

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 28 RESPONSES BY HH+EC;

18 OF THEM FOLLOWED THE INSTRUCTIONS; THERE ARE 9 QUESTIONS FOR FURTHER HELP AND 1 NEUTRAL RESPONSE “DOES NOT SEEM TO REQUIRE ANYTHING BY US”

UNDERLININGS WERE ADDED TO THE RESPONSES THAT FOLLOWED THE INSTRUCTIONS BY HH

EDITORIAL COMMENTS

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

13 July 2016

GENERAL

Thank you for responding to comments provided by Liz. Data corrections have been checked, and the editorial assessment continued to include compliance with Cochrane methods and style, as well as grammar and expression. You can access the (recently updated) Cochrane style guide from <http://community.cochrane.org/style-manual/>

The edit check found some aspects that need to be considered by authors to enhance readers' comprehension and comply with current Cochrane requirements.

Please revise your review to:

- Express in past tense, especially in Methods and Results sections—you are telling readers what you did and what you found.
- Write in active voice.
- Avoid using pejorative terms.
- Refer to study participants rather than groups.
- When writing about people use 'who' not 'that': People *who* take vitamin C... not People *that* take...
- Avoid split infinitives.
- Ensure subject-verb agreement is achieved.

- Avoid redundancies in expression, such as ‘in order to’, where ‘to’ would suffice.
- Avoid using superlatives, such as ‘a vast majority of’; use ‘most’.
- There is overuse of ‘thus’, both to begin sentences and as a conjunctive.
- Avoid use of single inverted commas—if it is a direct quote, use double inverted commas. Do not use single inverted commas to add emphasis to the narrative text.

Before you check your review back in for editorial assessment, please run a validation check (in RevMan →File →Reports→Validation report). Please ensure that no warnings or errors are reported. Please run a spell check (UK English spelling).

HH+EC: Liz Chalker read the text carefully and did her best to improve the language according to the above instructions. English is not Harri's first language.

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.

ABSTRACT

Limit for this section is 700 words. Edits have been made to reduce the word count, but it is still a little over the maximum limit.

HH+EC: we shortened the abstract to 696 words.

MAIN RESULTS

Please amend: how many new studies were added for this update, and the number of participants. Indicate total number of reports associated with the 71 included studies.

HH+EC: we added the number of studies. We added the total number of reports

PLAIN LANGUAGE SUMMARY (PLS)

The limit for the PLS section is 400 words; this section has been edited to comply with this standard, and mandatory headings added. The PLS should be pitched for readers with no clinical or scientific knowledge. Some text has been deleted or modified to meet this requirement.

Please add numbers of studies information as highlighted in the RevMan file.

HH+EC: The text is less than 400 words. We added the number of reports.

METHODS

TYPES OF INTERVENTIONS

The final paragraph:

“We included studies in which vitamin C had a co-intervention if the control group has only the co-intervention so that the only difference between the groups is vitamin C administration”

is difficult to understand. Please clarify.

HH+EC: Our definition that we compare vitamin C group to a placebo group covers studies in which both groups can have widely different life styles and other medications, but they must be the same except for vitamin C. We wanted to emphasize that there may be co-interventions which are the same in both compared groups. We deleted that sentence since you considered it confusing.

ELECTRONIC SEARCHES

Current review reporting requirements require presentation of the flow of study selection to be presented in a PRISMA flow diagram. Would you please translate the study selection for the review to Figure 2? We understand that constructing the figure to accommodate search results and study selection from years ago may not be possible; please add the results for the 2016 update. Delete redundant sections of Appendix 1 after populating the study flow diagram at Figure 2.

HH+EC: We constructed a flow chart in which we show the new results for the 2016 update.

We refer to Appendix 1 for the previous searches.

DATA EXTRACTION AND MANAGEMENT

Please include a description of processes undertaken for this update: specify how data were extracted from reports of included studies, clarifying how many people were involved (and whether you worked independently), and how disagreements were handled. Describe data collection processes for any reports requiring translation. Indicate if any attempts to contact authors for further data (or clarification) were made (such as Carillo). List the types of information that were sought from reports of included studies.

