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Cochrane Database of Systematic Reviews 2015, Issue 4. Art. No.: CD001364.

DOI: [10.1002/14651858.CD001364.pub5](https://doi.org/10.1002/14651858.CD001364.pub5).

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Zinc for the common cold (Review)

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[Intervention Review]

Zinc for the common cold

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Editorial group: Cochrane Acute Respiratory Infections Group.

Publication status and date: Withdrawn from publication for reasons stated in the review, published in Issue 9, 2016.

Citation: Singh M, Das RR. Zinc for the common cold. *Cochrane Database of Systematic Reviews* 2015, Issue 4. Art. No.: CD001364. DOI: [10.1002/14651858.CD001364.pub5](https://doi.org/10.1002/14651858.CD001364.pub5).

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REASON FOR WITHDRAWAL FROM PUBLICATION

September 2016 updated withdrawal notice

This Cochrane Review was withdrawn in April 2015, and this withdrawal notice was updated in September 2016.

The review was withdrawn as result of comments submitted via the Cochrane Library by Harri Hemilä in February 2015. Hemilä identified multiple errors in this Cochrane Review and made allegations of plagiarism of text and data from a previously published systematic review (Hemilä H. Zinc Lozenges may shorten the duration of colds: a systematic review. *Open Respiratory Medicine Journal* 2011;5:51-58. [dx.doi.org/10.2174/1874306401105010051](https://doi.org/10.2174/1874306401105010051)). The comments referred to the version of this review first published in June 2013 (Singh M, Das RR. Zinc for the common cold. *Cochrane Database of Systematic Reviews* 2013;(6):CD001364. <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001364.pub4/full>).

The Cochrane Acute Respiratory Infections Group, which maintains the review, withdrew the review in April 2015, pending an assessment of the errors reported, and the group referred the allegations of plagiarism to the Editor in Chief. The Editor in Chief notified the authors of the concerns, and followed the Committee for Publication Ethics (COPE) guidelines.

Replication of text was identified in the Cochrane Review. This was limited to copying of short phrases and was acknowledged by the authors. The level of text plagiarism was minor and at a level that would be addressed by a correction. The Editor in Chief carried out further investigation into the alleged plagiarism of data, with the co-operation of the review authors, who provided supplementary information in support of their work. The allegations related to the derivation of means and standard deviations of data from some of the included studies. Although the authors acknowledge and cite the Hemilä 2011 review, the Editor in Chief considered that the authors' explanation regarding some similarities in presented data between the two reviews was not conclusive.

This version of the review will therefore remain withdrawn.

April 2015 withdrawal notice

This review was withdrawn due to concerns raised via the feedback mechanism regarding the calculation and analysis of data in the review in April 2015. Whilst it is not unusual for reviews to be withdrawn, the editorial group took the view that it would be better to take a cautious approach and explore the source and calculation of data used in the analysis in more detail, rather than keep the review on the Cochrane Database of Systematic Reviews for the time being.

The editorial group responsible for this previously published document have withdrawn it from publication.

FEEDBACK

Zinc for the common cold feedback: the Eby 1984 report, flavor and flavor masking issues, and what is next, 23 February 2011

Summary

My congratulations are extended to Meenu Singh and Rashmi R Das for a very comprehensive review of the zinc for common cold literature. However, some comments are needed concerning the Eby et al. 1984 report, flavor issues and where we need to go next.

Concerning the original 1984 Eby, Davis and Halcomb article

Our original 1984 article[1] started this line of inquiry by showing that it was possible to shorten common colds by 7 days ($P = 0.0005$) with 23 mg zinc (zinc gluconate) lozenges when taken each two wakeful hours. These lozenges (unflavored and unsweetened dietary supplement tablets) lasted about 30 minutes in the mouth which provided sufficient time for local absorption into oral tissues. This protocol was developed after observing that 50 mg zinc (zinc gluconate) tablets slowly dissolved in the mouth of a 3-year old child with acute lymphocytic leukemia (T-cell) resulted in her severe common colds disappearing within 2 hours without further treatment and many similar informal observations in the general community.

Our report has drawn some criticism, mainly since the taste of the zinc gluconate lozenges was modestly objectionable resulting in more dropouts in the zinc-treated group than in the placebo-treated group. Bias would occur if zinc-treated subjects who received little or no benefit selectively dropped out or failed to return reports. We were concerned about this potential for bias, and to protect our results we estimated the maximum effect of such bias by assuming that all dropouts and all non-reporters in both zinc and placebo treatment groups received no benefit and responded as if they were on placebo. The effect of zinc in that analysis remained substantial and statistically strong ($P = 0.007$), and this potential bias was shown to be irrelevant. These modifications to our main results were published in our Discussion section on page 23 right-hand column, but they have been ignored in reviews by others, thus adversely biasing results of several critical reviews. Therefore, I am disappointed that this error was also committed by Singh and Das.

Flavor and flavor-masking issues

Concern about blinding evolved from concern over “bad taste” of zinc lozenges. There is much difference in the taste of zinc lozenges, which should be considered in evaluating bias. Zinc gluconate in tablets with no other soluble ingredients¹ are moderately objectionable tasting, but tolerable, to most people. Zinc gluconate releases 72% of its zinc as ionic zinc at physiologic pH 7.4.[2] Zinc gluconate can be sweetened without bitterness using a fructose tablet base as was done in the Al-Nakib trial at the Great Britain Common Cold Unit.[3] However, mixing zinc gluconate with any other sweetener, especially sucrose and/or dextrose, results in products that age within 30 days to be as bitter as the bitterest substance known, sucrose octaacetate. This unexpected and adverse effect caused researchers to search for alternatives to zinc gluconate and for ways to flavor-mask zinc gluconate. Extreme bitterness likely affected only the results of Weisman et al., although they compensated by using very small amounts of zinc.[4]

