PLOS ONE,
Editors,

Re: 09-PONE-RA-14368R1-A
Zinc lozenges may shorten the duration of colds: a systematic review

Dear Sirs,

On June 16, 2010 I received comments on my manuscript by Dr. Dr. Tom Jefferson (Academic Editor, PLoS ONE) (The text is at the bottom).

After reading Tom's comments, and thinking quite a lot, I made some rather large changes to the manuscript:

1) Supplementary Table 2
I added a table in which I describe:
* the characteristics of the included trials
* calculation of daily Zn dose
* definition of the common cold by the original authors
* the results of the studies, including the explanation of the calculation of P-values for Table 1 and
* the reasoning for the mean and SD values which I am using in Figure 1

2) Supplementary Table 3
Several of the trials reported the results as survival curves. I measured the curves and transformed the curves to the distribution of common cold duration. This gives the best estimate of mean and SD.
In most studies the participants were not followed long enough so that all of them would have recovered during observation. I imputed the recovery day for the few that had colds longer than the last follow-up day. This imputation is based on the trend of the survival curve before the last follow-up day.
Since this imputation requires subjective decisions, I also carried out sensitivity analyses in which I made two assumptions:
1) all “long-ill” participants recover on the day after the last follow-up day (Rapid recovery)
2) the rate of recovery is half of the basic approach (Slow recovery)
Page 2 of supplementary table 3 shows that this variation in assumptions has no relevant effect on the main findings: there is strong evidence of heterogeneity over all 13 comparisons, and over the high-dose comparisons.
The sensitivity analysis does show that the pooled effect of the high dose non-acetate trials changes depending on the assumptions. However, even the smallest effect (by Rapid recovery) shows statistically highly significant effect by zinc.

Both of these supplementary tables considerably increase transparency. Inside the manuscript they would substantially decrease readability, but with the modern technology they can be added as links to the main manuscript. Therefore, a more interested reader can find out the details of the trials and my calculations.

3) Figure 1
Because I can estimate a mean and SD for each trial, I constructed a forest plot of the 13 studies. This does not affect discussion, but makes an important improvement. I am keeping the Fisher

method, because that refutes any suggestions that my subjective imputations might simply cause some artefact differences between the zinc and placebo groups.

These changes above answer to the comment on the definition of common cold in the primary studies, and they put more emphasis on estimation. In the original version of the manuscript, Table 3 (same table remains) pooled the results of high dose zinc acetate trials, and in that respect the manuscript was not just calculating P-values. Also, in the original version, Table 1 showed the duration of colds in the low-dose zinc trials (same table remains) and the new Fig. 1 pools their results, but there is no new information generated by the pooled estimate. However, I am glad for the encouragement to think about increasing the role of quantitative analysis, which led to Fig. 1, which I consider important improvement in this version.

I have done lots of small changes in the manuscript. However, they are scattered all over, and I do not list them. The arguments are not changed.

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Other issues:

TJ: Your inclusion criteria are hard to follow and the suggestion of using a PICODT structure is helpful

HH: I do not quite understand this issue.
Intervention and outcome are stated in the title.
There are no restrictions in participants (adults and children are included; there are no restrictions by health status other than obviously they must have the common cold if treatment of common cold is tested); thus I do not understand how I should improve my description of Population.
Methods subsection in the abstract states that the comparison group is a placebo group.
Thus, I do not understand what I am expected to rewrite.

TJ: When it was pointed out that you are lone author and this is unusual practice in reviews, the referee is right. Your response was hard for me to justify.

HH: I will briefly describe my own experiences:

If there is a strict requirement that there must be more than one author, this has two possible consequences for topics that are unpopular:
1) systematic reviews are not carried at all, because there is only one person in the world seriously interested in the topic, and that is not many enough
2) honorary authorships are used to fulfil the requirement for several authors.

