UNDERLININGS WERE ADDED TO THIS VERSION TO POINT OUT THAT HH+EC FOLLOWED MOST OF THE INSTRUCTIONS AND ASKED A NUMBER OF QUESTIONS FOR FURTHER HELP.
HH COUNTED THAT THERE ARE 20 NEW RESPONSES BY HH+EC (RED ARE THE NEW);

12 OF THEM FOLLOWED THE INSTRUCTIONS; THERE ARE A FEW QUESTIONS FOR CLARIFICATIONS AND 1 INCONSISTENCY IN REFERENCES CAUSED BY ARI EDITORS REMOVING A PART OF TEXT BUT NOT REMOVING THE REFERENCE LINKED WITH THAT TEXT, AND 1 INCONSISTENCY BETWEEN THEIR EARLIER INSTRUCTIONS.

BOLD UNDERLINING WAS ADDED TO THE RESPONSES THAT FOLLOWED THE ARI GROUP INSTRUCTIONS

EDITORIAL COMMENTS: ROUND 2

VITAMIN C FOR PREVENTING AND TREATING THE COMMON COLD (A066)

10 October 2016

Thank you for revising and resubmitting your review. Where aspects of your review have been resolved, these have been deleted from the following report. The editor's comments (and responses to queries) are presented in red.

Edits have been applied throughout the review for compliance with current Cochrane style and methods, and to improve flow. Please retain edits, but correct any errors.

October-November 2016 responses by HH and EC are marked by red background and black text like this.

GENERAL

We do not understand the comment on “Avoid using pejorative terms.” We have not intended to be pejorative (meaning to express contempt). If you consider that some part of our text is pejorative, could you please point out that (those) specific parts.

By avoiding use of pejorative terms, we mean that terms, such as ‘sufferer’ be omitted, especially where positive alternatives can be applied. In this instance, using a term such as sufferer assumes the person’s health state; only the person with the disease or condition has the prerogative to use the term. Use of such terms by others may convey an ill-founded assumption.

Pejorative terms can be either nouns or adjectives, and can lead to negative impressions for readers where none was intended. For this reason, we ask that any terms that could belittle, make assumptions that may not be shared with the disease or condition, or express disapproval, be avoided.

HH+EC: OK; we did not interpret "sufferer" in that way**. We rewrote** those

METHODS

DATA EXTRACTION AND MANAGEMENT

This section edited to provide the required information. Please retain edits

ASSESSMENT OF RISK OF BIAS (ROB) IN INCLUDED STUDIES

This section has been re-written by the editors. Please retain.

RESULTS

DESCRIPTION OF STUDIES

INCLUDED STUDIES

Please report numbers of included studies—not numbers of comparisons.

HH+EC: How do you define a “study” and what do you mean with the above comment?

Study: a publication reporting a systematic, scientifically rigorous investigation of a healthcare problem. This may also be called a trial report.

We mean: report the number of included studies. Do not report numbers of comparisons made by the authors in the analyses.

HH+EC: That definition above seemed clear to us.

However, we were later instructed to write:"We included four new studies reported in three publications for this update" (Ann Jones 27 October and Liz Dooley 4 November).

That new instruction is inconsistent with the instruction above: "Study: a publication reporting a systematic, scientifically rigorous investigation of a healthcare problem. This may also be called a trial report."

The Carillo report ("trial report") should be counted as a single "study" on the basis of your defintion above. However, on your instructions 27 October and 4 November, you instruct that the Carillo report should be counted as two studies.

We cannot use different defintions for a "study" in different parts of our review. In our flow diagram we write that we found "3 studies of vitamin C and common" for the 2016 update. We must be consistent in the Results text section.

When there is a three arm trial, with placebo compared with, say, low vitamin C and high vitamin C. Is that one study or two studies?

This is one study reporting one three-armed trial

HH+EC: OK

In our text, we had used term "comparison" to refer to the comparisons of low vitamin C vs placebo and high vitamin C vs placebo. Thereby we refer to two comparisons.

The three arm trial is a single study. Thus, do you mean we should rename the "comparisons" as "studies"? That causes confusion for the readers. The Anderson 1974 study gives us 6 comparisons although it is a single study.

No. Studies are distinct and separate from comparisons. I can see why you may be confused. Studies with more than 2 arms have been treated as separate studies (such as Anderson 1974); this is not consistent with current Cochrane methods. However, because this has been applied in a previous update, it is not feasible to change.