Although pure zinc acetate, which releases 100% ionic zinc at physiologic pH 7.4,² tastes vastly more vile than pure zinc gluconate, it is easily flavor-masked by a variety of sweeteners in either hard-candy compositions such as the lozenges tested by Prasad et al.[5] or compressed tablets as tested by Prasad et al.[6] and Petrus et al.[7] These zinc acetate lozenges did not contain flavor-masking additives. Zinc acetate tastes and works best when present in a 1:100 ratio with dextrose in very highly compressed tablets which last about 30 minutes when being dissolved in the mouth. One failure occurred in effervescent lozenges containing zinc acetate which were flavor-masked with tartaric acid and sodium bicarbonate, resulting in elimination of ionic zinc.[8],[9]

Citric acid was used to flavor-mask the objectionable taste of zinc gluconate in a corn syrup and sucrose hard candy lozenge.[10] Citric acid has a high affinity for ionic zinc and no zinc ions were available for absorption into oral tissues, resulting in clinical failure.² Due to its pleasant taste, this formula is commonly used in commercial zinc lozenges in the United States resulting in no effect against common colds other than nutritional support.

Glycine was used to flavor-mask zinc gluconate in several clinical trials, with two[11],[12] showing efficacy and one[13] showing lack of efficacy. Variability in results may have been caused by glycine since it eliminates about one half (or more) of the ionic zinc from lozenges.²

NOTE: This formula does not release “over 90% ionic zinc” at physiologic pH 7.4 as portrayed by Sing and Das, but it does release that amount at pH 5.0, a nonsense pH.

Availability of ionic zinc is dependent upon a number of variables including pH, concentration, temperature and compound being tested, and such is a subject of extensive research by solution equilibrium inorganic chemists.²

Consequently, to say that effective zinc lozenges have an objectionable taste that can bias clinical trials is not necessarily factual. The worst possible taste and most bias in effective zinc lozenges results from zinc gluconate in a non-fructose carbohydrate hard candy or tablet base, which was found only in the Weisman trial.⁴ Zinc gluconate in a non-soluble tablet base is about 1/10th as objectionable,¹ while zinc gluconate in a fructose tablet base,³ zinc gluconate-glycine^{11, 12, 13} and zinc acetate^{5,6,7} in a 1:100 dextrose tablet base are each commercially acceptable in taste. However, zinc acetate lozenges are potentially the most effective, use the least zinc, and are the best

tasting. Zinc acetate lozenges also had the least potential for bias due to their pleasant taste, although they had an astringent mouth-feel demonstrating release of zinc ions. A perfect placebo would have been astringent in mouth-feel, perhaps like tannin. Pursuit of a pleasant tasting and effective zinc lozenge has led to both clinical successes and failures, and the large variety of formulations has greatly complicated the analytical picture.

What is next?

As the researcher that originally discovered the effect of ionic zinc from throat lozenges on the duration of common colds, I am very concerned that the statement "zinc is good for colds" released on nearly every U.S. national TV news program, radio station and newspaper (and perhaps also in Europe, Australia and elsewhere) due to loose journalistic interpretation of the Singh and Das report. It is far too broad and too simplistic to be accurate, and it will likely lead to OTC products that will not have the features necessary to shorten colds more than a day, thus 26 years of zinc lozenge research could be lost and perhaps not regained for decades or a century. These features were previously described in my 2009 review.² That review showed dose-response linearity of lozenges by their ionic zinc content on the duration of colds. It showed that reductions in the mean ($P=0.001$) and median ($P=0.004$) durations of common colds were statistically significant and meaningful.

It also showed that the effects of a compressed dextrose tablet containing 18 mg of zinc (zinc acetate dihydrate - 60 mg), glycerol monostearate as a tablet lubricant and peppermint oil on silica gel, which happens to be a 2X homeopathic *Zincum aceticum* formula, is expected to shorten common colds by 7 days. These lozenges released the same amount of ionic zinc as did our 23 mg zinc gluconate lozenges tested in 1984.¹ They are 1.9 cm (¾ inch) diameter and 1.27 cm (1/2 inch) thick tablets which are best produced on heavy production machines like a Stokes 328-2 tablet press. Magnesium stearate was not used as a lubricant due to concerns about concentrated magnesium greatly stimulating rhinovirus replication.^[14]

These zinc acetate lozenges are pleasant tasting and taste like peppermint candy. If these tablets are compressed to a sufficient hardness, they will dissolve in the mouth in about 30 minutes. Fick's laws of membrane permeability show that the amount of a solute absorbed across a membrane is time and concentration dependent. Thirty minutes is a reasonable time for oral dissolution. Also, the dextrose-based formula does not excessively promote saliva production. I suggest that it is now time to focus on this basic formulation and go forward with research on it. I see no necessity to focus on zinc compounds that do not release 100% of their zinc as ionic zinc, or on products that dissolve too fast for significant oral absorption, or on products that contain too little ionic zinc to be effective. From the time of contact with the oral mucosa aspects of Fick's laws, the use of syrups or orally ingested tablets to treat common colds are not advised if large reductions in their duration are desired.

Perhaps there is also a requirement to consider how ionic zinc works in shortening colds and the work of Merluzzi et al. in showing that ionic zinc, but not bound zinc, inhibits the replication of rhinoviruses should be considered vital,^[15] along with the extensive pioneering work of Korant and Butterworth in showing the inhibitor effects of ionic zinc on rhinoviral replication.^{[16], [17],[18], [19], [20], [21], [22], [23]} These articles should give support to the notion that the main effect of ionic zinc in treating common colds is by rhinovirus replication inhibition.

