Previous reviewer comments:

Journal Name: Clinical Epidemiology

Title: Zinc Lozenges May Shorten the Duration of Colds: a Systematic Review

ID: 15728

Author: Dr Hemila

The manuscript was rejected on the basis of the following three reviewer comments.
However, I was encouraged to submit the manuscript to Clinical Pharmacology after taking into account the reviewer comments.

Replies to the reviewer comments by Harri Hemilä 24 Nov, 2010

The *reviewer comments* are in italics
Harri Hemilä's comments are followed after the bold **HH:**

REVIEWER 3 EVALUATION
General comments:

1. I would suggest the use of first person "I" be dropped

HH: Many journals explicitly encourage active writing:
We selected, we calculated...
I can change the style if the editor suggests so.

2. Throughout the presentation of methods, results and discussion there is a great deal of mixing. The author needs to revise this and avoid excessive interpretation when describing the methods and results.

HH: I do not understand this comment, what the reviewer means by mixing.
In the Methods section, I describe the rationalization for the methods. I do not understand what the reviewer means by: ”interpretation … [in] the methods”.

3. The text accompanying the figures and tables is far too complex + lengthy and requires the reader to move back and forth between them and even the supplements. These require major revision.

HH: Table 1 has long footnotes, but they are about details. They are needed if some critical reader wants to take a close look at the meta-analysis. For an ordinary reader they are not relevant in the main text section. Similarly, the description of the study characteristics and the imputation of SD values in the supplement tables is presented for those (rare) readers that would like to take a close look at the details. The main text does not require that the ordinary reader goes to the supplement tables or reads the footnotes of Table 1. There is no requirement to move back and forth for the

ordinary reader, whereas a critical reader needs details.

4. The text is excessive in length and quite rambling.

HH: Proper description of methods needs space. Discussion consists of short sub-sections that focus on issues directly relevant for this analysis, and they refer to other publications for more details. Introduction is only one page long.
I do not think that the ”excessive length” is reasonable criticism when the paper carries out a meta-analysis of 13 comparisons on a controversial issue.

Abstract: "results" missing

The conclusion does not follow from what was addressed in this review.

HH: The end of the Abstract was rewritten.

Introduction:

Omit the first paragraph. Considerable controversy remains regarding the zinc-ARI relation.

HH: I do not understand the basis for this suggestion. There is some evidence that zinc supplementation can affect respiratory infections in developing countries, for which I give references. The reported benefit can be explained, at least partly, by zinc deficiency. In the first paragraph I point out that it is unlikely that zinc supplementation would affect respiratory infections in Western countries because there is no wide-spread zinc deficiency, and I refer to two controlled trials which did not find benefit. The message of this section is that, zinc plays a role in the immune system, but - if zinc lozenges are effective in Western countries - they probably have biological explanations other than curing zinc deficiency. Reviewer 3 does not point out that any of the references for the first paragraph is unreliable.

There is no mention of previous reviews in the introduction, nor is a clear case made for the need of this review.

HH: Introduction describes the biological rationalization of the study. Previous reviews are discussed in the Discussion section.

”nor is a clear case made for the need of this review”
At the end of the Introduction I write ”The purpose of this systematic review is to examine the relationship between the total daily dose of zinc from the lozenges and the effect of the zinc lozenges on the duration of colds in patients who had natural common cold infections.”
Reviewer 3 does not describe what he or she means by the above comment. Does he or she consider that there is no justification to examine the possible dose-dependency, or is the end of Introduction just poorly formulated.
Reviewer 1 writes: ”*Background, nature, scope and importance of the problem that led to the review/meta-analysis is well described.”*
Reviewer 2 writes: ”*The introduction ... provides adequate background and justification for the review.*
Thus, there is no unanimous view by the reviewers that there is ”no case for the need of this

review."

In the discussion two reviews are critiqued, however there are others, including the Cochrane systematic review of zinc treatment for common colds.

HH: First, I do not think the purpose of a manuscript is to list all previous reviews that have been published. If there are many reviews, one must focus on the most relevant and influential reviews. Second, as far as I know, the Cochrane review on zinc and the common cold has been withdrawn a few years ago:
http://www.ncbi.nlm.nih.gov/pubmed/17636670

Methods:

The decision to apply % reduction as the primary outcome does have statistical merits, but is not of pragmatic utility. The author does need to address the absolute reduction in illness duration.

HH: The main goal of this study was to find out whether the effect of zinc lozenges is heterogeneous. If the zinc effect is heterogeneous, then there is no single estimate that would apply for all people. Furthermore, the duration of the common cold depends on viruses and the definition of the cold etc., and therefore an "absolute, pragmatic effect" of e.g. 0.5 or 1-day decrease in the duration is context-dependent and has little information without the duration of colds in the control group. Furthermore, Table 1 shows the absolute duration of colds and the difference between zinc and placebo group gives the pragmatic effect (with the control group level also given).

Was an intention to treat analysis an inclusion criteria?

HH: Inclusion/exclusion criteria are explicitly described in the Methods. In many studies not all randomized participants are available at the end of the trial: ideal ITT is therefore often not possible.
The three high-dose Zn-acetate trials are described at the end of the Results:"... In the Petrus trial, only one participant was lost from follow-up [22]; in the first Prasad trial, two participants in the placebo group dropped out on day 2 [25], whereas there were no drop-outs in the second Prasad trial [21]." Thus, two of these studies could not do ideal ITT, but they are included.

"What proportion of subjects stopped taking zinc due to side effects and how did this differ between high and low dose zinc subgroups?"

HH: There are 11 publications with 13 zinc comparisons. This question above can be considered for all 13 comparisons. Thus, reviewer 3 requires the reporting of technical data for 13 studies, but he/she simultaneously criticizes that "the text is excessive in length" (above). Supplement table 2 described the "losses to follow-up" which partly is caused by bad taste. In the "safety" sub-section in Discussion I write "In the most recent trial on zinc acetate, there were no significant differences between the zinc and placebo groups in the occurrence of adverse [...including bad taste problems...] effects although the daily dose was 92 mg [20]."
More space might be used for the taste question. However, taste does not explain the benefit observed, in particular, in the high-dose Zn-acetate trials, and reviewer 3 stated that the text is already "excessive in length".

Results:

Table 1: incomplete presentation of effect column. This should include 95% CIs.

HH: As described in the Methods, the strength of the Fisher method is that no imputations for SDs are needed. That also means that Table 1 cannot present confidence intervals because many SDs are missing. However, CI:s are shown in the forest plot (many of them based on imputed SD).

Table 2 not necessary

HH: This study is a meta-analysis of the effect of zinc on the common cold duration. I am using two methods for pooling the study findings. The results for the second method are shown as the forest plot, and the results of the first method (Fisher method of pooling P-values) are shown in Table 2. What is the point of this work, if the the results of the meta-analysis would not be shown. How does the reviewer read this manuscript, if he/she considers that the main results are ”not necessary”?

Figure S1 should not be a supplement.

HH: I do not think that the figure is so important that it deserves space within the actual article. If the editor considers that it is better within the actual article, it can be moved inside.