Concerns about unattributed copying of text and data, and about numerous other problems in the Cochrane review "Zinc for the Common Cold" by Singh M, Das RR (2013)

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This is a comment on:
Singh M, Das RR: Zinc for the common cold.
Cochrane Database Syst Rev **2013**, CD001364.
http://www.ncbi.nlm.nih.gov/pubmed/23775705
http://dx.doi.org/10.1002/14651858.CD001364.pub4

My **Feedback (2011)**, which commented on the previous version of
Cochrane Review on "Zinc for the Common Cold"by Singh M, Das RR **(2011)** is available at:
http://hdl.handle.net/10138/39188
http://www.mv.helsinki.fi/home/hemila/H32P.pdf
A summary of the Feedback (2011) is available at PubMed Commons:
http://www.ncbi.nlm.nih.gov/pubmed/21328251#cm21328251_7867

Hereafter the Cochrane reviews by Singh M, Das RR (2011) and by Singh M, Das RR (2013) are respectively referred to as
Singh and Das (2011) and
Singh and Das (2013) in this document.

Hemilä (2011) refers to the Review on zinc and the common cold by Hemilä**.**

Feedback (2011) refers to the Feedback written by Hemilä (see above), commenting on Singh and Das (2011).

References to other publications in this document are given as the first author (year). The reference list gives the whole author lists for the cited papers.

Italics is used to indicate texts by Singh and Das (2011) and Singh and Das (2013).

This is the second Cochrane review which I have found to be significantly misleading to readers.

The first one was Cochrane review on “vitamin C for asthma”. In 2009, I pointed out severe errors in the extraction of data and in data analysis. For example, in one comparison that Cochrane review used un-paired t-test and calculated P = 0.42, whereas the correct calculation would have used paired t-test and would have calculated P = 0.00012 from the same data. Thus, the errors that I pointed out were not minor. Most of the errors were already present in the first version of that Cochrane review, which was published in 2001. Thus, that review misled readers from 2001 until 2013, at which time it was withdrawn. However, the editors of the journal have not informed the readers about the errors in that review.
See the details of the problems in Cochrane review “vitamin C and asthma” in the following documents:
http://hdl.handle.net/10138/38500 (Comments in 2009)
http://hdl.handle.net/10138/40816 (Comments in 2013)

Thus, the Cochrane review “Zinc for the common cold” by Singh and Das (2013) is not the only Cochrane review that has considerably misled its readers.

> ... Since then I never pay any attention to anything by ‘experts.’
> I calculate everything myself.
> I’ll never make that mistake again, reading the experts’ opinions.
> Of course, you only live one life, and you make all your mistakes, and learn what not to do, and that’s the end of you.
>
> Richard Feinman, 1985
> “Surely You're Joking, Mr. Feinman”

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Unattributed copying of means (SDs) for the duration of colds

In the Results section, Singh and Das (2013, p. 12) wrote that:

> *"Fourteen trials… reported the duration of symptoms. Among these,*
> *five trials have provided the original data…*
> *The mean and SD were calculated either from the survival curves (Macknin 1998; Mossad 1996; Prasad 2000; Smith 1989; Turner 2000a; Turner 2000b; Turner 2000c; Weismann 1990)*
> *or from t/P value (Douglas 1987; Godfrey 1992) reported in other trials"*

Thus, 5 studies reported means and SDs, which could be directly extracted for the Cochrane review by Singh and Das (2013). The remaining 10 studies reported survival curves (n=8) or t/P-values (n=2).

Singh and Das (2013) state that, for the 10 studies with missing means (SDs):

> *"The mean and SD were calculated either from the survival curves... or from t/P value"* (Results, p. 12)
>
> *"In trials with missing statistics (such as SDs ...), we calculated the data from the available information"* (Methods, p. 10, Singh and Das 2013),

In the "Discussion" section Singh and Das emphasize that the imputed mean (SD) values were based on their own original work:

> *"We extracted data from survival curves or t/P values given in studies that did not provide original data"* (Discussion, p. 23, Singh and Das 2013).

However, in their "Methods section", Singh and Das (2013) do not give any description of how the imputations of means (SDs) were actually carried out. Thus, the imputations for the 10 studies with missing means (SDs) are not transparent. Measurements of published survival curves (recovery time from colds [in days] curves) to calculate the number of participants at the specific day of recovery involves inaccuracies when the number of patients is large such as in the study by Macknin (1998), which had 247 patients. Furthermore, in many instances the curves did not continue until all patients had recovered. Therefore, imputation of individual level duration for some patients is needed, without these imputations the mean (SD) cannot be estimated from the survival curves. Thus, calculations of mean (SD) from published curves involve inaccuracies and subjective decisions.

Previously, Hemilä (2011) calculated the mean (SD) values for zinc lozenge trials from published curves and from t/P-values. The imputations are reported in the Supplementary Files at PMC:
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3136969
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3136969/bin/TORMJ-5-51_SD1.zip

Supplementary File 3 of the review by Hemilä (2011) describes the measurements of the curves and the imputations made about missing common cold durations for patients who had not recovered by the end of the curve. That file also includes 2 sensitivity analyses, carried out to test the influences of different imputation approaches (page ii, File 3, Hemilä 2011).

The mean (SD) values imputed and published by Hemilä (2011) are shown on page 6 of this document, from p. xiv, Supplementary File 2.

The mean (SD) values used in the Singh and Das (2013) review are shown on page 7 of this document. All the mean (SD) values within the red rectangles in Analysis 1.1 (also published as Fig. 3), of Singh and Das (2013) are identical with those previously imputed by Hemilä (2011), compare the tables on pp. 6 and 7 of this document.

In the review by Hemilä (2011), the estimation of means (SDs) for 5 studies required the imputation of individual duration for certain patients. In the study by Mossad (1996), cold duration was imputed for 4 patients (4% of 99), in the study by Weismann (1990) imputations were made for 8 patients (6% of 130), in the study by Macknin (1998) imputations were made for 10 patients (4% of 247), in the study by Turner (2000) for 26 patients (9% of 279), and in the study by Smith (1989) imputations were made for 53 patients (48% of 110). This makes a total of 101 patients that required imputation for individual duration in the 5 studies.

Imputing cold duration for patients who had missing duration involves a substantial subjective element in a calculation. In particular, when 48% of common cold durations had to be imputed in the study by Smith (1989), it is not plausible that Singh and Das (2013) independently reached mean (SD) values for both zinc and placebo groups that are identical to 3 digit accuracy with the means (SDs) imputed 2 years earlier by Hemilä (2011), compare the tables on pp. 6 and 7 of this document. The probability of such an event occurring purely by chance would be vanishingly small.

Singh and Das (2013) do not cite Hemilä (2011) as the source of their imputed mean (SD) values, instead they claim that:

> *"The mean and SD were calculated either from the survival curves… or from t/P value",*
>
> *"In trials with missing statistics (such as SDs), we calculated the data from the available information",* and …
>
> *"We extracted data from survival curves or t/P values given in studies that did not provide original data".*

Yellow is added to emphasize that Singh and Das (2013) strongly imply that the imputed mean (SD) values is the result of their own original work.

Furthermore, in the Supplementary File 2, on page xiv of my review (Hemilä 2011), I used a notation that the Godfrey (1992) and Douglas (1987) mean (SD) values were calculated "from t/P", which is not a common notation, see the footnote in the table on p. 6 of this document. That notation is also copied by Singh and Das (2013).

It is thus not plausible that Singh and Das (2013) independently calculated the mean (SD) values they show in their Analysis 1.1 (also published as Fig. 3 in Singh and Das 2013).

In Comment 6 of my Feedback (2011) on Singh and Das (2011), I wrote that:
"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".

In addition, Singh and Das (2013) had also read the review by Hemilä (2011) as indicated by the copying of parts of the Hemilä (2011) review to their Cochrane review zinc for the common cold (Singh and Das 2013), see pp. 12 and 14 of this document.

The mean (SD) values imputed by Hemilä (2011) and the transformation to %-units

This table was published as page xiv in Supplementary File 2:

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3136969/bin/TORMJ-5-51_SD1.zip
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3136969

The values on the right side are used in Fig. (**1**).

These values are calculated by dividing the figures on the left side with the duration in the placebo group on the left side.

This leads to percentage scale so that all differences between Zn and placebo groups are percentages.

Trial	Duration is Based on:	Duration of Colds (Days)				Duration of Colds (% of Placebo)			
		Zn		Placebo		Zn		Placebo	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD
Eby 1984 [7]	Fig	3.92	2.61	7.54	3.18	52	35	100	42
Smith 1989 [19]	Fig	7.23	2.29	7.57	3.01	96	30	100	40
Godfrey 1992 [20]	from t	4.86	2.70	6.13	2.70	79	44	100	44
Prasad 2008 [21]	Report	4.00	1.04	7.12	1.26	56	15	100	18
Petrus 1998 [22]	Report	3.80	1.63	5.10	2.96	75	32	100	58
Turner A 2000 [23]	Fig	7.41	3.88	7.55	3.96	98	51	100	52
Mossad 1996 [24]	Fig	5.20	2.83	9.38	5.47	55	30	100	58
Prasad 2000 [25]	Report+Fig	4.50	1.60	8.10	1.80	56	20	100	22
Turner B 2000 [23]	Fig	6.89	3.35	7.55	3.96	91	44	100	52
Douglas 1987 [26]	from P	12.10	9.80	7.70	9.80	157	127	100	127
Macknin 1998 [27]	Fig	9.37	4.81	9.50	4.53	99	51	100	48
Weismann 1990 [28]	Fig	7.16	2.62	6.72	2.29	107	39	100	34
Turner C 2000 [23]	Fig	7.90	4.25	7.55	3.96	105	56	100	52

[a] "Report" indicates that the mean and SD were reported in the study report.

"from t/P" indicates that the t or P was reported and the corresponding SD was calculated from it.

"Fig" indicates that the results were reported as a survival curve: see Table S3 for the calculation of the mean and SD.

Analysis 1.1. (also Fig. 3) in Singh and Das (2013)

Analysis 1.1. Comparison 1 Zinc versus placebo, Outcome 1 Duration of cold symptoms.