Although I cannot see into the future, I have proposed here what I believe to be the most likely route to successful treatment of common colds, and I hope that new zinc lozenge researchers will follow my advice. If they do follow my advice, they should be able to demonstrate in a coordinated manner the massive benefits of zinc in treating colds in just a few years, rather than in the decades or centuries that I expect from future distortions of the literature if researchers continue to test faulty products and publish those results. Provided with good results, manufactures can follow through with products that will shorten colds by a week in the general public. Then, and only then, can we say that there is a cure for the common cold!

George Eby

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Reply

We thank Dr Eby for his comment on the review as well as giving his expert opinion on the future direction of zinc cold research. Addressing the issue of bias that has occurred in their trial (which has also been highlighted in many other reviews), we want to point out that, though the author (Eby et al) have discussed about the bias resulting from increase drop out in their study in the designated paragraph described above, it should be noted that there are many drawbacks in their trial that make the quality score of a trial poor (please refer to the Cochrane handbook on bias before giving good score to a randomized clinical trial and thus qualifying them for inclusion in a review).

Regarding Dr Eby's description of how zinc acts in the treatment of common cold, it is very true that it is the ionic zinc that plays major role and we hope that authors of future trials will take these issues into account before any meaningful conclusion can be drawn from a particular trial (we have also highlighted these facts in the present review). However, this mechanism might not play important role in the preventive act of zinc for the common cold. But, as zinc has been found in clinical trials to have preventive role for the common cold (zinc also has role in prevention of lower respiratory tract infection/pneumonia, found in a recent Cochrane review), other mechanisms might play role, including enhancement of innate as well as acquired immunity and correction of underlying zinc deficiency. Only future research in this area can answer these questions.

Contributors

Meenu Singh and Rashmi R Das

Comment from Ronald Turner, 1 March 2011

Summary

The authors of this review state that our paper (Turner RB, Cetnarowski WE. Effect of treatment with zinc gluconate or zinc acetate on experimental and natural colds. *Clin Infect Dis* 2000;**31**:1202-1208) was excluded for poor methodology as the study was not randomized.

The study was in fact randomized as stated in the methods section of the paper. If there was confusion on this issue, I would have gladly supplied the original study protocol to the authors of this review.

Ronald Turner

Submitter agrees with default conflict of interest statement:

I certify that I have no affiliations with or involvement in any organization or entity with a financial interest in the subject matter of my feedback.

Reply

This paper by Turner et al, though described as a randomized trial, was excluded because of the poor quality score (not because of randomization only, as commented by the author).

Contributors

Meenu Singh and Rashmi R Das

Are we really sure zinc is an effective treatment for the common cold?, 3 March 2011

Summary

We are concerned regarding a number of aspects of this updated review on the use of Zinc for the treatment and prevention of the common cold[1]. The review concludes that “zinc is beneficial for the common cold in healthy children and adults living in high-income countries.” We are concerned that the threats of potential biases on the review have not been considered carefully enough.

Below we include contour enhanced funnel plots[2] of the two primary treatment outcomes of the review – duration of illness and severity of symptoms (see Figure).

Figure: Funnel plots for the two primary treatment outcomes in the review (http://dl.dropbox.com/u/21306757/funnel_plot_zinc.jpg)

Although these plots contain relatively small numbers of studies (6 and 5 respectively), there is a concerning trend in both graphs that the smaller the trials the increasingly larger the effect sizes observed. Additionally, the most precise studies (towards the top of the plots) have effect sizes which are either 0 or very close to it. One possible explanation, and we acknowledge this is not the only explanation, for such “small study effects” trends is publication bias, which would imply that outcomes from trials with less beneficial/harmful effects have been suppressed. This could be due to the suppression of whole trials which have never been published, or, it could be due to suppression of particular outcomes from certain trials (outcome reporting bias)[3] or a combination of the two. Outcome reporting bias is perhaps a particular concern because we infer from the review that 13 treatment trials (including 1 trial excluded from the statistical overview[4]) were identified but only 10 studies reported on each of the primary outcomes, with fewer trials still reporting both outcomes. From this initial position of potential outcome reporting bias, further selection occurred to include these trials into each meta-analysis (6 and 5 respectively), because the review authors believe the results were not reported in a compatible format, although we suggest that it may well be possible to include at least one further study [5] reporting a dichotomous version of the outcome using previously described methods[6, 7]. Some of these studies excluded from the meta-analysis are discussed in the results section, with at least one study having no effect (Douglas 1987[8] for severity of symptoms). Unusually for a review with small study effects, the studies identified as being industry-sponsored are the largest, but are also those closer to the null effect suggesting much smaller effects. The smaller studies indicating greater effects are noted as medical research foundation sponsored, which may support an alternative explanation to the one we propose.

The authors identified heterogeneity between studies and thus used random effects models in the meta-analysis. As this model gives more weight to the smaller, imprecise, studies (than the fixed effect one), in the presence of funnel plot asymmetry, this has the effect of producing larger effect sizes than the fixed effect alternative; both estimates with their 95% confidence intervals are included on the figure (although both approaches will lead to statistically significant benefits of zinc)[9]. With so few studies, alternative formal approaches to unpicking the heterogeneity, such as meta-regression on dose or dose-duration values would be difficult to undertake.

In the methods section, the authors report making an assessment of publication bias “by examining the funnel plot for asymmetry” and reference a highly cited paper on testing for publication bias[10]. Curiously, there is no further mention or discussion of the results of any assessment for publication bias in the paper. While any formal test on the data is likely to have low power due to the relatively small numbers of studies[6], we believe scrutinising the above funnels is helpful, although the asymmetry is so extreme we initially identified the problem simply by looking at the presented forest plots.

Additionally, we do not understand the author’s statement that “we assessed risk of bias due to selective reporting of outcomes for the study as a whole, rather than for each outcome” For the reasons outlined above, we think some outcome specific consideration would be helpful.