We interpreted that you want comparisons to be renamed as studies and we made that change.

We ask that you please report according to the primary and secondary outcomes defined for your review; not by comparisons or by studies.

HH+EC: In the above comments we were asked to "Please add numbers of studies information as highlighted in the RevMan file" to the Abstract and the PLS.

As a study is defined as the primary study report**, <u>we revised</u>** the figures in Abstract and PLS.

****

19 Oct
Dear Harri,

...
Changes applied that impact on reported numbers of excluded studies from previous updates should be noted in the 'Differences between protocol and review' section with a brief explanation for the change; 'Excluded studies' section; the PRISMA flowchart (Figure 2) as well as any mentions in the 'Discussion', 'PLS' or elsewhere in the review.

We hope this additional explanation is helpful.

Kind regards,
Liz
****

HH+EC: In the 'Differences between protocol and review' section we describe addition of flow chart as item 20. **We added** to that item a description that we describe the search results by "studies" defined as primary study reports, and that also led to some revision in the excluded studies list.

This section contains a lot of information reported elsewhere and needs to be edited to reduce repetition.

HH+EC: Please, be more specific which sections or paragraphs you consider repetitive. In a long text some issues need to be discussed in different places. For example, not all readers are reading a review from the very beginning to the very end and therefore some repetitions are needed. What are the too extensive repetitions?

Authors are discouraged from assuming which sections will be read and those that won't. Cochrane reviews are carefully structured to reiterate key concepts for readers' ease of comprehension, and there is already quite a lot of repetition of key concepts. We value clarity and concision in authors' reviews, so please report information as guided by the Handbook and editors' feedback.

HH+EC: We did our best to look for repetitions in the "included studies" section, but we did not see any.

On 26 October, Harri asked Liz Dooley for some specific examples of "repetitions"

in the "included studies" section.

Ann Jones responded October 27 that "Because we work with limited resources, especially in terms of time, it's quite difficult to explain duplicated (or misplaced) reporting."

"Because we work with limited resources, especially in terms of time"

is not a reasonable response to Harri's question (October 26):

"Could you please be more specific and describe what is/are the repetition(s) in that section that are reported elsewhere."

Reviewing scientific manuscripts should be based on facts and not on speculations.

It is not reasonable comment about our draft that there might be some repetition somewhere, but you dont have time to find out where the repetition is, and if there actually is some repetition.

Ann Jones is paid for the job she is doing. We write and update the review with absolutely no funding, and we have lots of other commitments. If Ann has too much work, it is not our fault. However, it is not reasonable for Ann to speculate that there might be some problems and then leave for us to find out if there actually are some.

When Harri pointed out (October 27) that Ann's response (October 27) did not point out any specific examples of repetitions in the “included studies” section, Liz Dooley responded by resending (November 4) the same file that Ann Jones had send already (October 27), without any additional comments.

Resending the same file – without any single example of “repetitions” - is not at all helpful in our revision of the review. Furthermore, the text file had essentially all text underlined and it was difficult to see what were the actual changes in the text. There was no track-change system used to help us see what is old text and what is new text, and how some sentences should be interpreted.

The file that Ann Jones (October 27) and Liz Dooley (November 4) sent to us instructed us to write "We included four new studies reported in three publications for this update" which is inconsistent with your previous instructions, see above.

That file has some small changes in the text, such as instruction to write some words with a capitaletter: Nnaturally and Llaboratory but that is not a question of repetition.

Since you do not point out any case or repetition in the “included studies” section, we cannot make any corrections to a problem that we cannot see ourselves, and about which you will not give any actual examples.

EXCLUDED STUDIES

List key excluded studies and provide justification for all exclusions—22 studies are addressed in reasons for exclusions, but there were 30 excluded studies.

HH+EC: We added all reasons for exclusions.

There are now 35 reasons for 31 excluded studies. Where studies were excluded for more than 1 reason, please report this clearly or simply report the most significant reason for exclusion. Reported numbers must balance or offer a clear, concise reason why there are more reasons for exclusion than studies.

Please avoid mixing terms - use either 'trials' or 'studies' to indicate numbers of papers that were excluded.