Review: Zinc for the common cold

Comparison: 1 Zinc versus placebo

Outcome: 1 Duration of cold symptoms

The rectangles indicate the data that has been copied from Hemilä (2011), see **p. 6** of this document.

Study or subgroup	Zinc N	Zinc Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Douglas 1987	33	12. (9.8)	30	7. (9.8)		1.7 %	4.40 [-0.45, 9.25]
Godfrey 1992	35	4.8 (2.7)	38	6.1 (2.7)		7.1 %	-1.27 [-2.51, -0.03]
Kurugol 2006a	97	4.7 (0.8)	97	5.3 (0.7)		9.1 %	-0.60 [-0.81, -0.39]
Kurugol 2007	60	5.5 (1.97)	60	6.5 (1.97)		8.3 %	-1.00 [-1.70, -0.30]
Macknin 1998	123	9.37 (4.81)	124	9.5 (4.53)		7.3 %	-0.13 [-1.30, 1.04]
Mossad 1996	49	5.2 (2.83)	50	9.38 (5.47)		5.9 %	-4.18 [-5.89, -2.47]
Petrus 1998	52	4.4 (1.4)	49	5.1 (2.8)		8.0 %	-0.70 [-1.57, 0.17]
Prasad 2000	25	4.5 (1.6)	23	8.1 (1.8)		7.8 %	-3.60 [-4.57, -2.63]
Prasad 2008	25	4 (1.04)	25	7.12 (1.26)		8.5 %	-3.12 [-3.76, -2.48]
Smith 1989	57	7.23 (2.29)	53	7.57 (3.01)		7.7 %	-0.34 [-1.35, 0.67]
Turner 2000a	68	7.41 (3.88)	71	7.55 (3.96)		6.9 %	-0.14 [-1.44, 1.16]
Turner 2000b	68	6.89 (3.35)	71	7.55 (3.96)		7.1 %	-0.66 [-1.88, 0.56]
Turner 2000c	72	7.9 (4.25)	71	7.55 (3.96)		6.8 %	0.35 [-1.00, 1.70]
Weismann 1990	61	7.16 (2.62)	69	6.72 (2.29)		8.0 %	0.44 [-0.41, 1.29]
Total (95% CI)	**825**		**831**			**100.0 %**	**-1.03 [-1.72, -0.34]**

Heterogeneity: Tau² = 1.37; Chi² = 120.07, df = 13 (P<0.00001); I² =89%

Test for overall effect: Z = 2.92 (P = 0.0035)

Test for subgroup differences: Not applicable

-10 -5 0 5 10

Favours zinc Favours placebo

Triple counting of the placebo participants (N = 71) in Turner (2000). See **p. 24-25** of this document.

In Feedback (2011) to Singh and Das (2011), I pointed out that 4.4 is **not** the zinc group mean, instead it is the mean for zinc and placebo groups combined.

Petrus reported the zinc group mean (SEM) as 3.8 (0.2) days, see **Comment 2, p. 17** of this document. Still, Singh and Das (2013) reiterate the wrong value (4.4) in the updated review.

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"Plagiarism is the use of others' published and unpublished ideas or words (or other intellectual property) without attribution or permission, and presenting them as new and original rather than derived from an existing source. The intent and effect of plagiarism is to mislead the reader as to the contributions of the plagiarizer. This applies whether the ideas or words are taken from abstracts, research grant applications, Institutional Review Board applications, or unpublished or published manuscripts in any publication format (print or electronic)."

And the document further states:

"A Cochrane Review is expected to be an original piece of academic work produced by the listed authors. Material copied from other sources may be used but should always be acknowledged. If direct quotes of more than a few words of original material are included, these should generally be indicated both by using quotation marks **and** by citing the source (citation alone is not enough)".

http://www.cochrane.org/editorial-and-publishing-policy-resource/plagiarism (accessed Jan 30, 2015)

COPE Discussion paper (26 April 2011)

states that copying "data / findings" belongs to the "most severe type" of plagiarism (Table 1, p. 3).

http://publicationethics.org/files/COPE_plagiarism_discussion_%20doc_26%20Apr%2011.pdf
http://publicationethics.org/ (accessed Jan 30, 2015)

and also states:

"...the theft of data (which may constitute not only plagiarism but also data fabrication since the work was not done by the copier)" (p. 5).

ORI states under title "Plagiarism of Ideas" that:

"Appropriating an idea (e.g., an explanation, a theory, a conclusion, a hypothesis, a metaphor) in whole or in part, or with superficial modifications without giving credit to its originator."

"ideas, data, and conclusions that are borrowed from others and used as the foundation of one's own contributions to the literature, must be properly acknowledged."

http://ori.hhs.gov/plagiarism-4 (accessed Jan 30, 2015)

Unattributed copying of the idea for subgroup analysis by zinc dosage

In my Feedback (2011) to Singh and Das (2011), the previous version of their Cochrane review, I had 2 comments relevant to subgroup analysis, see:
http://hdl.handle.net/10138/39188
http://www.mv.helsinki.fi/home/hemila/H32P.pdf

Comment 5: “Different methods of administering zinc should be analyzed separately”

I pointed out in my Feedback (2011) that zinc lozenges most probably have local effects within the pharyngeal region, whereas swallowed zinc tablets and syrups go straight to the stomach and therefore they cannot have similar local effects within the pharyngeal region as achieved by slowly dissolving lozenges.

Comment 8: “Subgroup analysis should be carried out”

I pointed out in my Feedback (2011) that the statement made by Singh and Das (2011) that “*subgroup analysis was not possible as there were not enough studies for each variable*” was incorrect.

I stated that there was a 6-fold variation in the total zinc dose (30 to 207 mg per day) in the zinc lozenge studies, and that I had divided 13 zinc lozenge trials into 3 subgroups on the basis of the total daily dose of zinc and the type of lozenge. I went on to state that none of the 5 trials with the lowest doses of zinc found a benefit from the lozenge treatment, which suggests that these trials had probably been using too low a dose. In the high-dose trials, discernible benefits were seen in 3 trials with zinc acetate, and smaller benefits in 5 other trials with zinc in the form of other salts.

I also wrote in the Feedback (2011) that:

> “Further research should focus, in particular, on high doses of zinc acetate (providing 80-90 mg/day of zinc). 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.”

In the updated version, Singh and Das (2013) followed my advice in Analysis 1.2. and presented syrup and lozenge studies separately. However, in the main Analysis 1.1 the two syrup studies were pooled with the zinc lozenge studies (see Comment 8 on p. 27 of this document).

In Analysis 1.2, Singh and Das (2013) also divided studies into low and high dosage studies using 75 mg/day as the cut-off level. That cut-off level was the very same as that used by Hemilä (2011), in which it was introduced as a pragmatic choice. Hemilä (2011) chose 75 mg/day because it provided a useful separation of zinc trials into low and high dosage studies and so that the correlation between benefit and dose could be effectively visualized.

In the Cochrane review, Singh and Das (2013) wrote:

> *"We did subgroup analysis for the following: dose (≥ 75 mg/day versus < 75 mg/day), types of lozenges (gluconate versus acetate), formulation (lozenges versus syrup) and age group (children < 16 years versus adults)"* (p. 13, right column close to bottom).
>
> *"In a subgroup analysis, the results were significant for the dose of zinc lozenges ≥ 75 mg/day"* (p. 21, left column, in the middle).
>
> *"... the observation that zinc lozenges releasing positively charged ionic zinc shorten colds in a dose-response manner can be seen in a more plausible light. This is also supported by finding of usefulness of ≥ 75 mg/day of zinc lozenges in reducing the duration of common cold in the present review"* (p. 21, left column close to the foot of the page).

By these comments, which make no attribution or acknowledgement to Hemilä (2011), Singh and Das (2013) lead the reader to assume erroneously that the selection of the 75 mg/day dosage is entirely based on the original work by Singh and Das (2013).

In the section "*Agreements and disagreements with other studies or reviews*" Singh and Das (2013) did refer to Hemilä (2011) and that Hemilä used 75 mg/day as the cut off level in dividing studies into low and high dose studies. However, the reader will not easily be able to ascertain from reading the Singh and Das (2013) publication that the idea of dividing studies by dosage and using the 75 mg/day as the particular cut off level was an original idea first described by Hemilä (2011). In the absence of attributing this to Hemilä (2011) the reader will be left with the impression that the original idea was by Singh and Das (2013).

Approaches of previous studies and reviews can be copied, but the origin of novel approaches and their acknowledgement must be specifically cited. Singh and Das (2013) instead explicitly state in their text that zinc dosage explains the heterogeneity between published studies and that this is the "*finding … in the present review*" (see above) and this false attribution misleads the reader about the true role of Singh and Das (2013) in innovating a useful way to explain heterogeneity in the zinc lozenge study findings.

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And the policy document further comments:

"A Cochrane Review is expected to be an original piece of academic work produced by the listed authors. Material copied from other sources may be used but should always be acknowledged. If direct quotes of more than a few words of original material are included, these should generally be indicated both by using quotation marks **and** by citing the source (citation alone is not enough)".

http://www.cochrane.org/editorial-and-publishing-policy-resource/plagiarism (accessed Jan 30, 2015)

COPE Discussion paper (26 April 2011)
states that copying an "idea" belongs to the "most severe type" of plagiarism (Table 1, p. 3).

http://publicationethics.org/files/COPE_plagiarism_discussion_%20doc_26%20Apr%2011.pdf
http://publicationethics.org (accessed Jan 30, 2015)

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"Appropriating an idea (e.g., an explanation, a theory, a conclusion, a hypothesis, a metaphor) in whole or in part, or with superficial modifications without giving credit to its originator."