The authors conclude their assessment of “Potential biases in the review process”, that although there was the potential that they may have missed studies referring to the common cold as upper respiratory tract infection, “there are no other obvious sources of potential bias”, we urge the authors to reconsider this statement. In light of the above, and particularly considering the data presented on side effects, we would like to suggest that the conclusions of this review are toned down taking into account the threat of potential reporting biases.

A further issue to have come to light in examining this meta-analysis is that the primary outcome – duration of cold symptoms – is stated to be measured in days. However, the meta-analysis is conducted using the standardised mean difference. If all studies measure the outcome on the same scale (days) it is unclear why the outcome needed standardising and the results would be better presented on the (untransformed) mean difference scale where clinical interpretation is much easier and less strong statistical assumptions are required.

Yours sincerely,

Jaime L Peters, Santiago G Moreno, Bob Phillips, Alex J Sutton.

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Zinc for the common cold (Review)

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Submitter agrees with default conflict of interest statement:

I certify that I have no affiliations with or involvement in any organization or entity with a financial interest in the subject matter of my feedback.

Reply

Thanks for pointing out some important issues related to the review. We also have the same concern regarding the final conclusion (which we have discussed more or less in the review) and that's why no recommendation could presently be made on use of zinc for the common cold. Regarding the publication bias, we agree with the authors (Jaime L Peters, Santiago G Moreno, Bob Phillips, Alex J Sutton) that publication bias could not be ruled out which might also compromise the findings of the present review. But what's important is that, though publication bias alerts to the problem, they do not provide a solution to it. Moreover, funnel plots have their own limitations. So, what Eby et al described above regarding the future direction is more important, as they provide a solution to the problems in the zinc common cold research. But in the next updated version, we will add the funnel plot. Regarding the application of random and/or fixed model effect in the meta-analysis, they have their inherent problems. Last concern regarding inclusion of MD instead of SMD, we have replied it below [actually, the MD for the duration of cold is -1.48 (around 2 days)].

Contributors

Meenu Singh and Rashmi R Das

Comment from Christopher Cates, 7 March 2011

Summary

Dear Sir,

I have not personally started taking zinc tablets for the common cold, as I do not think the average answer tells me enough to justify a change in practice (too much heterogeneity and a very wide predictive interval [-4.2 to 1.2 days when analyzed as mean difference]. See method in: Riley RD, Higgins JPT, Deeks JJ. Interpretation of random effects meta-analyses. *BMJ*. 2011;342:d549). Prasad seems to me to be measuring something different to the other studies, as the mean difference of 3 days in these studies is incompatible with all the other study results?

It would be easier for readers to understand these results if they were presented as a mean difference in days (rather than SMD). Surely the overall average result is of limited usefulness when there is such diversity between the study results?

Yours faithfully,
Chris Cates
MA FRCGP

Submitter agrees with default conflict of interest statement:

I certify that I have no affiliations with or involvement in any organization or entity with a financial interest in the subject matter of my feedback.

Reply

The mean difference (in days) for the duration of cold is -1.48 (around 2 days). We agree with the authors regarding the heterogeneity of results, as a result of which no recommendation was possible about zinc for the common cold (already described in conclusion).

Contributors

Meenu Singh and Rashmi R Das

Comment from Catherine McIlwain, 14 March 2011

Summary

I'd like to request that one line of text ("Zinc inhibits rhinoviral replication") in the plain language summary be restated in simpler terms. That phrasing resulted in quite a few comments from consumers who don't understand virus replication.

If you are amenable to a change, I would recommend using the word 'virus' instead of 'rhinoviral' throughout the plain language summary. In addition, would it be acceptable to change 'rhinoviral replication' to 'the spread of the virus' only in the plain language summary, of course.

Catherine McIlwain

Submitter agrees with default conflict of interest statement:

I certify that I have no affiliations with or involvement in any organization or entity with a financial interest in the subject matter of my feedback.

Reply

No. replication and spread of virus does not mean necessarily the same thing. But we can say it as follows: zinc inhibits replication of common cold virus.

Contributors

Meenu Singh and Rashmi R Das

The zinc for the common cold review by Singh and Das has a number of problems which should be considered when the review is next time updated, 5 September 2011

Summary

1) Search of the studies:

Eby and Halcomb (2006) reported a randomized double-blind placebo-controlled trial on zinc for the common cold [1], which is missing from the review. The trial is included in MEDLINE (PMID: 16454145) and Singh and Das should have found it and listed among the trials requiring an assessment.

2) Extraction of data:

Singh and Das describe that "The lead review author (MS) entered data directly into Review Manager. An independent coder verified accuracy of data entry". However, looking at their Analysis 1.1 led me to wonder how can they claim that the findings of the Petrus (1998) trial were non-significant (the 95% CI covering the "no effect"), given that Petrus (1998 p. 600) wrote that "t-test showed that the mean duration of all symptoms was significantly lower in the zinc group (3.8±0.2 days) than in the placebo group (5.1±0.4 days)(P=0.008)". In their Analysis 1.1, Singh and Das give the mean duration of colds in the zinc group as 4.4 days, and not as the 3.8 days reported by Petrus (above). The value of 4.4 days is given in the Petrus (1998) Table II as the overall mean duration of colds, i.e. the mean for all zinc and placebo participants combined, but Table II also gives the 3.8 days for the duration of colds in the zinc group. In their paper, Petrus (1998) gives the accuracy of the mean as the SE (standard error), whereas the Review Manager needs the SD (standard deviation). The SE values reported by Petrus (1998) are highly inaccurate (above), yet Singh and Das calculated the corresponding SD estimates from them. To get the accurate Petrus (1998) trial results, I contacted the statistician of the group and got their results: 3.797 (SD 1.630) days in the zinc group and 5.106 (SD 2.955) in the placebo group (Ken Lawson, email 4 Mar 2009). The Petrus (1998) values in Analysis 1.1 should be replaced with these correct and accurate values.

