeeding is recommended and supplementation would be inappropriate.
Page 20. In Table 2, I see that zinc supplementation resulted in a significant increase in the prevalence of LRTI. Is this something which needs more attention?	No. In addition to statistical significance, we considered the quality of the evidence, which is so poor for this outcome that we don't believe it merits further comment. (This analysis includes 4% of the participants in the review; the results are noise.)