"ideas, data, and conclusions that are borrowed from others and used as the foundation of one's own contributions to the literature, must be properly acknowledged."

http://ori.hhs.gov/plagiarism-4 (accessed Jan 30, 2015)

Unattributed copying of original phrases from the conclusions of Hemilä (2011)

In the review by Hemilä (2011), I wrote in the abstract as follows:

"CONCLUSIONS: This study shows strong evidence that the zinc lozenge effect on common cold duration is heterogeneous so that benefit is observed with high doses of zinc but not with low doses.
The effects of zinc lozenges should be further studied to determine the optimal lozenge compositions and treatment strategies."

http://www.ncbi.nlm.nih.gov/pubmed/21769305

In the "*Implications for practice*" section, Singh and Das (2013, p. 24) wrote as follows. The start of the text that is identical with sentences in the Hemilä (2011) conclusions (above) is indicated by the red arrow:

Implications for practice

Evidence shows that zinc is beneficial for the common cold in healthy children and adults living in high-income countries. Pooled results from the trials showed that zinc reduced the duration (not the severity) of common cold symptoms when used therapeutically. However, the effect of zinc lozenges on common cold duration is heterogeneous so that benefit is observed with high doses but not with low doses of zinc. The effects of zinc lozenges should be further studied to determine the optimal lozenge compositions and treatment strategies. Zinc also reduced the incidence

A retyped version of the Singh and Das (2013) text below shows the identities with the conclusions of Hemilä (2011) by yellow.

***"Implications for practice"* [in Singh and Das 2013]**

*"Evidence shows that zinc is beneficial for the common cold in healthy children and adults living in high-income countries. Pooled results from the trials showed that zinc reduced the duration (not the severity) of common cold symptoms when used therapeutically. However, the effect of zinc lozenges on common cold duration is heterogeneous so that benefit is observed with high doses but not with low doses of zinc.
The effects of zinc lozenges should be further studied to determine the optimal lozenge compositions and treatment strategies."*

Conclusions of previous papers may be copied, but the origin of novel conclusions should be attributed and cited. When a conclusion is copied word for word the passage should be enclosed within quotation marks, even when the reference is given, see below.

Cochrane Collaboration policy

"A Cochrane Review is expected to be an original piece of academic work produced by the listed authors. Material copied from other sources may be used but should always be acknowledged. If direct quotes of more than a few words of original material are included, these should generally be indicated both by using quotation marks **and** by citing the source (citation alone is not enough)"

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copying an "original phrase" belongs to the "most severe type" of plagiarism (Table 1, p. 3).

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http://ori.hhs.gov/plagiarism-4 (accessed Jan 30, 2015)

and under title "Plagiarism of Text" that:

"Guideline 2: Any verbatim text taken from another author must be enclosed in quotation marks.

Guideline 3: We must always acknowledge every source that we use in our writing; whether we paraphrase it, summarize it, or enclose it quotations."

http://ori.hhs.gov/plagiarism-6 (accessed Jan 30, 2015)

Irrespective of the issue of unattributed copying, the positioning of the copied sentences is poor in Singh and Das (2013). Instead of being written in the section "*Implications for practice*", the above sentences would be much better placed in the section "*Implications for research*", see p. 32 of this document.

Minor unattributed copying in Singh and Das (2013)

The 2 following paragraphs below were written by Hemilä (2011, p. 56), see: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3136969

"Two groups of reviewers concluded that there is no evidence that zinc lozenges are beneficial against colds. Jackson et al. [47,48] found statistically significant heterogeneity between the zinc trials. They calculated a pooled estimate of effect, although the evidence of heterogeneity seriously challenges the validity of any single overall estimate. Faced with heterogeneous results, the main focus of the reviewers should be on trying to understand the sources of the heterogeneity [49]. Although Jackson suggested that some of the negative results might be explained by low zinc ion availability, they did not examine the issue"

…

"In another systematic review, Caruso et al. used the quality scoring approach, so that for the trials identified they gave one point for each of 11 quality items if it was satisfied [50]. Only four of the identified trials obtained the maximum of 11 points, and Caruso et al. suggested that the positive findings in the zinc trials might be explained by methodological faults. However, such a quality scoring approach is discouraged, for example, in the Cochrane Handbook, which states that 'the use of scales for assessing quality or risk of bias is explicitly discouraged in Cochrane reviews. While the approach offers appealing simplicity, it is not supported by empirical evidence' [18]."

These 2 lower paragraphs (in italics) below were written 2 years later by Singh and Das (2013, p. 23). Yellow highlights mark the passages that are identical with the 2 paragraphs above.

"In the revisit of their previous meta-analysis, Jackson (Jackson 2000) found statistically significant heterogeneity between the zinc trials. They calculated a pooled estimate of the zinc gluconate lozenges in colds using the random-effects model of DerSimonian and Laird from eight trials. The summary OR for the presence of "any cold symptoms" at seven days was 0.52 (95% CI 0.25 to 1.2). They concluded that despite numerous randomised trials, the evidence for the effectiveness of zinc lozenges in reducing the duration of common colds is still lacking. Although, according to them, some of the negative results might be explained by low zinc ion availability, they did not examine the issue. Moreover, they have not looked for the effect of any other formulations, as well as high or low doses of zinc.

…

In a systematic review of trials published between 1966 and 2006, Caruso 2007 used 11 features of experimental design affecting signal quality, chance, bias and blinding to evaluate 14 placebo-controlled trials. They gave one point for each of the 11 quality items if it was satisfied, after which only four trials obtained the maximum of 11 points. Based on this, they suggested that the positive results in the zinc trials might be explained by methodological flaws. However, the use of scales for assessing quality or risk of bias is strongly discouraged in Cochrane systematic reviews. Moreover, such an approach, though simple, is not supported by evidence (Higgins 2011)."

In my view, the above copying is less harmful than the copying described on p. 4-12 of this document. Nevertheless, copying of so many words, phrases and clauses from another author's paper without using quotation marks, and without giving a reference, does not seem appropriate.

Within-publication text recycling by Singh and Das (2013)

In Singh and Das (2013), on **page 6**, left column bottom, starting on line 5 of "*Description of intervention*", the text is identical with text on **page 20**, left column, except that *"tartaric acid, mannitol and sorbitol"* is added to the latter text.

This is the text of 147 words published on page 6 of Singh and Das (2013):

"It has been hypothesised that there is a direct correlation between reductions in the duration of common cold symptoms and the daily dosage of all positively charged zinc species released from lozenges at physiologic pH (Eby 1995). The reanalysis of 10 double-blind, placebo-controlled zinc trials by solution chemistry methods showed a significant correlation between total daily dosages of positively charged zinc species and a reduction in the mean duration of common colds (Eby 2004). Zinc gluconate and zinc acetate have very low chemical stability and mainly release positively charged zinc ions in aqueous solutions at physiologic pH, but stronger complexes do not (Eby 2004). Adding a strong zinc-binding ligand, such as glycine or citric acid, to a solution containing a zinc complex that is weakly bonded results in the sequestration of zinc to the stronger ligand, reducing or eliminating the benefits of zinc lozenges (Eby 2004).

The start of the text recycling is shown by the red arrows on these copies from pp. 6 and 20.

Page 6

Description of the intervention

The effect of zinc lozenges on the incidence, duration or severity of common cold symptoms has been examined in different studies since 1984. In 1984, Eby et al (Eby 1984) reported for the first time on the efficacy of zinc gluconate lozenges for treatment of the common cold. However, later trials have given variable results. It has been hypothesised that there is a direct correlation between reductions in the duration of common cold symptoms and the daily dosage of all positively charged zinc species released from lozenges at physiologic pH (Eby 1995). The re-analysis of 10 double-blind, placebo-controlled zinc trials by solution chemistry methods showed a significant correlation between total daily dosages of positively charged zinc species and a reduction in the mean duration of common colds (Eby 2004). Zinc gluconate and zinc acetate have very low chemical stability and mainly release positively charged zinc ions in aqueous solutions at physiologic pH, but stronger complexes do not (Eby 2004). Adding a strong zinc binding ligand, such as glycine or citric acid, to a solution

containing a zinc complex that is weakly bonded results in the sequestration of zinc to the stronger ligand, reducing or eliminating the benefits of zinc lozenges (Eby 2004). In the review by Marshall it was concluded that zinc gluconate lozenges were effective in re-

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discomfort and diarrhoea found by Macknin 1998, may have been related to the use of different ligands (gluconate, acetate) rather than to zinc itself.

Much of the controversy surrounding the use of zinc lozenges in the treatment of the common cold has concerned whether formulations used in trials showing no benefit failed to release sufficient zinc ions to be effective. It has been hypothesised that there is a direct correlation between reductions in the duration of common cold symptoms and the daily dosage of all positively charged zinc species released from lozenges at physiologic pH (Eby 1995). The reanalysis of 10 double-blind, placebo-controlled zinc trials by solution chemistry methods showed a significant correlation between total daily dosages of positively charged zinc species and a reduction in the mean duration of common colds (Eby 2004). Zinc gluconate and zinc acetate have very low chemical stability and mainly release positively charged zinc ions in aqueous solutions at physiologic pH, but stronger complexes do not (Eby 2004). Adding a strong zinc-binding ligand, such as glycine, citric acid, tartaric acid, mannitol and sorbitol, to a solution containing a zinc complex that is weakly bonded results in the sequestration of zinc to the stronger ligand, reducing or eliminating the benefits of zinc lozenges (Eby 2004). The extent to which the zinc ion was released from formulations reporting no benefit is not known. However, experimental evidence suggests that in saliva the ioni-

COPE comments text recycling (self-plagiarism) as follows:
http://publicationethics.org/resources/guidelines
http://publicationethics.org/text-recycling-guidelines

"...it may be entirely appropriate to have overlap in a methods section of a research article (referring to a previously used method) with citation of the original article. However, undisclosed overlap, or overlap in the results, discussion, or conclusions is unlikely to be acceptable."

Usually text-recycling means that text of an old publication is copied to a new publication by the same author. Text recycling within the same document may be so rare that COPE seems not to have formulated specific comments on it.

Inadequate responses, omissions and inaccurate statements made by Singh and Das (2013) to the Feedback (2011)

In my Feedback (2011), I formulated 10 comments.
http://hdl.handle.net/10138/39188
http://www.mv.helsinki.fi/home/hemila/H32P.pdf

Singh and Das (2013, p. 87) responded to my Feedback (2011).
In this section I point out the problems in their responses.