3) The characteristics of included studies table:

In the Characteristics of included studies table, Singh and Das write about the Al-Nakib (1987) trial that there was "unclear risk" for the item "incomplete outcome data addressed?". However, Singh and Das write that "there were no drop-outs or withdrawals". Lack of drop-outs does not justify their judgment ("unclear risk"). Furthermore, Singh and Das state that in the Al-Nakib trial there is "high risk" for the item "free of selective reporting?". The statement that there is "high risk" calls for justification, whereas none is given. Furthermore, Singh and Das list six outcomes for the Al-Nakib (1987) trial, yet only one of them is relevant to the review: "the severity of symptoms". However, I cannot see this outcome in any of their Analysis tables. The outcome section of the included studies table should list only those outcomes that are used in the review. Furthermore, it would help the reader if the included studies table describes in which Analysis the values of the outcomes are presented. Singh and Das state that in the Smith (1987) trial there is "low risk" for the item "incomplete outcome data addressed?". Smith started with 176 participants and reported the results for only 110 participants, which means that they reported data for only 62% of the initial participants. In their Methods section, Singh and Das write that "we considered that incomplete outcome data had been adequately addressed if 85% or more of the participants were included in the analysis, or if less than 85% were included but

adequate steps were taken to ensure or demonstrate that this did not bias the results.” In their included studies table, Singh and Das do not describe why the analysis of 62% of initial participants is acceptable for the Smith (1987) trial although they give the limit of 85% in their Methods. Stating that the Smith (1987) trial has “low risk” with the 38% drop-out rate, and the Al-Nakib (1987) trial has “unclear risk” with no drop-outs (above) is puzzling. Singh and Das use an inclusion criterion “randomized controlled trials”. Weismann (1990) did not report the method of allocation in their trial report. Nevertheless, Singh and Das describe in their included studies table the Weismann (1990) trial: “Methods: randomized trial”. Since their report did not describe the method of allocation, I contacted Kaare Weismann, who wrote to me “It was a consecutive allocated study with the same number of patient in the two groups” (email 2 Jul 2010). Thus, the Weismann (1990) trial was not randomized. Given their inclusion criteria, Singh and Das should exclude the Weismann trial or they should re-write the inclusion criteria so that they also include pseudo-randomized trials which have used, for example, alternative allocation. Furthermore, Singh and Das state that there is “unclear risk” for the item “allocation concealment?” in the Weismann (1990) trial, even though the trial was double blind. The term double-blind means that both the patients and researchers are unaware of the type of treatment until the trial is concluded. Consequently, neither of them can know to which group a patient had been allocated. Thus, double-blind means that there must have been allocation concealment. Otherwise the patients and researchers could not remain blind after randomization. This same error is seen in the description of the Al-Nakib (1987) and Petrus (1998) trials, which also were double-blind trials. As a consequence of this error, Figure 1 gives an impression that several studies were methodologically less satisfactory than they actually were. More details of the trials should be given in the included studies table. For example, in their “implications for practice”, Singh and Das state that “We could not find any trials conducted in low-income countries, so our results cannot be applied to people living in low-income countries.” However, three trials by Kurugol (2006a, 2006b, 2007) were carried out in Turkey, and one trial by Vakili (2009) was carried out in Iran. These are low-income countries. According to World Bank statistics, the GDP per capita in Turkey and Iran is 80% and 90% lower than in Germany, as an example. Thus, the above statement is false although there are countries which are much poorer than Turkey and Iran. To help the reader to understand the contexts of the trials, it would be useful to describe the country and the settings of the trials. Such information affects the generalization of the findings. Studies in Turkey and Iran cannot be directly extrapolated, for example, to the western countries.

4) The characteristics of excluded studies table:

In the Characteristics of excluded studies table, Singh and Das comment on the Eby (1984) trial: “Intention-to-treat analyses were not conducted; analyses were only conducted on a subset of those originally enrolled in the trial.” However, this is also true for the Smith (1987) trial, which included only 62% of the initial participants in the analysis (above). Eby (1984 p. 20-21) described: “Of 146 original volunteers, 120 subjects returned reports. Initially, to use as much of the data as possible, we analyzed the 80 complete reports from 108 subjects who had been ill for 10 days or less at the start of treatment. ... this report is restricted to those 65 subjects who reported being ill for 3 days or less before starting the experiment.” Singh and Das use an inclusion criterion “interventions commenced within three days of participants developing common cold symptoms”. Given such a criterion, Eby’s post-randomization restriction to 65 subjects who were ill for 3 days or less before the treatment started is relevant data. In any case, Singh and Das should treat Eby (1984) and Smith (1987) trials consistently, so that both are included or excluded on the basis of the high rate of participants not included in the analysis. Singh and Das further criticise the Eby (1984) trial: “The trial relied on subjective assessment of symptoms by subjects.” However, this applies to essentially all zinc and common cold studies. In evidence-based medicine, the subjective symptoms are most essential outcomes. Subjective symptoms determine whether a patient goes to work or school, stays at home, or visits a physician. Double-blinding prevents systematic bias in the subjective assessment of symptoms, and therefore “subjective” per se cannot cause bias in a double-blind trial. Furthermore, if Singh and Das consider that “subjective assessment” is a basis to exclude the Eby (1984) trial, they should apply the same criterion to the other trials. Singh and Das also comment on the Eby (1984) trial: “Inclusion criteria were not adequately addressed and therefore there may have been potential for selection bias to occur.” In randomized trials, the primary concern is the comparability of trial arms, so that there are no systematic differences that could lead to bias. All randomized trials use inclusion criteria of some kind, but that has nothing to do with the question whether the trial arms are comparable. Inclusion criteria are relevant when we consider the possibility to generalize the results, but not when considering the internal validity of a trial. Finally, Singh and Das conclude their criticism of the Eby (1984) trial: “In addition, no information was provided on how allocation to treatment groups was concealed, the power of the study was not stated and viral studies were not conducted”. First, in most other zinc and common cold studies there is no information about how allocation was concealed (i.e. how blinding was maintained). Second, statistical power is relevant when planning a trial, but not after the trial is concluded, since the confidence interval gives the same information. Third, given that the primary goal in evidence-based medicine is to find out whether a treatment has clinically important effects, viral studies are not relevant. All these issues are missing in most of the zinc and common cold studies. Thus, if Singh and Das consider that these arguments give a sound basis to exclude the Eby trial, they should apply the same criteria also to the other trials. In the Characteristics of excluded studies table, Singh and Das comment on the Turner (2000) trial: “Poor methodological quality. Not a randomised trial”. However, Turner writes “Subjects who met the criteria for randomization to treatment were randomly assigned to 1 of the 4 treatments in accordance with the drug-randomization code” (p. 1202), [for induced colds:] “Subjects were randomized to receive study medication 24 h after challenge if they had a total daily symptom score ≥ 3 ” (p. 1203), [for natural colds:] “Subjects who presented to the study sites with a common-cold illness of ≤ 1 calendar day’s duration (effectively 36 h), reported ≥ 2 different symptoms, and had a total symptom score of ≥ 2 were randomized to receive 1 of the 3 treatments” (p. 1203). Thus, the statement by Singh and Das is false, unless they have information that disproves the text of the Turner (2000) report. In such a case, they should present their evidence. The Turner (2000) trial was reported as a randomized placebo-controlled double-blind study, and there is no basis to claim that it was of “poor methodological quality”.

5) Different methods of administering zinc should be analyzed separately:

The majority of the zinc trials examined zinc lozenges in the western countries. Three trials by Kurugol (2006a, 2006b, 2007) and one trial by Vakili (2009) administered zinc as syrup or tablets; however, all these trials were carried out in low-income countries, Turkey and Iran.

Thus, it is possible that the benefit of zinc supplementation in these trials is caused by biological mechanisms that are different from the mechanisms of the zinc lozenges, which are intended to be dissolved slowly in the mouth. The daily dose of zinc in the Kurugol and Vakili studies varied from 10 to 30 mg per day, whereas the total daily dose of zinc in the zinc lozenge studies varied from 30 to 207 mg per day [2]. Thus, it is possible, or probable, that the benefits of the low dose zinc supplementation found by Kurugol and Vakili are explained by a sub-optimal dietary intake of zinc by children in Turkey and Iran. In contrast, it is possible that high dose zinc is needed in the lozenges to get benefit from them. Although Singh and Das restrict their systematic review to tablets, syrup and lozenges, they should also take a look at the other zinc literature. A few studies have examined the use of nasal administration of zinc to treat colds and found significant benefit [3,4]. Still, patients should not be exposed to intranasal zinc, since there are cases of anosmia caused by such a therapy [5]. Nevertheless, the benefit of local application of zinc to the nose indicates that the effect of zinc lozenges may be caused by local effects in the mouth-throat region, instead of systemic effects such as those caused by the ingestion of tablets and syrup. Therefore it is inappropriate to pool the tablet and syrup trials with the lozenge trials. This is a good example of the apples and oranges problem.

6) The duration of the common cold should not be dichotomized:

Singh and Das present three tables which show “number of participants symptomatic after N days of treatment”, N being 3, 5 and 7. Dichotomization of continuous variables has been criticized [6]. Moreover, there is no need to dichotomize the duration of colds when analyzing the zinc lozenge trials. Although several trials did not report the mean and SD for the duration of colds in the trial arms, all of them reported data that makes it possible to calculate the mean and SD for cold duration [2]. The use of continuous outcome for common cold duration would also simplify the review as three redundant tables can be removed.

7) Duration of the common cold should be normalized so that placebo groups have length 100%:

There is substantial variation in the duration of colds in the placebo groups of the zinc lozenge trials, from 5.1 days to 9.0 days and 10.8 days [2]. Although part of this variation is evidently caused by random variation, it is also caused by actual variations in the severity of disease in different patient groups and in differences in outcome definitions. Therefore, the relative effect of zinc on the common cold duration should be calculated in percentages, because the relative effect partly adjusts for the variations between patient groups and outcome definitions.

For example, if a 6-day cold is shortened by 1 day, it is not equivalent to a 1-day cold being shortened by the same amount although both differences are equal in absolute units. Consequently, it is much more reasonable to calculate the relative effect of zinc, so that a 6-day cold shortened by 2 days and a 1-day cold shortened by 0.33 days both correspond to an equivalent 33% reduction. Calculating the relative effect corresponds to the normalization of all control groups to an episode duration of one unit or 100%. Therefore, in our Cochrane review on vitamin C and the common cold we calculate the relative effect [7]. The use of relative effect in the analysis of common cold duration corresponds to using the risk ratio in the analysis of binary data. In their Analysis 1.1, Singh and Das pool the results by the SMD method, which means normalizing the duration by the SD (i.e. 1 unit in the scale corresponds to the SD of each study). However, using such a scale (SD units) is very difficult for an ordinary reader to understand. In their abstract,, Singh and Das write: “Intake of zinc is associated with a significant reduction in the duration (standardised mean difference (SMD) -0.97)”. However, reporting should always give the unit of the measurement. In the SMD method, the unit is the SD unit. Thus, the above sentence should be re-written more accurately: “zinc shortened the duration of colds by 0.97 SD units”. Such accurate reporting would reveal the main problem of the SMD procedure: what does the SD-unit mean? I pooled the results of three large-dose zinc acetate lozenge trials and I found that “zinc shortened the duration of colds by 42%” [2], which is easy to understand. Most people can form an opinion whether 42% is small or large, but few people can form an opinion whether 0.97 SD units is small or large, or whether it is more or less than 42%. Thus, a relative scale would make the analysis of zinc trials easier to understand for the ordinary readers compared with the SD scale. The Cochrane Handbook comments (9.2.3.2): “The standardized mean difference [SMD] is used as a summary statistic in meta-analysis when the studies all assess the same outcome but measure it in a variety of ways (for example, all studies measure depression but they use different psychometric scales).” Thus, the SMD can be useful, for example, in psychiatry. In the case of common cold duration, the relative effect in percentages is much easier for readers.