Please add links to the studies that were excluded rather than enumerate how many were excluded for each reason listed

HH+EC: **We listed** the excluded studies after the reason for the exclusion. This version does not have numbers of excluded studies so that they would cause confusion. Those that have several causes are simply listed under the different reasons for exclusions

****

27 Oct 2016:
Dear Harri

Thanks for contacting Liz about your questions and suggested solutions.

It is not necessary to define 'study' in the review.

You need to identify three aspects of multi-arm included studies for review readers:

- overall, each unit is a 'study', as in 'we included xx studies'.
- studies may include more than two arms (these can be called 'study arms' or 'trial arms').
- within each study, there can be many comparisons. Report with the aim of making it clear which interventions are being compared.

Studies that report on more than one trial need to be identified and explained for readers. Because you have opted to assign individual study IDs for parts of studies, this needs to be made clear to readers.

We discourage use of the term 'trial comparisons'. Please use 'comparisons'.

Kind regards

Ann
******

HH+EC: **We added** a description that a "study" is being defined as a primary study report, and we added descriptions that some studies have several trials and some other studies have several vitamin C arms.
We also added a description that we use letters to indicate individual comparisons.
We use term “comparison” for the 71 vitamin C comparisons

RISK OF BIAS IN INCLUDED STUDIES

Summarise the risk of bias across domains for each key outcome for each included study, and ensure that these are supported by the information presented in the risk of bias tables.

HH+EC: What does this mean? “Across domains”?

Across domains means that we want you to give an overall assessment of all domains that were assessed for risk of bias. Was RoB high overall? Unclear? You have already mentioned domains in your review – these are what we refer to here.

Following the 'Risk of bias in included studies' heading, please add a very brief summary of your overall RoB assessment. Indicate outstanding or noteworthy assessments – were there domains that overall were assessed as unclear or high RoB?

HH+EC: **Revised**. The handbook does not give useful instructions how to describe the RoB conclusions in the Results section. We looked at some other reviews as examples and constructed our RoB comments in the Results section on the basis of analogy. We hope that the revised presentations is sufficient.

ALLOCATION (SELECTION BIAS)

Reporting is lacking: please indicate how many included studies (not comparisons) were RCTs. Quantify numbers of studies that applied allocation concealment. Provide an overall assessment of RoB for this domain—high, low, unclear.

HH+EC: We counted the number of studies that were randomized and used allocation concealment.

Please expand on randomisation methods. How was randomisation achieved?

What is the information in "overall assessment"? How does that help any reader? it does not seem to be relevant.

We see this as essential reporting. Generalising RoB findings in the narrative helps to convey the rigour of included studies in important methodological areas.

In our previous comments, we asked that authors "Provide an overall assessment of RoB for this domain - high, low, unclear." This has not been applied. Please resolve.

HH+EC: **Rewritten**

Science is about specific questions. One specific question is what are the methods in subgroup 3 of analysis 1.1. which found 50% decrease in common cold incidence. "Overall assessment" does not tell us anything about the reliability of that 50% estimate. Could you give further instructions.

Reporting RoB assessment is an important, mandatory aspect of Cochrane reviews. Please consult the Handbook's chapter on RoB assessment for further details about reporting requirements.

HH+EC: The Handbook sections given below give instructions on how to fill the RoB tables. They do not give instructions on how to summarize the RoB tables in the Results section. It seems to us that the problem here is what should be written to the Results section, and not whether our assessment of RoB is appropriate in the included studies table. **We looked at some other reviews as examples and constructed** our RoB comments in the Results section on the basis of analogy. We hope that the revised presentations is sufficient.

BLINDING (PERFORMANCE BIAS AND DETECTION BIAS)

Please see handbook sections 8.11.2 *Assessing risk of bias in relation to adequate or inadequate blinding of participants and personnel* and 8.12.2 *Assessing risk of bias in relation to adequate or inadequate blinding of outcome assessment* to ensure that standard reporting of assessment for the blinding domain is addressed.

HH+EC: Obviously, we had read that chapter previously and now we both re-read it.

What is the specific issue in your mind? Do you consider that some specific study(-ies) is not described properly, or do you consider that overall our general approach is not consistent with the Handbook. If so, how?

Please expand on how blinding was handled. Who were blinded and how? Please include information about overall judgement for this domain. How many studies were assessed at high risk of bias, unclear risk, and low risk?

HH+EC: The Handbook sections give instructions on how to fill the RoB tables. They do not give instructions on how to summarize the RoB tables in the Results section.