Italics indicates the responses of Singh and Das (2013, p. 87) to the comments of my Feedback (2011) (my original comments are not copied here, they are available through the links above).

In the following, Hemilä's comments (this document) about the response by Singh and Das (2013, p. 87) are in upright writing.

1) Response to my comment 1 is reasonable, but the other 9 responses are not.

2) "*The Petrus (1998) values in Analysis 1.1 has been replaced with these correct and accurate values in this updated review*" (response by Singh and Das 2013).

This statement is not true.

In my Feedback (2011) to Singh and Das (2011) I wrote:

> "In their Analysis 1.1, Singh and Das [2011] 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" (Feedback 2011).

Even the abstract of Petrus (1998) reports the duration of colds in the zinc group as 3.8 days: "Overall symptom duration was significantly less in the zinc group than in the placebo group (mean, 3.8 day vs 5.1 days)" (see the abstract through links below).
http://dx.doi.org/10.1016/S0011-393X(98)85058-3
http://www.currenttherapeuticres.com/article/S0011-393X%2898%2985058-3/pdf

A copy of Petrus' Table II is shown below (see the first row for the duration of colds):

Table II. Mean duration and mean severity of symptoms by treatment group. Values are given as mean (SEM).

Variable	Overall (n = 101) Mean (SEM)	Zinc (n = 52) Mean (SEM)	Placebo (n = 49) Mean (SEM)	*t* test*	*df*	*P*
Duration of all cold symptoms (days)	4.4 (0.2)	3.8 (0.2)	5.1 (0.4)	–2.7	73.8†	0.008
Duration of longest-lasting cold symptom (days)	6.1 (0.3)	5.3 (0.4)	7.1 (0.6)	–2.7	82.2†	0.009
Mean severity rating‡ (all symptoms)	1.45 (0.03)	1.41 (0.04)	1.50 (0.04)	–1.4	99	0.161

SEM = standard error of the mean.
* Independent groups *t* tests were used to determine whether differences existed between the zinc and placebo group means.
† Results using estimates assuming unequal group variances.
‡ Symptom severity rating scale: 0 = absent; 1 = mild; 2 = moderate; and 3 = severe.

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Contrary to the response of Singh and Das (2013) to my Comment 2, Singh and Das (2013) still state in Analysis 1.1 (also published as Fig. 3) that the mean duration of colds in the zinc group of Petrus (1998) study was 4.4 days, see p. 7 of this document.

It may be that Singh and Das (2013) did not intentionally deceive their readers, but it could be that they failed to check whether the correction had actually been done, or not, and have just recollected in error.

3) "*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...*" (Singh and Das 2013).

It is false to state that I handled the Weismann trial as if it was a randomized trial.

In the systematic review on zinc lozenges and the common cold, Hemilä (2011, p. 53) wrote: "Weissman et al. used consecutive allocation, but all the other trials were randomized".

In my Feedback (2011) to Singh and Das (2011), I wrote that I had contacted Weismann and he informed me that the study used consecutive allocation:
"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)" (Feedback 2011).

> "… *So, there is no point in excluding this* [Weismann 1990] *trial or lebeling* [sic] *this as a 'pseudo-randomized trial'* " (Singh and Das 2013).

I cannot see any justification for that statement.

Cochrane Handbook states that:

> "Systematic methods, such as alternation... sometimes referred to as 'quasi-random'... An important weakness with all systematic methods is that concealing the allocation schedule is usually impossible, which allows foreknowledge of intervention assignment among those recruiting participants to the study, and biased allocations" (Higgins 2011, sec 8.9.2.2).

Therefore, Singh and Das (2013) response that:
"*there is no point in … lebeling this* [Weismann 1990] *as a 'pseudo-randomized trial'* "
does not make sense.

Reviewers may include quasi-randomized trials, but reviewers must be transparent about it and explicitly state that quasi-randomized trials are included, and the quasi-randomized trials should be clearly identified. Furthermore, given that Singh and Das (2013) used randomization as an inclusion criterion (see Comments 1 and 6 on pp. 24 and 26 of this document), they should either exclude Weismann (1990) or change the inclusion criteria accordingly.

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 remoed* [sic] *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"* (Singh and Das 2013).

Singh and Das (2013) missed my point.

In my Feedback (2011) I did not actually propose that they should include the Eby (1984) study in their meta-analysis. Instead, I required that the Eby (1984) and Smith (1989) studies should be treated equally since they have similar problems.

I wrote in Comment 4 of the Feedback (2011) that:

> "In any case, Singh and Das should treat Eby (1984) and Smith (1989) trials consistently, so that both are included or excluded on the basis of the high rate of participants not included in the analysis" (Feedback 2011).
>
> "... 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" (Feedback 2011).

Smith (1989) randomized 174 patients and reported the results for 110 of them, and the duration of colds was published for only 57 patients (33% of those randomized). The common cold duration had to be imputed for 53 participants, which is 48% of all reported (53/110).

Eby (1984) randomized 146 patients and after exclusion of those who had colds lasting >3 days before the study (a reasonable post-randomization exclusion of long delays before initiating treatment), they reported data for 65 patients, and the duration of colds was published for 45 patients (31% of those randomized). The common cold duration had to be imputed for 20 participants, which is 31% of all reported (20/65).

Both of the studies above have limitations with so many patients being excluded after randomization and with the high proportion of missing data. In the Smith (1989) study, the need for imputations is even greater than that for the Eby (1984) study (48% vs. 31%, respectively).

Singh and Das (2013) excluded Eby (1984), but included Smith (1989) although the problems are quite similar for both of these studies; in fact Smith (1989) needed even more imputations. Thus, Singh and Das (2013) are inconsistent in treating these 2 marginally acceptable RCTs. In another meta-analysis, Hemilä (2011) included both, but subsequently conducted a sensitivity analysis from which both studies were excluded, which is non-biased treatment of these 2 marginally acceptable RCTs.

5) *"Different methods of administering zinc have been analyzed separately in the updated review"* (Singh and Das 2013).

This statement is not true.

Although Analysis 1.2 (also published as Fig. 4 in Singh and Das 2013) does show a separate subgroup of lozenge studies (as subgroup 1.2.5) and of syrup studies (1.2.6), the main Analysis 1.1 (= Fig. 3) still pooled the lozenge studies and the syrup studies (by Kurugöl) together, see p. 7 of this document.

In the Abstract, Singh and Das (2013, p. 1) reported

> "*Intake of zinc was associated with a significant reduction in the duration (days) (mean difference (MD) -1.03 ...*",

a statement that was based on Analysis 1.1. (= Fig. 3), which pooled the syrup studies and the lozenge studies together. Thus, in the main analysis, Singh and Das (2013) did not "*analyze separately*" "*different methods of administering zinc*" although they claim to have done so in their response.

In Feedback (2011) I gave on Singh and Das (2011), I pointed out that lozenges most probably have local effects within the pharyngeal region, whereas tablets and syrups go straight to the stomach and thereby they cannot have similar local effects within the pharyngeal region.

6) *"Regarding the duration of the common cold should not be dichotomized, we did not make any change. They are actually not visible, if somone* [sic] *does not really want to visualise them"* (Singh and Das 2013).

Singh and Das (2013) ignore the problem of low statistical power.

First, a continuous outcome contains more information and dichotomization leads to loss of information, and therefore to less statistical power, see:
http://www.ncbi.nlm.nih.gov/pubmed/16675816
http://www.ncbi.nlm.nih.gov/pubmed/16217841
http://www.ncbi.nlm.nih.gov/pubmed/24682179

Second,
Analysis 2.1 (the number of participants symptomatic after 3 days of treatment) and
Analysis 2.2 (the number of participants symptomatic after 5 days of treatment)
both include only 3 studies.

In comparison, Analysis 1.1 includes 14 studies and Analysis 1.2.5 (lozenge studies) includes 12 studies. Thus, the number of studies with the dichotomized outcome of 3 or 5 days is small compared with the outcome of continuous common cold duration. Therefore, the much smaller number of studies with dichotomous outcome exacerbates the problem of low statistical power analysis of the dichotomized data by Singh and Das (2013). Thus, the lack of significant difference in Analyses 2.1 and 2.2 is explained by the low statistical power. Those analyses do not adequately test the significant effects on common cold duration by zinc seen in Analyses 1.1 and 1.2.

Using dichotomized data is reasonable when there are no continuous data available. However, all 3 studies included in Analyses 2.1 and 2.2. were already included in the Analysis 1.1 (see p. 7 of this document). Therefore the analysis of dichotomized data by Singh and Das (2013) does not give additional information and is not sound.

The analyses of the dichotomized cold durations are not invisible. The analyses data are presented in 3 tables in the analysis section and as 192 words in the Results section (p. 17, Singh and Das 2013).

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*" (Singh and Das 2013).

This statement is not true.

The meta-analysis of Singh and Das (2013) is based on the absolute duration of colds (i.e. in days). It is much better than the usage of the SMD method in the previous version of Singh and Das (2011). However, absolute duration is not expressed as percentages. If the durations of the common colds are normalized to 100% in each study, then the pooled estimate has to be given in percentage units. Singh and Das (2013) have not normalized these data so that the duration of colds in all placebo groups would be 100%, see p. 7 of this document.

In my Feedback (2011) I illustrated the meaning of percentage calculation as follows:

> "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%."

Page 6 of this document shows how Hemilä (2011) transformed duration in days to the relative durations, so that the placebo group mean duration is set at the 100% level.

Singh and Das (2013) claim to have made this transformation but I can find no place in their review where this transformation was actually done.

8) "*Subgroup analysis has been carried out in the updated review*" (Singh and Das 2013).

Yes, but subgroup analysis that ignores the dose of zinc is an incorrect approach,
see Comment 8 on p. 27 of this document.

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*" (Singh and Das 2013).

This argument is not logical.

If "*pooling the adverse effects of all zinc trials is unsound*"
how could such pooling be "*useful*" for anyone?

It is reasonable to consider the adverse effects of treatments in systematic reviews, but pooling studies that used very different types of treatments is useless, it is an example of the classical "apples and oranges" problem.