8) Subgroup analysis should be carried out:

Singh and Das write in the Background section that a “significant correlation between total daily dosages of positively charged zinc species and a reduction in the mean duration of common colds” has been reported. Therefore, the daily dose of zinc should be considered in the statistical analysis. However, in their Result section Singh and Das claim that “subgroup analysis was not possible as there were not enough studies for each variable.” This is not correct. As noted above, there is a 6-fold variation in the total zinc dose (30 to 207 mg per day [2]) in the zinc lozenge studies. Given that the results of the zinc lozenge trials diverge so that some found no effect whereas some others found highly significant benefit, the relation between the dose and effect should be analyzed. Dose-response relation is a basic concept in pharmacology. I analyzed 13 zinc lozenge trials and divided them into three subgroups on the basis of the total daily dose of zinc and the type of lozenge [2]. None of five trials with the lowest doses of zinc found benefit of the lozenge, suggesting that they may have been using too low a dose. In the high-dose trials, greater benefit was seen in three trials with zinc acetate, and smaller benefit in five non-acetate trials [2]. Further research should focus, in particular, on high doses of zinc acetate (providing 80-90 mg/day of zinc) [2]. Thus, subgroup analysis is possible and it indicates a path to research that is needed. The syrup and tablet studies with children in the low-income countries should be presented as a separate group, on a separate Analysis table.

9) Pooling the adverse effects of all zinc trials is unsound:

Eby has pointed out that the adverse effects of zinc lozenges, such as bad taste, can be explained largely by the differences in the composition of the lozenges [8-10]. In their Discussion, Singh and Das acknowledge this possibility: “the increased incidence of bad taste and nausea ... may have been related to the use of different ligands (gluconate, acetate) rather than to zinc itself.” In addition, it is obvious that dissolving a high zinc dose lozenge slowly in the mouth causes different adverse effects compared with ingesting a low zinc dose tablet or syrup straight to the stomach. Nevertheless, Singh and Das combine the adverse effects of the tablet and the zinc lozenge trials together

as if they could estimate a “universal adverse effect of zinc” in the dose range of 15 to 192 mg per day. Nevertheless, the lack of “mouth irritation” by zinc syrup in the Kurugol studies (Analysis 2.19) is fully uninformative for a reader who is interested in the possible adverse effects of zinc lozenges. Thus, it would be much more informative to summarize the adverse effects as text, instead of pooling the results of such different trials. In the most recent zinc acetate lozenge trial, there were no significant differences between the zinc and placebo groups in the occurrence of adverse effects although the daily dose was 92 mg (Prasad 2008). Thus, it seems possible to formulate zinc lozenges that have minimal adverse effects. Furthermore, a patient suffering from acute adverse effects such as bad taste can simply stop taking the lozenges, whereas those who don't suffer from such adverse effects could benefit from the lozenges. Although Singh and Das restrict their systematic review to treating the common cold, they should also take a look at other zinc literature for information about zinc safety. For certain patients, zinc has been administered at high doses, 150 mg/day, for therapeutic purposes for months [2,11-12]. On the basis of such long-term studies with high zinc doses, there does not seem to be any basis for assuming that treating the common cold for a week with high doses of zinc (80-90 mg/day) in the form of lozenges might cause unanticipated harm.

10) Credit should be given to earlier work on the same topic:

In their Introduction, Singh and Das write “The last review of all available RCTs of zinc for the common cold was published in 1999”, which is erroneous. Although it is not reasonable to discuss in detail all the earlier literature on the topic, the main reviews should be cited and briefly commented. Jackson's [13] and Caruso's [14] systematic reviews on zinc and the common cold were published after 1999. In the Discussion section, RevMan proposes a subtitle “Agreements and disagreements with other studies or reviews”. Evidently, the same issue can be discussed under some other title. In any case, it would be important for Singh and Das to describe to what extent their review agrees and disagrees with the earlier reviews, such as [13,14]. If the conclusions do not differ from earlier reviews, then a new review does not increase our understanding about the topic. If the conclusions are different, then the reasons for the differences should be briefly discussed.

Harri Hemilä

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Submitter agrees with default conflict of interest statement: I certify that I have no affiliations with or involvement in any organization or entity with a financial interest in the subject matter of my feedback.