It seems to us that the problem here is what should be written to the Results section, and not whether our assessment of RoB is appropriate in the included studies table. We looked at some other reviews as examples and **constructed** our RoB comments in the Results section on the basis of analogy. We hope that the revised presentations is sufficient.

INCOMPLETE OUTCOME DATA (ATTRITION BIAS)

Please see Handbook section 8.13.2 *Assessing risk of bias from incomplete outcome data* for information about what must be assessed and reported here.

HH+EC: Obviously, we had read that chapter previously and now we both re-read it.

What is the specific issue in your mind? Do you consider that some specific study(-ies) is not described properly, or do you consider that overall our general approach is not consistent with the Handbook. If so, how?

Please report on any issues found relating to attrition bias. How might this have influenced reported outcomes in the included studies? How many studies were assessed at high risk of bias, unclear risk, and low risk?

HH+EC: **Rewritten**

SELECTIVE REPORTING (REPORTING BIAS)

Please see Handbook section 8.14.2 *Assessing risk of bias from selective reporting of outcomes* for guidance about reporting assessment for this domain

HH+EC: Obviously, we had read that chapter previously and now we both re-read it.

What is the specific issue in your mind? Do you consider that some specific study(-ies) is not described properly, or do you consider that overall our general approach is not consistent with the Handbook. If so, how?

This domain relates to any gaps you found in reporting among the included studies. Please indicate if all study outcomes were reported, and if they weren't, were compelling rationales provided> How many studies were assessed at high risk of bias, unclear risk, and low risk?

HH+EC: **Rewritten** and we added RoB item "selective reporting"

EFFECTS OF INTERVENTIONS

This section should tell the story of what was found in your analyses. At present, the reporting structure of highlighting the specific analysis detracts from the story. Links to presentation of forest plots as figures have been deleted. Including forest plots as figures duplicates information to be published in the Data and analyses section of the finalised review. Refer to the analysis instead. In many instances, you will need to revise advice to readers to consider (for example) 'the bottom of Analysis 1 Subgroup 3'. This should be expressed more concisely as 'Analysis 1.3.x'. You can insert a link to second level analyses, but you will need to type in subgroup numbers. Current descriptions rely on visual cues, which may not suit all readers.

HH+EC: "Including forest plots as figures duplicates information to be published in the Data and analyses section of the finalised review."

That is correct, but the RevMan guide states: "You can select the most important forest plots and funnel plots to be displayed more prominently as figures within the published review" (p 50).

That is certainly true. However, the maximum number of figures should not exceed 6 in total.

Thus, the guide explicitly encourages adding the most important forest plots as figures within the text.

Now we followed the instructions of the ARI group, but we point out that your instructions are inconsistent with the RevMan instructions.

These are not ARI group instructions: it is a validation requirement in RevMan. If more than 6 figures are included, this is highlighted for authors in RevMan's validation report as a warning.

HH+EC: We interpreted the instructions above so that we may put back the two major forest plots within the text – so they are more visible to readers - yet the total number of figures is not over 6.

CHARACTERISTICS OF STUDIES

CHARACTERISTICS OF INCLUDED STUDIES

ABBOTT 1968

The outcomes reported here are symptoms—not outcomes. Were outcomes of the therapeutic intervention reported in the study report? If the outcome was improvement of cold symptoms, then please express this here.

HH+EC: We do not understand this comment. The common cold is defined by symptoms. The duration of the common cold is defined by the time it takes from the onset of the symptoms to the end of the symptoms. Thus, the symptoms are elementary observations if we study the duration and severity of colds.

Please report study outcomes: that is, outcomes defined by study investigators. These may differ from review outcomes and must be reported here for all studies.

HH+EC: We do not see any specific outcome(s) defined by Abbott
Abbott et al. wrote as follows:
"Clinical data.—The following records were made: age and sex, smoker or non-smoker, and month of onset of the cold. Assessments were then made of improvement in those of the following symptoms which were present: sore throat, stuffy nose, sneezing, watery nasal discharge, purulent nasal discharge, headache, and aching back and limbs. In addition, temperature was recorded and a note made of whether the patient was confined to bed and whether any other treatment was given. These records were made daily and a four-point scale was used to record the severity of individual symptoms."