In my Feedback (2011) on the previous version of their review (Singh and Das 2011), I wrote:

> "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, in Analyses 2.12, 2.13 and 2.14 Singh and Das pooled "*any adverse events*", "*bad taste*" and "*nausea*" for different zinc lozenges and for the 2 studies with zinc syrup (by Kurugöl) and write in the Abstract that:

> "*Overall adverse events (OR 1.58, 95% CI 1.19 to 2.09) (P = 0.002), bad taste (OR 2.31, 95% CI 1.71 to 3.11) (P < 0.00001) and nausea (OR 2.15, 95% CI 1.44 to 3.23) (P = 0.002) were higher in the zinc group.*" (p. 2, Singh and Das 2013).

Thus, the reporting in the Abstract is based on the pooling of different types of zinc lozenges with zinc syrup, which is pooling of "apples and oranges".

In Analysis 2.12.1, Singh and Das (2013) did report a subgroup analysis of zinc lozenge studies and they summarized that pooling as follows:

> *"the lozenges formulation (OR 2.00, 95% CI 1.40 to 2.86) (P = 0.0001) was more like* [sic] *to produce any adverse events than the syrup formulation (OR 1.03, 95% CI 0.64 to 1.66) (P = 0.9)"* (p. 19, Singh and Das 2013).

In the "Authors' conclusions, Singh and Das (2013) write:

> *"When using zinc lozenges (not as syrup or tablets) the likely benefit has to be balanced against side effects, notably a bad taste and nausea"* (p. 2, Singh and Das 2013).

However, the lozenge subgroup in Analysis 2.12.1 did not include any of the 3 high dose zinc acetate lozenge studies, which together obtained the mean 42% reduction in the common cold duration reported (Hemilä 2011).

Some types of zinc gluconate lozenges end up tasting bad after an extended period of storage, but zinc acetate does not have such a problem, see Eby (2004, p. 34-35):

> "Taste problems and oral irritation using zinc gluconate (ZG) caused most if not all of the problems found in commercializing zinc lozenges for colds. To reduce or eliminate the ZG/dextrose reaction and oral irritation, some manufacturers either used low amounts of ZG or added strong zinc binding agents, which reduced or eliminated efficacy. Although pure ZG is bland and chalky in taste, it reacts with dextrose and related carbohydrates (excluding fructose) upon aging of lozenge compositions to produce noisome bitterness and compliance-related inefficacy. ZG releases large amounts of neutrally charged hydroxide species likely to cross cell membranes and causes oral irritation. Bitterness occurs in all ZG lozenges except those that either do not contain carbohydrates (excluding fructose), or that contain strong extramolar zinc binding agents, which results in something other than ZG. For these reasons, ZG is no longer believed suitable for use in zinc lozenges for treating colds.
>
> On the other hand, ZA allows the production of pleasant tasting, flavor stable lozenges releasing large amounts of iZn [free zinc ions] either in hard candies or compressed tablets without flavor or stability issues. The mouth-feel produced is sufficiently like the mouth-feel of tea (slight astringency) to allow using tannic acid without added bitter agents as a placebo in clinical trials"

None of the high dose zinc acetate lozenge trials (Petrus 1998, Prasad 2000, Prasad 2008) reported bad taste to be a problem and there was no substantial difference between the zinc and placebo groups in the recorded adverse effects, and only a few drop-outs occurred. For example, the most recent of these studies, Prasad (2008) reported in Table 3 of their publication that sour taste was more common in the zinc group (7/25 vs. 2/25, but P = 0.14) whereas nausea (3 vs 1) or constipation (2 vs 1) and diarrhea (1 vs 1) did not differ considerably between groups. Thus, the zinc acetate lozenge did not seem to cause substantial acute harm, either as bad taste or on the GI region. Furthermore, when a common cold patient suffers from acute adverse effects such as bad taste, the particular patient can simply stop taking the zinc acetate lozenges.

Given that the strongest evidence of benefit is found for high dose zinc acetate lozenges (Hemilä 2011), the possible bad taste of zinc gluconate lozenges is not a relevant issue. In particular, the bad taste of some zinc gluconate lozenges cannot be extrapolated to infer bad taste of the zinc acetate lozenges.

For these and similar reasons, pooling the adverse effects of all different lozenge studies together, or pooling the adverse effects of lozenge and syrup studies together, is uninformative and misleading.

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"* (Singh and Das 2013).

This is not a response to my criticism.

In my Feedback (2011) on Singh and Das (2011), I wrote:

> "Credit should be given to earlier work on the same topic: In their Introduction, Singh and Das [2011] write
> *'The last review of all available RCTs of zinc for the common cold was published in 1999'*, which is erroneous."

I pointed out that the reviews by Jackson (2000) and Caruso (2007) had been published after 1999.

Ignoring my comment, Singh and Das (2013) still wrote in the Background:

> *"The last review of all available RCTs of zinc for the common cold was published in 1999... It is therefore important to update the information and include all new clinical trials."*

Thus, the Background of Singh and Das (2013) still mislead their readers about previous systematic reviews on zinc and the common cold.

Jackson (2000), Hulisz (2004), and Caruso (2007) reviews were published after 1999 but before 2011, which is the year of the first Cochrane review version by Singh and Das (2011).

Two further reviews were published after the first version of the Cochrane review by Singh and Das (2011), one review by Hemilä (2011) and another by Science (2012).

Thus, there are 5 reviews on zinc and the common cold that had been published after 1999, yet Singh and Das still claim in the Background section of Singh and Das (2013) that:
"The last review of all available RCTs of zinc for the common cold was published in 1999. It is therefore important to update the information and include all new clinical trials."

The purpose of the Background section of scientific papers is to describe what is already known and what information is scare or non-existent, before the current work. The omissions and incorrect statement in Singh and Das (2013) mislead the reader into believing that their review is more novel and informative than it actually is.

Some further problems in Singh and Das (2013)

1) Singh and Das (2013) Fig. 1 (p. 9) is inconsistent with the inclusion criteria (p. 7)

Singh and Das (2013, p. 7) states under the heading "*Criteria for considering studies for this review*" that "*randomised controlled trials"* were included.

In Fig. 1, Singh and Das (2013) marked the Al-Nakib (1987), Petrus (1998), Vakili (2009), and Weismann (1990) studies with the minus mark, indicating that they were not randomized. When the inclusion criterion is randomized trials, there should not be any minus marks in the random sequence column in Fig. 1.

In fact, only the Weismann (1990) study is truly non-randomized, see Comment 3 on p. 18 of this document, whereas the coding of the other trials with the minus mark is just erroneous, see Comment 5 on p. 26 of this document. In any case, the authors should have seen the inconsistency between Fig. 1 and their inclusion criteria.

2) Lack of thoroughness in trying to contact the original investigators (pp. 8 and 10)

> *"We made no attempt to contact investigators. Most trials were conducted over 10 years ago and in view of the information required to be provided by the investigators, we thought that they would be unable to comply"* (p. 8, Singh and Das 2013).
>
> *"As many trials were conducted 10 years ago, we thought that the investigators would be unable to compile the missing data, so we did not contact them"* (p. 10, Singh and Das 2013).

I do not consider it reasonable that Cochrane review authors categorically decide that they will not even try to contact any original investigators, on the basis of speculation that the investigators might not be reached or would be unable or willing to reply. In my opinion this is a lack of rigor as even 10-year-old data will be recorded on computer hard drives and should be accessed relatively easily by their authors.

I was able to contact Kaare Weismann, Ananda Prasad, and Ken Lawson (statistician of the Petrus 1998 study) and each of them provided me with useful and pertinent additional information for my own analyses of controlled trials on zinc and the common cold. This took the guesswork out of the analyses.

3) Unit of analysis issues (p. 10)

Singh and Das (2013) states that [there are no unit-of-analysis problems, since]

> *"We included only randomised, double-blind, placebo-controlled trials in this review. None of the trials were cross-over or cluster-randomised trials."*

That comment misleads the readers.

There is a serious unit-of-analysis problem in Singh and Das (2013).

The placebo participants of the Turner (2000) trial were counted 3 times in Analysis 1.1 (Fig. 3), see p. 7 of this document. Because of this triple counting, 142 (= 2 * 71) of the total number of patients (N = 831) in the placebo column of that analysis are actually non-existent. The same problem of multiple counting can be found in several other analyses in Singh and Das (2013).

This issue is briefly discussed in the Cochrane Handbook:

> "A serious unit-of-analysis problem arises if the same group of participants is included twice in the same meta-analysis (for example, if 'Dose 1 vs Placebo' and 'Dose 2 vs Placebo' are both included in the same meta-analysis, with the same placebo patients in both comparisons)" (Higgins 2011, sec 9.3.9).

4) Dealing with missing data (p. 10)

Singh and Das (2013) wrote that:

> *"As many trials were conducted 10 years ago, we thought that the investigators would be unable to compile the missing data, so we did not contact them. For all the outcomes, we considered that incomplete outcome data had been adequately addressed if 80% or more of the participants were included in the analysis, or if less than 80% were included but adequate steps were taken to ensure or demonstrate that this did not bias the results. We performed intention-to-treat (ITT) analysis where the above was not clear. In trials with missing statistics (such as SDs or correlation coefficients), we calculated the data from the available information."*

Smith (1989) randomized 174 patients and reported the results for 110 of them (63% of 174), however, explicit data were published for just 57 participants (33% of 174).

Thus, only 63% of the randomized patients were included in Smith (1989) analysis. This is much less than the limit of 80% stated by Singh and Das (2013) in the above excerpt. Furthermore, the duration of colds was published for just 57 patients, which is 33% of those randomized (57/174).

I cannot figure out how Singh and Das (2013) were convinced that in the study by Smith (1989) that *"adequate steps were taken to ensure or demonstrate that this did not bias the results"*. Transparency is important in systematic reviews. However, the reader of the review by Singh and Das (2013) will be mislead when the actual basis for including the Smith (1989) study in Singh and Das (2013) was 63%, whereas Singh and Das (2013) stated that 80% of patients had to be included in the study analysis, to include a particular study to their Cochrane review, see the above excerpt.