I have a two-decade interest in vitamin C and the common cold. As I read the literature in early 1990s, I could see that there were no other people seriously interested in the topic. In the middle of 1990s, I learned that prof. Bob Douglas in Australia was starting a Cochrane review on vitamin C and the common cold, and I was of course worried because I understood that I had a competitor. In any case, in early 2000s, Bob contacted me and wrote that he was retiring and he did not want to keep the responsibility of the Cochrane review, because he was changing his projects. He knew that I was the only person in the world that was interested in the topic to such a degree that it was reasonable to ask, whether I would take charge of the review. First I wrote no, because I had so much else to do at that time, but Bob contacted me again some two years later (there were no other

people he could have asked; both of use knew that). This time I wrote that I will take the charge of the review if we make an agreement that we are fully rewriting it together. He agreed and we rewrote it. That was very enjoyable collaboration, because both of us turned other ones heads around on some issues. We also corrected other ones numbers. Thus, I can see your point when you state that it is better to do work with someone else (I have had other good collaborations also).

Then I was interested in the effect of vitamin C on pneumonia (5 controlled trials) and tetanus (1 trial). I started to register those topics to Cochrane groups, but they wrote back that they will accept registration only when/if I find a co-author. As I knew the literature, I knew that there was no-one seriously interested on those topics in the whole world. In the academic world these are even less popular than vitamin C and the common cold (2 people interested in the middle of 2000s, see above).
Also, even if there would be someone interested, it is not obvious that the way of thinking is similar enough that a collaboration turns out to be fruitful. One of my colleagues at our department is a pediatrician (Pekka Louhiala) and I asked him to participate in the review on pneumonia, and I asked another person with microbiological background (Teija Koivula) to participate in the review on tetanus. Authorship is currency in the academic world and therefore it is possible to get people do some work when one promises that the person gets the author status. Nevertheless, both of these people were more motivated by helping me to get my work forward, rather than getting their name to the review. Both of them were somewhat annoyed when they were putting their name to the protocol and review. They did read the manuscripts, and they did independently extract the data from the study reports etc. as we promised in our protocols, but my work was well over 95% of the whole work. None of us three were satisfied when Pekka and Teija put their names to the protocols and reviews, but when I explained to them that it was absolutely the only possibility for me to get the Cochrane reviews forward, they accepted to put their names to the reviews.
Bob was seriously interested in vitamin C and the colds (that makes 2 in the world, rather unpopular topic in the academic world). That is the reason, why our collaboration was fruitful.
Pekka and Teija were/are not interested in vitamin C, and therefore they did not have such a familiarity with literature and they were not ready to put so much time to the reviews that it would have been fruitful collaboration.

I am not the only one who considers that there is a problem of “honorary authorships” in Cochrane reviews. In JAMA (2002) there was a paper: Prevalence of honorary and ghost authorship in Cochrane reviews. http://www.ncbi.nlm.nih.gov/pubmed/12038907
Much of the problem was caused by including people who had assessed quality or who had abstracted data to the review, without fulfilling other requirements for authorship.

When you state that it is useful to have another person to check the numbers etc., of course, I do not disagree.
However, competent people are not unemployed or under-employed. There is no queue where I could pick a competent person who is interested in vitamin C and pneumonia/tetanus or zinc lozenges and the common cold. Furthermore, people have different ways of thinking and it is not obvious that simply having a competent person interested in the same topic makes a good collaboration (I have also some bad experiences).

I think I have used a few hundreds or hours with the zinc and cold topic. Therefore I know rather well the literature. In my manuscript I point out that two previous systematic reviews on zinc and colds were erroneous – even though both reviews had more than one author. Although I am interested in collaborations, I will not collaborate with people who are doing so poor quality work even if they might be ready.
Then there is one further person who has the greatest interest in the whole world on the topic, George Eby, who started this field and who has several papers as references in my manuscript. I

have been in some contact with him. However, he is a chemist and he has no reasonable background in systematic review and meta-analysis. In addition, since he started the field, I feel that he has a conflict of interest type of problem, whereas I am much more independent person to summarize the results.