Please, look at the Abbott report yourself, can you find an outcome definition?

http://www.mv.helsinki.fi/home/hemila/CC/Abbott_1968_ch.pdf

If we are interested in the effect of vitamin C, we can eg calculate the severity of specific symptom(s) or an average symptom for each day of the study and compare if there are systematic differences between vitamin C and placebo groups.

Abbott wrote: "With both preparations severity of the following symptoms was maximal during the first four to five days, and then fell off sharply: sore throat, stuffy nose, sneezing, watery nasal discharge, headache and aching back and limbs. In the case of purulent nasal discharge, the severity was relatively low on the first day, building up to a maximum by the fifth day and gradually falling off with both preparations. With regard to the comparative results with the two preparations, there were virtually no differences at all in respect of any of these individual symptoms. Lack of space prevents giving the detailed figures for all these different assessments, but table I shows the results for the first symptom recorded, sore throat."

Our Table 2 is for "included trials with no data suitable for our meta-analyses"

Abbott did not transform their symptom recordings to a summary outcome per patients and therefore we cannot extract data for our meta-analyses and we present the study in Table 2. We do not see your point in claiming that the common cold symptoms are not outcomes of a common cold trial.

If you consider that our description of the Abbott study is not appropriate, please guide us further.

FIGURES

Please insert captions for figures 1 and 4: legends/notes have been provided.

HH+EC: what does this mean? There were texts explaining the figures. Please instruct further.

A caption is a brief description of the figure. Captions are often listed in lists of figures; so concision is needed.

Figure 1. Please delete "Brown 1945 is not shown in the figure". Add this information as a footnote and explain why Brown was excluded.

****

19 Oct
Dear Harri,
Regarding question 1, let me re-express our comments as indeed a Footnote is not possible. Could you please reduce the caption text in Figure 6 and just explain, in less than 15 words preferably, what the Figure depicts. You can move the current caption text to the text of the review where you refer to Figure 6.
....
Kind regards,
Liz
****

HH+EC: The Brown study was excluded to shorten the time scale. If we start the figure from year 1940, then the relevant part, from Ritzel (who motivated Pauling) to the great surge of RCTs in the 1970s after Pauling's book was published, is compressed towards the right hand side with the left hand 20 years containing only one - not very interesting - RCT.

In this revision we extended the scale to start from year 1940. Then we do not need to comment on Brown and the caption is shorter.

Figure 2. The study flow describing selection of studies for this update is hard to follow:

- 4 records assessed for eligibility
- 1 abstract excluded with reasons (you need to add what that reason was to the figure)
- This flows down to: ''4 studies added in 2016". (4 – 1 = 4?) Would you please clarify?

HH+EC:

In the previous version, we used term "record" to indicate the publication and "study" to indicate the vitamin C vs placebo comparison. One record had two studies.

We clearly stated "4 – 1 = 3 reports" and we stated that they included "4 studies"

Now we revised to show the number of studies on the basis of primary study reports

Figure 4. The figure is low resolution and too large to accurately reproduce on some screens and printers. (See the validation report). Would you please re-draw to reduce its size and improve resolution?

The caption for this figure should be re-examined. The notations provided are better accommodated as a figure footnote. Please derive a concise caption and present additional information as a footnote.

HH+EC: Our validation report did not give any warnings for figure 4 of the previous version. Neither for the revised figure – now fig 6 - of the revised version.

Too large means that the resolution is high and not low. All the details of the figure can easily been seen with the current accuracy and in that respect resolution is not too low.

Validation report does give warnings for fig 2 and fig 3, but we have no options to change those figures

We moved large parts of the caption for current fig 6 to the text section.

WHAT TO DO NOW

You review can be accessed by authors. Please apply changes as indicated, and insert response to editorial feedback within this document, and send as an attachment when you resubmit your review.

We will invite the statistics and contact editors to assess your revised draft and provide feedback.

Please run the Validation Report (File > Reports > Validation Report) before you check in your review for editorial approval and amend any Warnings, e.g.Reference: Higgins 2003 Reference is not linked from the text

HH+EC: We have been using the Validation testing.

Our version 28 Sept did have the reference Higgins 2003 in text:

"Assessment of heterogeneity: We assessed heterogeneity using the Chi² test and the I² statistic (Higgins 2003; Higgins 2011)."

You have rewritten the section "Assessment of heterogeneity" and dropped Higgins 2003 after our submission. Thus, the inconsistency was not generated by us.

We added Higgins 2003 back to that section.