Replies to the reviewer comments on:

Title : Zinc lozenges may shorten the duration of colds: a systematic review
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Reviewer comments received by Hemilä at August 17, 2009

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Hemilä's replies (HH) to Reviewer 2 comments Oct 21, 2009:

Referee 2:

http://www.biomedcentral.com/imedia/3538566202829538_comment.pdf

Reviewer's report
Title: Zinc lozenges may shorten the duration of colds: a systematic review
Version: 1 **Date:** 11 June 2009
Reviewer: marzia lazzerini
Reviewer's report:

1) Usually, it's recommended that two authors collaborate for a review. This is necessary to have a double check on data extraction and input in Revman.

HH: Two authors are not necessary for double-checking. I have checked myself several times that the numbers in original publications and in my tables are identical.

2) It's recommended to include only randomized controlled trials. Delete the sentence: "As an inclusion criterion, I required a concurrent placebo-group, because clinically relevant common cold outcomes are largely subjective, and explicitly different interventions (i.e. no placebo in one arm) might bias the comparison". This is one statement about methods which is not necessary.

HH: There is no basis to require that systematic reviews should be universally restricted to randomized trials. I am in charge of three Cochrane reviews, and none of them uses "randomization" as a selection criterion. Furthermore, if we could draw firm conclusions only from randomized trials, there would be no evidence that smoking causes lung cancer, etc.

The sentence mentioned by the reviewer is important because it gives justification for the inclusion criteria. In some cases the outcomes are objective and given our understanding about pathology we can draw firm conclusions even without the use of a placebo (e.g. new cases of lung cancer). Common cold symptoms are largely subjective and that gives justification to the placebo group requirement. The decision about inclusion/exclusion criteria depends on the topic and must be decided and justified case by case. Therefore the sentence mentioned by the reviewer is necessary.

3) Include also a methodological assessment of trials, including the assessment of the methods of randomization.

HH: In the start of Results section I wrote “All these trials were double-blind… all trials [except Weissman] were randomized.” Thus, I am describing the main methodological features.

The specific method of randomization (tossing coin, random number table, generating with a computer, etc) is not relevant to the goal of this study (relation between zinc dose and the size of the effect), and listing the various methods that were used to reach the randomized groups would direct reader’s attention to issues that are not relevant for the objective of the manuscript.

4) Please define the clinical question it in term of:

- Population: specify adult and children. If children included than comment on dosage.

HH: In Methods, I did not describe restriction by age, which implicitly means that children and adults were both included.

In Results, I state that “All studies examined young and middle-aged adults, except the Macknin et al. [26] trial which examined schoolchildren.” which describes that studies with children were included but only one trial was identified.

I added a sentence “Studies with adults and children were included ” to the Methods.

Reviewer’s comment on “dosage”: There is no simple transformation so that the zinc dose in a child study would correspond to 1.5 or 2.0 times the dose of adults. If there would be several studies with children they could be analyzed separately, but there is only one child trial.

- Intervention: zinc lozenges- define what do you mean for. lozenges, would you include also chewing ones? Define this, as later in discussion you state (second line of “Lozenge composition”) that chewing would decrease the pH of saliva, and this could be a factor influencing the effect.

HH: Lozenge is a common word and I think that the ordinary readers must be familiar with common words. The few readers that are not familiar with common words must look at a dictionary. None of the three previous reviews on zinc lozenges for the common cold that I refer to used space to define “lozenge” (Refs. 44-46).
Merriam-Webster defines: Lozenge: a small usually sweetened and flavored medicated material that is designed to be held in the mouth for slow dissolution.

Reviewer comments “you state that chewing would decrease the pH of saliva”: In the sentence I do not state that chewing decreases the pH of saliva. Instead, I state that citric acid decreases the pH of saliva: “Martin assumed that chewing a zinc-citric acid lozenge would decrease the pH of saliva to 2.3”

- Comparison: placebo

HH: In Methods I wrote explicitly “I required a concurrent placebo-group”

- Outcomes: give pre-defined outcomes, include safety outcomes

HH: In Methods I described that the outcome of interest is “duration of colds”

Strongest evidence of safety can be drawn from studies that are longer and that used higher doses of zinc than the short-term common cold studies. This is discussed in the section “safety of zinc”.

5) Objective of the review: The primary objective should be to assess efficacy and safety of zinc lozenges. The fact if there is a dose-response effect should be a secondary objective. Also, dose should be a pre-specified group to explain heterogeneity, and this should be done as sub-group analysis.

HH: The reviewer does not give any justification to the statement “The primary objective should be to assess efficacy and safety of zinc lozenges.”
Based on the previous literature, I can formulate that my primary objective is to examine the dose-dependency.
Reviewer: “… this should be done as sub-group analysis.”
Table 2 showed the subgroup analyses.

6) Methods of pooling the results: need to be checked by a statistician, this are not the standard methods (that can be found, for example, in the Cochrane handbook).

HH: The Fisher method, which I use to test whether zinc and placebo differ, is a standard method, see e.g.:
http://en.wikipedia.org/wiki/Fisher's_method
http://www.jstor.org/stable/2284230
http://dx.doi.org/10.1016/j.csda.2003.11.020
(the chi-square test in this last paper is the Fisher method)

RESULTS AND DISCUSSION
1) Need to be rewritten after adjusting the methods.

HH: The reviewer does not show any need for “adjusting the methods”

2) Modifying factors could be discussed in introduction, and study could be examined in a subgroup analysis according to these factors.

HH: The reviewer does not specify what the “modifying factors” means in the context of the above sentence. In the Introduction I describe that the dose of zinc might modify the size of the effect and thus the dose is a potential modifying factor. However, that is already discussed in the Introduction.

3) Safety: adverse effect should be reported more accurately.

HH: To draw conclusions about adverse effects, I refer to studies that are much longer than the common cold studies. If longer studies with larger zinc doses do not find harmful effects, that gives much stronger evidence for safety compared with the short-term common cold studies.

4) Previous review: move part of this in introduction. Delete all subjective statement.

HH: Putting much text to the Introduction makes it difficult for a reader to see the motivation of the current study. In Discussion section it is more appropriate to consider the consistency and inconsistency of the current findings with other reviews.

5) State the limitations of the study.
Minor Essential Revisions:
1) Abstract- results: report all searched databases, as according to the text
HH: done

2) Abstract- Results: report result in brackets, not only the statement " highly significant"
HH: rewritten

3) Abstract: the unit of measure of outcomes is missing (is this days?)

HH: In the Abstract, I write: "a 42% reduction in the duration of colds". This is a relative effect which means that there is no unit. The relative effect is the same irrespective of the unit (days, hours, weeks,…). In general, a relative effect does not have a unit.

4) Abstract- Conclusion: cut second statement. Report on Side Effect must be more precise. Report if side effects are reversible.

HH: In Discussion I give references to the safety of zinc. If there would be evidence that zinc is harmful for some people, the issue should be discussed more extensively in the Abstract. Given the lack of harmful effects in the references mentioned in Discussion, I do not see that there is need to write more on the topic to the Abstract.

5) Introduction- second line : Zinc supplementation, , specify that this is oral supplementation

HH: In the case of vitamins and minerals, "supplementation" means administration by the oral route.

6) Introduction: Please define "lozenges", Lozenge composition- last sentence: what does it mean?

HH: see above

Quality of written English: Needs some language corrections before being published

HH: The text had been checked by a professional linguist at the Language Center of our University.