5) The contradiction of "Searching for further information" (p. 11)

On p. 11 (Assessment of reporting biases) Singh and Das (2013) wrote:

> "*We sought further information from trial authors, although this was not possible for the current meta-analysis as many of the studies were very old."*(p. 11, Singh and Das 2013).

Thus, here they state that "*we sought*" supplementary information (p. 11), but elsewhere they state that *"We made no attempt to contact"* (p. 8) and *"we did not contact them"* (p. 10), see Comment 2 above. These are contradictory statements about what they might have been doing.

6) Allocation: randomization (p. 13)

> *"Adequate sequence generation was described in seven studies (…). However, it was not clear in seven studies (Farr 1987a; Prasad 2000; Prasad 2008; Smith 1989; Turner 2000a; Turner 2000b; Turner 2000c) and not generated in four studies (Al-Nakib 1987; Petrus 1998; Vakili 2009; Weismann 1990)"* (Singh and Das 2013).

This statement is ambiguous.

What do Singh and Das (2013) mean by:
"adequate sequence generation was … not generated in four studies" (see above).

They use randomization as an inclusion criterion, see Comment 1, p. 24 of this document. Does *"inadequate sequence generation"* mean that the study was not randomized. If it does, why are the studies included. If it does not, what does *"inadequate sequence generation"* mean in that case? Singh and Das (2013) do not explain what they mean by stating then that *"sequence generation"* was *"not clear"* or *"not generated"*.

In the methods sections:

> Al-Nakib (1987) states "were randomly allocated to receive..." (p. 894) and "were allocated randomly to receive..." (p. 895), and
> Petrus (1998) states "... this randomized…study" (p. 597), and
> Vakili (2009) writes "A total of 200 children (aged 78 to 120 months) were randomly assigned to..." (p. 377).

In some study reports the methods are reported erroneously. Nevertheless, the default assumption should be that the reporting of methods is precise and accurate. Unless there are explicit reasons to suspect the reported methods, the description of the authors must be trusted. Singh and Das (2013) fail to justify the statement that *"adequate sequence was … not generated"* in the 3 above studies.

7) Incomplete outcome data (p. 13)

Singh and Das (2013) stated:

> *"Data were fully detailed in 15 studies and in the remaining three* [sic] *studies (Al-Nakib 1987; Turner 2000a; Turner 2000b; Turner 2000c) details of attrition and exclusions from the analysis were unavailable."*

First, the 3 studies by Turner and the 1 study by Al-Nakib make 4 studies in total, not 3.

Second, as described on pp. 4-5 of this document, cold duration was not reported for 4 patients in the study by Mossad (1996), not reported for 10 patients by Macknin (1998), not reported for 8 patients by Weismann (1990), and not reported for 53 patients by Smith (1989). In addition, Douglas (1987) and Godfrey (1992) did not report the SDs for the duration of colds. Thus, up to 53 patients had missing data in 4 studies, and 2 studies did not report SD values. Nevertheless, none of these studies falls into the group of the 4 exceptions listed by Singh and Das (2013), see above. Instead, according to Singh and Das (2013), *"data were fully detailed in them"*

since they are not in the list of the "*three* [= 4] *studies*", see above. Thus, what does *"data were fully detailed"* mean in such a context?

8) Subgroup analyses by Singh and Das (2013) ignores zinc dosage and are not reasonable

In Analysis 1.2 (= Fig. 4), Singh and Das (2013) showed that the dose of zinc is an important explanation for the heterogeneity in zinc effects.
For 5 low dosage (<75 mg/day) studies, the effect of zinc is: 95% CI: –0.54 to +0.79 days.
For 7 high dosage (>75 mg/day) studies, the effect of zinc is: 95% CI: –3.1 to –0.85 days.

The 95% CIs for these 2 subgroups do not overlap, which indicates that the difference between the subgroups is not explained by chance alone. The dosage seems thus to be a genuine factor that determines whether zinc treatment has an effect or not. Therefore, dosage should be taken into account in all further comparisons of zinc studies.

By analogy, if we compare the incidence of lung cancer in men and women, and ignore variations in their cigarette smoking habits, we would get false estimates of differences in risk between the sexes. In epidemiology this is called confounding.

In Analysis 1.2 (= Fig. 4), Singh and Das (2013) carried out subgroup analysis by the zinc salt (gluconate vs. acetate) and by age (children vs. adults) without taking into account the variation in zinc dosage in these subgroup analyses. Thus, the subgroup analyses for zinc salts and for age groups are confounded by zinc dosage. These subgroup analyses are therefore useless. There might be differences between zinc salts and between children and adults, but the comparisons should take into account the differences in the dosages of zinc in various studies, in the same way as studies that compare lung cancer risk between sexes must take into account their differences in the level of smoking.

9) Dose ranges claimed for the studies are inconsistent

30 to 160 mg/day *"variable formulations (zinc gluconate or acetate lozenges, zinc sulphate syrup)"* (p. 13 right column)

30 to 190 mg/day *"trials used lozenge preparation at a daily dose varying from..."* (p. 21 left column, middle)

30 to 276 mg/day *"the trials using lozenge preparation used daily doses varying from..."* (p. 21 left column, bottom)

Singh and Das (2013) do not explain how the zinc doses were calculated in their review and the reader cannot know which of the 3 upper limits is the correct maximum in the included studies.

Hemilä (2011) calculated in his meta-analysis that the highest dose (207 mg/day) had been used by Smith (1989): 207 mg/day = 9 times per day * 2 * 11.5 mg.

This calculation was based on the instruction in the study by Smith (1989) to dissolve 2 lozenges in the mouth "every 2 hr while awake." (p. ix, Supplementary File 2, Hemilä 2011).

Smith (1989, p. 646) wrote: "Identical-appearing lozenges containing either 11.5 mg of elemental zinc... An initial dose of four lozenges was used, followed by two lozenges dissolved in the mouth every 2 h while awake".

10) Persistent and multiple errors in the extraction of data from the study by Petrus (1998)

In the Feedback (2011) I gave, I pointed out that Singh and Das (2011) extracted erroneous figures for the zinc group of the Petrus (1998) study. Despite pointing out this problem, the updated version by Singh and Das (2013) still had the same erroneous data for the zinc group, see pp. 7 and 17 of this document.

In addition, in Analyses 2.5, 2.6, and 2.8 of Singh and Das (2013), the data are erroneously extracted from Table III of the Petrus (1998) study.

Here is what Petrus (1998) reported in Table III:
http://dx.doi.org/10.1016/S0011-393X(98)85058-3
http://www.currenttherapeuticres.com/article/S0011-393X%2898%2985058-3/pdf

Table III. Mean duration and mean severity rating of each cold symptom by treatment group.

Symptom	Mean Duration of Symptoms: Overall Mean Days (SEM)	Mean Duration of Symptoms: Zinc Mean Days (SEM)	Mean Duration of Symptoms: Placebo Mean Days (SEM)	Mean Severity Rating*: Overall Mean Rating (SEM)	Mean Severity Rating*: Zinc Mean Rating (SEM)	Mean Severity Rating*: Placebo Mean Rating (SEM)
Headache	4.2 (0.4)	4.4 (0.4)	4.0 (0.6)	1.48 (0.06)	1.43 (0.07)	1.52 (0.10)
Fever	2.1 (0.5)	1.8 (0.5)	2.5 (0.9)	1.13 (0.08)	1.00 (0.00)	1.25 (0.14)
Myalgia	4.1 (0.5)	4.6 (1.1)	3.9 (0.6)	1.48 (0.09)	1.37 (0.15)	1.51 (0.11)
Sneezing	4.7 (0.4)	3.9 (0.4)	5.5 (0.8)	1.34 (0.05)	1.31 (0.06)	1.38 (0.07)
Nasal drainage	5.4 (0.4)	4.2† (0.4)	6.6† (0.7)	1.53 (0.05)	1.45 (0.07)	1.61 (0.07)
Nasal congestion	5.4 (0.4)	4.2‡ (0.4)	6.5‡ (0.7)	1.49 (0.05)	1.54 (0.08)	1.43 (0.05)
Sore throat	3.4 (0.3)	3.4 (0.4)	3.3 (0.5)	1.29 (0.06)	1.26 (0.06)	1.34 (0.11)
Scratchy throat	4.3 (0.4)	4.0 (0.5)	4.5 (0.5)	1.47 (0.06)	1.38 (0.10)	1.53 (0.08)
Cough	4.4 (0.3)	4.5 (0.5)	4.3 (0.4)	1.39 (0.06)	1.28 (0.07)	1.51 (0.09)
Hoarseness	3.8 (0.6)	2.7 (0.5)	4.7 (0.9)	1.39 (0.09)	1.35 (0.12)	1.43 (0.14)
Malaise	5.2 (0.7)	5.7 (0.7)	5.0 (0.9)	1.50 (0.06)	1.50 (0.09)	1.50 (0.08)

SEM = standard error of the mean.
* Symptom severity rating scale: 0 = absent; 1 = mild; 2 = moderate; and 3 = severe.
† *t* test results: $t = -3.1$, $df = 75$, $P = 0.003$.
‡ *t* test results: $t = -2.8$, $df = 71$, $P = 0.006$.

For the severity of cough 0.07 and 0.09 are SEM as described at the top of the column, not SD.

df=71 means that the t-test for nasal congestion was based on 73 participants, not on 101.

df=75 means that the t-test for nasal drainage was based on 77 participants, not on 101.

In **Analysis 2.5,** Singh and Das (2013) state that the number of participants in Petrus (1998) "nasal congestion" analysis was N = 101 (52+49), whereas Petrus reported N = 77 for the reported mean and SD, see previous page. Thus, Singh and Das (2013) have not properly read Table III of Petrus (1998) and thus misrepresent that study.

Analysis 2.5. Comparison 2 Zinc versus placebo, Outcome 5 Time to resolution of nasal congestion.