I understand that the Cochrane review groups have policy that they require more than one author, even though that leads to honorary authorships. That is something I must adapt to.
However, I do not accept that – having done a few hundreds of hours work on a topic – I should add a honorary author who is doing only a few hours of work, to a paper in a regular journal.

Because Pekka Louhiala is a close colleague for me, I asked him to check that the extractions from the trial papers are correct, and he did that. He actually found that one year was wrong (I do not believe that would have survived to the final version, because I an re-checking). I said to Pekka that I will thank him in acknowledgements, but I will not add him as a coauthor. However, checking the measurements and calculations in Supplement Table 3 would be a big job and I cannot ask such a job from Pekka.

TJ: "you can never be too careful"

HH: My approach is that I am checking, re-checking, re-re-checking etc. until I am satisfied. Of course, I cannot be sure that there never are errors in my papers, but no-one has pointed out errors so far.

Multiple authors is not a solution to the requirement that there should not be errors in systematic reviews. E.g.:
1) In my manuscript I describe briefly the problems of two previous zinc reviews by multiple authors.
2) Over a year ago I was reading the Cochrane review on vitamin C and asthma, and I found that it was full or errors. Initially there had been three authors (Kaur B, Rowe BH, Ram FS http://www.ncbi.nlm.nih.gov/pubmed/11687089) but one of them disappeared and a new one (E Arnold) appeared in the newest version (http://www.ncbi.nlm.nih.gov/pubmed/19160185).
I wrote a criticism and submitted that to the review group, see:
http://www.ltdk.helsinki.fi/users/hemila/CA/Coch_Asthma_09_03_23.pdf
I anticipated that my criticism would be published as feedback and that would lead to the correction of the errors. However, I received an invitation to take charge of the review. First, I was puzzled, but then we ended with an agreement with E Arnold that we will fully rewrite the review. That is under progress. Thus, the presence of multiple authors (Kaur B, Rowe BH, Ram FS) does not guarantee that a review is not full of errors...
3) there are numerous other examples...

TJ: I have marked up the relevent comment for you in the attached file.

HH: I looked through the attached file, but I do not quite understand.
Of course, I do not expect that all my comments are satisfactory to you, but still I do not quite understand how you would like me to respond to the parts that are marked by yellow.

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I hope that you will reconsider my manuscript to PLOS ONE.

Harri Hemilä

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Dear Harri, I have been asked to arbitrate on you review. I am co-author of some 20 Cochrane reviews and tried to approach your review is an unbiased manner.

Having read it and having gone through the previous referees' comments, I can see both sides but believe they are connected. Let me try and explain with an example. I agree with you that asking for a definition of the common cold is nonsense. How you define it is irrelevant, how the authors of the primary studies define it is the issue. Because you have not produced a tabulation describing the included studies this point is lost on the readers. When it was pointed out that you are lone author and this is unusual practice in reviews, the referee is right. Your response was hard for me to justify. I am famous for having entered the placebo and intervention arm data the wrong way round in metaview. It is easily done, and that is why I will never load data on my own or without at least 2 other people checking it. I am also famous for having made a turkey of myself by accepting what Roche and its KOLs published. The lesson is: you can never be too careful. Why do you not ask one of
your colleagues to check the data over for you and perhaps perfom some transformations for you (see below)?
If I understand correctly you resorted to bpure Fisherian probabilism because of heterogeneity of reporting. You rightly say that medians and ranges cannot be pooled with means and SDs. Why do you convert all outcomes into binary: "duration of common cold at day 5 Yes/No" ? If you do not want to do that there are methods for transformation using p values and 95% CIs.
Your inclusion criteria are hard to follow and the suggestion of using a PICODT structure is helpful.
This is good work on an important. With a little bit of extra effort you can get it in its rightful place.

With best wishes,

Tom.

PS I have marked up the relevent comment for you in the attached file.