Reply

- 1) The Eby and Halcomb (2006) trial has been mentioned under "excluded studies" in the updated review.
- 2) The Petrus (1998) values in Analysis 1.1 has been replaced with these correct and accurate values in this updated review.
- 3) About the Al-Nakib (1987) trial, for the item “incomplete outcome data addressed?”, the assessment has been changed into “low risk” in the characteristics of study table. Again, for the Al-Nakib trial, “high risk” for “free of selective reporting?” has been justified in the updated review. Furthermore, regarding the “the severity of symptoms” outcome reported in Al-Nakib (1987) trial, it was not possible to analyse

the data, as the same was not available and also the trial was conducted almost 26 years back. This might be the reason that, no meta-analysis till date has been able to pool this trial result. Regarding the Smith (1987) trial, in the updated review it has been changed to "high risk" for the item "incomplete outcome data addressed?". Regarding the inclusion of Smith (1987) trial in the meta-analysis, please go through the paragraph "dealing with the missing data". Regarding the inclusion of Weismann (1990) trial, it is a randomized trial, and previous meta-analyses (Jackson et al 2000, Hemilä 2011) has handled this as a randomized trial in their analyses. So, there is no point in excluding this trial or labeling this as a "pseudo-randomized trial". Regarding, contacting the authors, we have already mentioned that we did not try to contact authors of the trials conducted 10 years back. Infact, this trial was conducted almost 20 years back. More details of the Weismann (1990) trial, Al-Nakib (1987) and Petrus (1998) trial have been given in the included studies table in the updated review. The "implications for practice" section has been modified and the sentence "We could not find any trials conducted in low-income countries, so our results cannot be applied to people living in low-income countries" has been removed.

4) Regarding the exclusion of Eby trial (1984), please go through the inclusion criteria and dealing with the missing data section in the updated review. We have removed the points like "subjective assessment" and "viral studies were not conducted", as they are not stronger criterion to exclude the Eby (1984) trial. The other points made to exclude the trial are valid and >50% loss to follow up in any trial is not at all acceptable, even if the authors have tried to maintain the integrity of the data. So, we stand on our decision to exclude the Eby trial. Regarding the Turner (2000) trial, it has been included in the updated review.

5) Different methods of administering zinc have been analyzed separately in the updated review.

6) Regarding the duration of the common cold should not be dichotomized, we did not make any change. They are actually not visible, if someone does not really want to visualize them.

7) The duration of the common cold has been normalized so that the placebo group has length 100%. The changes have been made in the updated review.

8) Subgroup analysis has been carried out in the updated review.

9) Though pooling the adverse effects of all zinc trials is unsound, we still reported it as we thought it would be useful and is part of any systematic review. There is no clear cut mechanism postulated and all are assumptions how adverse events occur with zinc lozenges.

10) In the updated version, we have discussed about the earlier reviews by Jackson et al [2000] and Caruso [2007] under the subtitle "Agreements and disagreements with other studies or reviews". Please go through them.

Contributors

Meenu Singh and Rashmi R Das

Zinc for the common cold feedback, 8 April 2014

Summary

Were the Hirt and Mossad study that tested intranasal administration excluded from the analysis because of the route of administration? Or were there other reasons as well?

David Riley

I agree with the conflict of interest statement below:

I certify that I have no affiliations with or involvement in any organization or entity with a financial interest in the subject matter of my feedback.

Reply

We thank David Riley for the feedback on our paper. The Hirt and Mossad study that tested intranasal administration was excluded from the analysis because of the route of administration.

Regards,
Dr Rashmi Ranjan and Dr Meenu Singh.

Contributors

Meenu Singh and Rashmi R Das

WHAT'S NEW

Date	Event	Description
17 September 2016	Amended	This Cochrane Review was withdrawn in April 2015, and this withdrawal notice was updated in September 2016. See Published notes.

HISTORY

Protocol first published: Issue 1, 1999

Review first published: Issue 2, 1999

Date	Event	Description
30 April 2015	Amended	This review was withdrawn due to concerns raised via the feedback mechanism regarding the calculation and analysis of data in the review in April 2015. Whilst it is not unusual for reviews to be withdrawn, the editorial group took the view that it would be better to take a cautious approach and explore the source and calculation of data used in the analysis in more detail, rather than keep the review on the Cochrane Database of Systematic Reviews for the time being.
29 July 2014	Feedback has been incorporated	Feedback comment added to the review (number 7)
11 December 2013	Amended	Authors have readdressed their reply to the Feedback comment (number 6).
18 October 2013	Amended	Changes made in response to comments received from the Cochrane Editorial Unit
18 January 2013	New citation required but conclusions have not changed	Conclusion regarding the recommendation of zinc for the common cold remains unchanged.
18 January 2013	New search has been performed	Searches updated. Three new trials were included in this updated review (Turner 2000a;Turner 2000b;Turner 2000c) and two new trials were excluded (Eby 2006;Kartasurya 2012).
23 March 2012	Amended	Typographical errors to feedback comment amended.
9 January 2012	Feedback has been incorporated	Feedback incorporated.
7 September 2011	Amended	Authors' replies to Feedback comments added to review.
8 August 2011	Feedback has been incorporated	Feedback comments added to review.
17 February 2011	Amended	'Summary of findings' table amended.
29 June 2010	New citation required and conclusions have changed	A new team of review authors have updated this previously withdrawn review. In the previous review, the role of zinc for the common cold was inconclusive, as the results could not be pooled due to the paucity of trials measuring clinically relevant outcomes. In this updated review we were able to undertake pooling of results due to the addition of new trials and we found that zinc is beneficial for the common cold.

Date	Event	Description
1 June 2010	New search has been performed	Searches conducted. We included eight new trials (Kurugol 2006a;Kurugol 2006b;Kurugol 2007;Macknin 1998;Petrus 1998;Prasad 2000;Prasad 2008;Vakili 2009) and excluded three new trials (McElroy 2003;Turner 2000a;Veverka 2009) in this update.
17 June 2008	Amended	Converted to new review format.
4 May 2006	Amended	Review withdrawn.
24 February 1999	New search has been performed	Review first published Issue 2, 1999.

SOURCES OF SUPPORT

Internal sources

- Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, India.
- All India Institute of Medical Sciences (AIIMS), New Delhi, India.

External sources

- No sources of support supplied