Review: Zinc for the common cold

Comparison: 2 Zinc versus placebo

Outcome: 5 Time to resolution of nasal congestion

Study or subgroup	Zinc N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Kurugol 2006a	97	1.2 (0.8)	97	1.4 (1)		39.3 %	-0.20 [-0.45, 0.05]
Macknin 1998	103	7.5 (2.53)	109	8 (5.2)		20.4 %	-0.50 [-1.59, 0.59]
Petrus 1998	52	4.2 (2.88)	49	6.5 (4.9)		13.1 %	-2.30 [-3.88, -0.72]

In **Analysis 2.6,** Singh and Das (2013) state that the number of participants in Petrus (1998) "nasal drainage" analysis was N = 101 (52+49), whereas Petrus reported N = 73 for the reported mean and SD, see previous page. Thus, Singh and Das (2013) have not properly read Table III of Petrus (1998) and thus misrepresent that study.

Analysis 2.6. Comparison 2 Zinc versus placebo, Outcome 6 Time to resolution of nasal drainage.

Review: Zinc for the common cold

Comparison: 2 Zinc versus placebo

Outcome: 6 Time to resolution of nasal drainage

Study or subgroup	Zinc N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Kurugol 2006a	97	3 (1.5)	97	3.2 (1.8)		29.3 %	-0.20 [-0.67, 0.27]
Macknin 1998	99	7.5 (7.61)	107	7 (5.17)		15.7 %	0.50 [-1.29, 2.29]
Petrus 1998	52	4.2 (2.88)	49	6.6 (4.9)		17.6 %	-2.40 [-3.98, -0.82]

In **Analysis 2.8,** Singh and Das (2013) state that the SD in Petrus (1998) "cough symptom score" was 0.07 and 0.09 in the zinc and placebo group, respectively, see the Analysis below.

In Table III, Petrus (1998) reported that these were the SE values, see p. 28 of this document.

Because of this error, the P-value calculated by Singh and Das (2013) is vanishingly small and erroneous.

On p. 18, Singh and Das (2013) wrote that:

> *"Change in cough symptom score : In the study by Petrus 1998, a total of 101 participants were included and there was a significant decrease in the mean cough score in the intervention group (MD –0.23, 95% CI –0.26 to –0.2) (P < 0.00001) (Analysis 2.8)"*

To be more accurate, **Z = 14.28** (reported in Analysis 2.8, see a copy below) corresponds to:

$$\mathbf{P = 0.000\ 000\ 000\ 000\ 000\ 000\ 000\ 000\ 000\ 000\ 000\ 000\ 000\ 001 = 10^{-45}}$$

The correct "cough symptom scores" for all participants were actually:
mean 0.6916 (SD 0.69695, N = 52) and .7692 (SD 0.82644, N = 49)
(email from Ken Lawson 2014, April 11).

With these correct data, RevMan gives (MD –0.08, 95% CI –0.38 to +0.22) with **P = 0.6**, which has 44 fewer zeroes than the P-value corresponding to the calculated Z-value in Analysis 2.8 by Singh and Das (2013).

Thus the 95% CI and the P-value by Singh and Das (2013) are absolutely wrong.

In Table III, Petrus (1998) marked 2 comparisons, which they found significant (see p. 28 of this document), and other comparisons were found to be non-significant. Thus, Singh and Das (2013) should have wondered how is it possible that they calculated Z = 14.28, which corresponds to a P-value of 10^{-45}, whereas Petrus (1998) reported a non-significant difference (P > 0.05) in Table III for the same comparison.

Singh and Das (2013) should have carefully read Table III and should have contacted the authors to confirm that they correctly interpret the data correctly. Indeed I asked and received data and other relevant information of the Petrus (1998) trial.

Analysis 2.8. Comparison 2 Zinc versus placebo, Outcome 8 Change in cough symptom score.

Review: Zinc for the common cold

Comparison: 2 Zinc versus placebo

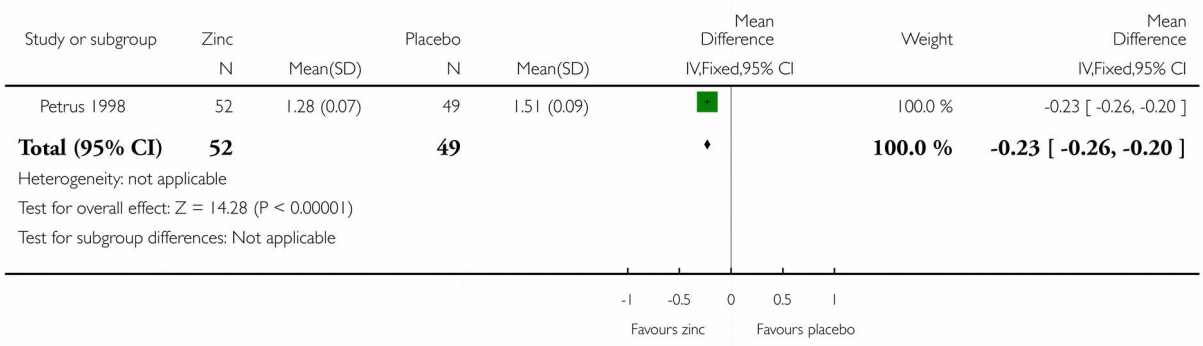
Outcome: 8 Change in cough symptom score

Study or subgroup	Zinc N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Petrus 1998	52	1.28 (0.07)	49	1.51 (0.09)		100.0 %	-0.23 [-0.26, -0.20]
Total (95% CI)	**52**		**49**			**100.0 %**	**-0.23 [-0.26, -0.20]**

Heterogeneity: not applicable

Test for overall effect: Z = 14.28 (P < 0.00001)

Test for subgroup differences: Not applicable



11) Singh and Das (2013) wrote that

> *"as there was a high degree of heterogeneity among the trials, the result should be interpreted with caution"* (p. 22, "*quality of the evidence*").
>
> "The very high heterogeneity means that the averaged estimates must be viewed with caution" (p. 2, Abstract)

No valid argumentation is given to support that statement. Unexplained heterogeneity is indeed a reason for caution, because we do not know for whom the treatment is useful and for whom it is useless, or which type of treatment version is effective and which kind is ineffective.

However, when a source of heterogeneity has been identified, heterogeneity *per se* does not necessarily lead to any caution. Low doses of zinc are uniformly ineffective in treating the common cold, but that is no argument against the benefit of high dose zinc acetate lozenges, which have reduced the duration of colds by a mean of 42%, see Hemilä (2011).

12) Singh and Das (2013) wrote that

> *"publication bias cannot be ruled out as shown by funnel plot asymmetry"* (p. 23, "*Potential biases in the review process*").

In the Results section (p. 19), Singh and Das (2013) also wrote:

> *"the funnel plot generated here shows that most of the precise studies (towards the top of the plots) have effect sizes which are either zero or very close to it (Analysis 1.1). One explanation for such asymmetry might be publication bias."*

However, funnel plot asymmetry *per se* is no evidence of publication bias, as pointed out by several papers: Tang (2000), Terrin (2005), Lau (2006), Ioannidis (2007), Sterne (2011). The last of them states that "funnel plot asymmetry is often, wrongly, equated with publication or other reporting biases". Asymmetry of the funnel plot can have numerous sources and therefore it does not tell anything specific about publication bias.

Cochrane Handbook states:

> "Results from tests for funnel plot asymmetry should be interpreted cautiously. When there is evidence of small-study effects, publication bias should be considered as only one of a number of possible explanations. In these circumstances, review authors should attempt to understand the source of the small-study effects, and consider their implications in sensitivity analyses." (Higgins 2011, sec 10.4.5).

When we consider using publication bias as an explanation for the pattern of the published findings on zinc lozenges and the common cold, there should be a strong correlation between the zinc dosage and the decision to publish the results. When low dose studies consistently show no evidence of an effect (even though these were published), and high dose zinc lozenge studies show strong evidence of benefit, a large number of high dose studies that show no effect should remain unpublished, to explain such a pattern. Thus, complex speculation about publication practices of authors and journals would be needed to explain the pattern of published findings as a result from publication bias, instead of explaining the pattern of findings simply as a result of dose dependency.

13) Many topics are dealt with under an irrelevant subtitle/subheading

***"How the intervention might work"* (p. 6 in Singh and Das 2013).**

Whole of the first paragraph (179 words), starting with:
"Interest in the use of zinc for the common cold grew following the results of a randomised controlled trial (RCT) conducted by Eby 1984..."
describes the history of zinc lozenges and does not seem pertinent under the heading "*How the intervention might work*".

The latter half of the second paragraph (67 words) staring with:
"Of the 18 trials conducted since 1984, 11 trials have shown zinc may be useful in the treatment of the common cold and seven have shown no benefit..."
describes the controlled trials that have been carried out on zinc lozenges and does not seem relevant under "*How the intervention might work*".

In total, the section "How the intervention might work" is 495 words long, so that half (246/495) of the text is not consistent with the heading.

***"Discussion: Part 1: methodology"* (pp. 19-20)**

Methodology in a systematic review of controlled trials indicates to most readers that potential biases, methods of interventions, methods of outcome measurements, etc of the included RCTs and methods of the systematic review will be comprehensively discussed under such a heading.

Consistently with such reasoning, the 4th line of the section states: *"We rated the methodological quality of the included trials as good, with two trials excluded because of poor quality..."*

However, p. 20 of Singh and Das (2013) has the 147 word text recycling (see p. 15 of this document) and other text about the ionization of zinc; and a paragraph about toxicology, which does not seem relevant under methodology in a systematic review.

The mechanism of effect and toxicology are indeed important topics, but the most appropriate section to cover this is not under "methodology" of a systematic review. Here too, substantial proportion of text is not consistent with the heading.

"Discussion: Part 2: results" (pp. 20-22)

Page 21 of Singh and Das (2013) discussed possible mechanisms of effect, *"There has been speculation regarding how zinc cures common cold"* (p. 20 left column middle, Singh and Das 2013). Page 21 also includes other text on the potential mechanisms of zinc effect.

Although the mechanism of zinc is important, it is not a relevant issue under the heading of "Results" of a systematic review of controlled clinical trials.

Implications for practice (p. 24)

As described above (p. 13 of this document), the unattributed copying of sentences from the abstract of Hemilä (2011) would be much more reasonable under the title "*Implications for research*".

14) There are many more problems with the Cochrane review by Singh and Das (2013), but it is not possible to cover them exhaustively in this document. The above comments deal with the major problems in that review.

References

Al-Nakib (1987)
Al-Nakib W, Higgins PG, Barrow I, Batstone G, Tyrrell DA. Prophylaxis and treatment of rhinovirus colds with zinc gluconate lozenges. J Antimicrob Chemother 1987; 20: 893-901.
http://www.ncbi.nlm.nih.gov/pubmed/3440773
http://dx.doi.org/10.1093/jac/20.6.893

Caruso (2007)
Caruso TJ, Prober CG, Gwaltney JM. Treatment of naturally acquired common colds with zinc: a structured review. Clin Infect Dis 2007; 45: 569-74.
http://www.ncbi.nlm.nih.gov/pubmed/17682990
http://dx.doi.org/10.1086/520031
see comments in: http://hdl.handle.net/10138/40817
see comments in: http://www.ncbi.nlm.nih.gov/pubmed/17682990#cm17682990_8518 (summary)

Douglas (1987)
Douglas RM, Miles HB, Moore BW, Ryan P, Pinnock CB. Failure of effervescent zinc acetate lozenges to alter the course of upper respiratory infection in Australian adults. Antimicrob Agents Chemother 1987; 31: 1263-5.
http://www.ncbi.nlm.nih.gov/pubmed/3307620
http://dx.doi.org/10.1128/AAC.31.8.1263

Eby (1984)
Eby GA, Davis DR, Halcomb WW. Reduction in duration of common cold by zinc gluconate lozenges in a double-blind study. Antimicrob Agents Chemother 1984; 25: 20-4.
http://www.ncbi.nlm.nih.gov/pubmed/6367635
http://dx.doi.org/10.1128/AAC.25.1.20

Eby (2004)
Eby GA. Zinc lozenges: cold cure or candy? Solution chemistry determinations. Biosci Rep 2004; 24: 23-39.
http://www.ncbi.nlm.nih.gov/pubmed/15499830
http://dx.doi.org/10.1023/B:BIRE.0000037754.71063.41

Feedback (2011) by Hemilä on Singh and Das (2011)
http://hdl.handle.net/10138/39188
http://www.mv.helsinki.fi/home/hemila/H32P.pdf
http://www.ncbi.nlm.nih.gov/pubmed/21328251#cm21328251_7867 (summary)

Godfrey (1992)
Godfrey JC, Conant-Sloane B, Turco JH, Mercer N, Godfrey NJ. Zinc gluconate and the common cold: a controlled clinical study. J Int Med Res 1992; 20: 234-46.
http://www.ncbi.nlm.nih.gov/pubmed/1397668

Hemilä (2011)
Hemilä H. Zinc lozenges may shorten the duration of colds: a systematic review. Open Respir Med J 2011; 5: 51-8.
http://www.ncbi.nlm.nih.gov/pubmed/21769305
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3136969
Supplementary Files: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3136969/bin/TORMJ-5-51_SD1.zip

Higgins (2011)
Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011.
http://handbook.cochrane.org

Hulisz (2004)
Hulisz D. Efficacy of zinc against common cold viruses: an overview. J Am Pharm Assoc 2004; 44: 594-603.
http://www.ncbi.nlm.nih.gov/pubmed/15496046

Ioannidis (2007)
Ioannidis JP, Trikalinos TA. The appropriateness of asymmetry tests for publication bias in meta-analyses: a large survey. CMAJ 2007; 176: 1091-6.
http://www.ncbi.nlm.nih.gov/pubmed/17420491

Jackson (2000)
Jackson JL, Lesho E, Peterson C. Zinc and the common cold: a meta-analysis revisited.
J Nutr 2000; 130(5S Suppl): 1512S-5S.
http://www.ncbi.nlm.nih.gov/pubmed/10801968
http://jn.nutrition.org/cgi/reprint/130/5/1512S

Lau (2006)
Lau J, Ioannidis JP, Terrin N, Schmid CH, Olkin I. The case of the misleading funnel plot.
BMJ 2006; 333: 597-600.
http://www.ncbi.nlm.nih.gov/pubmed/16974018

Macknin (1998)
Macknin ML, Piedmonte M, Calendine C, Janosky J, Wald E. Zinc gluconate lozenges for treating the common cold in children: a randomized controlled trial. JAMA 1998; 279: 1962-7.
http://www.ncbi.nlm.nih.gov/pubmed/9643859
http://dx.doi.org/10.1001/jama.279.24.1962

Mossad (1996)
Mossad SB, Macknin ML, Medendorp SV, Mason P. Zinc gluconate lozenges for treating the common cold: a randomized, double-blind, placebo-controlled study. Ann Intern Med 1996; 125: 81-8.
http://www.ncbi.nlm.nih.gov/pubmed/8678384
http://www.annals.org/content/125/2/81

Petrus (1998)
Petrus EJ, Lawson KA, Bucci LR, Blum K. Randomized, double-masked, placebo-controlled clinical study of the effectiveness of zinc acetate lozenges on common cold symptoms in allergy-tested subjects.
Curr Ther Res 1998; 59: 595-607.
http://dx.doi.org/10.1016/S0011-393X(98)85058-3

Prasad (2000)
Prasad AS, Fitzgerald JT, Bao B, Beck FW, Chandrasekar PH. Duration of symptoms and plasma cytokine levels in patients with the common cold treated with zinc acetate:
a randomized, double-blind, placebo-controlled trial. Ann Intern Med 2000; 133: 245-52.
http://www.ncbi.nlm.nih.gov/pubmed/10929163
http://dx.doi.org/10.7326/0003-4819-133-4-200008150-00006
http://george-eby-research.com/html/prasad.pdf

Prasad (2008)
Prasad AS, Beck FW, Bao B, Snell D, Fitzgerald JT. Duration and severity of symptoms and levels of plasma interleukin-1 receptor antagonist, soluble tumor necrosis factor receptor, and adhesion molecules in patients with common cold treated with zinc acetate. J Infect Dis 2008; 197: 795-802.
http://www.ncbi.nlm.nih.gov/pubmed/18279051
http://dx.doi.org/10.1086/528803

Science (2012)
Science M, Johnstone J, Roth DE, Guyatt G, Loeb M. Zinc for the treatment of the common cold: a systematic review and meta-analysis of randomized controlled trials. CMAJ 2012; 184: E551.
http://www.ncbi.nlm.nih.gov/pubmed/22566526
see comments in: http://hdl.handle.net/10138/40083
see comments in: http://www.cmaj.ca/content/184/10/E551/reply#cmaj_el_706238 (summary)

Singh and Das (2011)
Singh M, Das RR. Zinc for the common cold. Cochrane Database Syst Rev 2011, CD001364.
http://www.ncbi.nlm.nih.gov/pubmed/21328251
http://dx.doi.org/10.1002/14651858.CD001364.pub3
see comments in: http://hdl.handle.net/10138/39188
see comments in: http://www.mv.helsinki.fi/home/hemila/H32P.pdf
see comments in: http://www.ncbi.nlm.nih.gov/pubmed/21328251#cm21328251_7867 (summary)

Singh and Das (2013)
Singh M, Das RR. Zinc for the common cold. Cochrane Database Syst Rev 2013, CD001364.
http://www.ncbi.nlm.nih.gov/pubmed/23775705
http://dx.doi.org/10.1002/14651858.CD001364.pub4

Smith (1989)
Smith DS, Helzner EC, Nuttall CE Jr, Collins M, Rofman BA, Ginsberg D, Goswick CB, Magner A.
Failure of zinc gluconate in treatment of acute upper respiratory tract infections.
Antimicrob Agents Chemother 1989; 33: 646-8.
http://www.ncbi.nlm.nih.gov/pubmed/2665639
http://dx.doi.org/10.1128/AAC.33.5.646

Sterne (2011)
Sterne JA, Sutton AJ, Ioannidis JP, Terrin N, Jones DR, Lau J, Carpenter J, Rücker G, Harbord RM, Schmid CH, Tetzlaff J, Deeks JJ, Peters J, Macaskill P, Schwarzer G, Duval S, Altman DG, Moher D, Higgins JP.
Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ 2011; 343: d4002.
http://www.ncbi.nlm.nih.gov/pubmed/21784880

Tang (2000)
Tang JL, Liu JL. Misleading funnel plot for detection of bias in meta-analysis.
J Clin Epidemiol 2000; 53: 477-84.
http://www.ncbi.nlm.nih.gov/pubmed/10812319

Terrin (2005)
Terrin N, Schmid CH, Lau J. In an empirical evaluation of the funnel plot,
researchers could not visually identify publication bias. J Clin Epidemiol 2005; 58: 894-901.
http://www.ncbi.nlm.nih.gov/pubmed/16085192

Turner (2000)
Turner RB, Cetnarowski WE. Effect of treatment with zinc gluconate or zinc acetate
on experimental and natural colds. Clin Infect Dis 2000; 31: 1202-8.
http://www.ncbi.nlm.nih.gov/pubmed/11073753
http://dx.doi.org/10.1086/317437

Vakili (2009)
Vakili R, Vahedian M, Khodaei GH, Mahmoudi M. Effects of zinc supplementation
in occurrence and duration of common cold in school aged children during cold season:
a double-blind placebo-controlled trial. Iranian J Pediatrics 2009; 19: 376-80.
http://ijp.tums.ac.ir/index.php/ijp/article/view/928

Weismann (1990)
Weismann K, Jakobsen JP, Weismann JE, Hammer UM, Nyholm SM, Hansen B, Lomholt KE, Schmidt K.
Zinc gluconate lozenges for common cold: a double-blind clinical trial. Dan Med Bull 1990; 37: 279-81.
http://www.ncbi.nlm.nih.gov/pubmed/2192839
http://www.mv.helsinki.fi/home/hemila/birkhauser/Weismann_1990.pdf