HH+EC: We do not quite understand this question. We describe that HH entered the data to the spreadsheet. Thus, he re-read the publication tables and texts reporting the results to collect the date. We describe that both HH and EC checked the data against the original reports. HH wrote the procedures for the spreadsheet to calculate the transformations and EC checked that she agreed.

We had already extracted the data first in the 1990 by EC and Bob Douglas, and in 2004 fully again by HH and Bob Douglas. Thus, we could also check that there were no significant differences in our data compared with the previous update based on the 2004 data extraction.

We did some rewriting. Could you be more specific if you want some further descriptions in the Data extraction section.

Please revise the second paragraph—it was not possible to enter data into RevMan 2014 for the 2004 review.

HH+EC: revised

ASSESSMENT OF RISK OF BIAS (ROB) IN INCLUDED STUDIES

This section is too long and includes information better reported elsewhere, such as amendments made to RoB tables (correctly reported in 'Differences between protocol and review'). Edits have been applied to limit repetition of information reported elsewhere in the review.

In this section, please indicate:

- the tool used to assess RoB (Cochrane RoB tool)
- how the tool was implemented
- criteria used to classify studies (high, low and unclear RoB).

Interpret overall RoB for readers (as well as referring to Figure 3).

HH+EC:

We revised the text and added note that we used Cochrane RoB tool.

What does “Interpret overall RoB for readers” mean?

RESULTS

DESCRIPTION OF STUDIES

RESULTS OF THE SEARCH

Translate the first paragraph in this section to populate Figure 1.

Include a definitive statement about how many studies are new for this update; how many participants were involved, and how many reports are associated with these studies (if greater than the number of studies).

Report contact with Carillo in information about the search.

HH+EC: we constructed a flow chart. We added note that we contacted Carillo and Elwood.

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?

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?

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.

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

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?

Please restructure reporting to clearly describe:

Design

Sample sizes

Setting

Participants

Interventions

Outcomes

(These concepts can be added as subheadings). Include a statement about sources of data in the review—i.e. from published literature? By correspondence? Elsewhere?

HH+EC: We revised the text

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.

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”?

Judgements provided in RoB tables need to be expanded—it is not appropriate to simply refer readers to studies—authors need to interpret and report relevant information here. Neither is it appropriate to indicate a judgement by inserting a question mark. Given that many studies were published before it was usual to report these domains, we understand that many cannot be reliably reported. If this was the case, please indicate judgements as: “There was insufficient reporting to enable assessment”.

HH+EC: We replaced question marks with “There was insufficient reporting to enable assessment”.

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.

What is the information in “overall assessment”?

How does that help any reader? it does not seem to be relevant.

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.

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?

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?

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?

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).

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.

We transformed subgroup references to the versions instructed above (type: Analysis 1.1.x).

Other issues:

- write this section in past tense (telling readers what you found)
- write in active voice
- simplify and interpret summary data for each intervention group.

Paragraph 2 in 'Incidence of colds' is difficult to interpret: it makes assumptions that readers may find confusing. The mention (in the second sentence) of '35 comparisons' creates a disjointed flow of information. There is a lot of information, but it is hard to pick up the story being told by your findings. We suggest that you revise to clearly and concisely tell your compelling story by simplifying expression.

HH+EC: We revised that paragraph and we hope it appears more easy to follow.

DECLARATIONS OF INTEREST

Dols need to be the same as submitted on Col forms: this section has been updated.

HH+EC: does not seem to require anything by us.

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.

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.

Reporting of funding sources is highly encouraged. Although it has been reported elsewhere in your review that funding was seldom reported when many studies were published, please indicate this aspect in the 'other' domain for each included study.

HH+EC: We added a note about funding information.

Risk of bias

Please do not express judgements as 'see above', '?', or link to a study. Please add a brief narrative reason for your judgement in every domain for all studies. If the domain could not be assessed, please indicate this was the case.

HH+EC: we copied the texts to the “see above” places and we replaced ? with a statement that the domain could not be assessed.

FIGURES

Figures presenting forest plots have been deleted: the maximum number of figures that can be presented is six. Forest plots are published as part of analyses, and their presentation as figures creates duplication. Please link to relevant analyses. Links have been replaced as required.

HH+EC: This instruction is inconsistent with RevMan guide, which 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). Thus, the guide explicitly encourages adding the most important forest plots as figures within the text.

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

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.

WHAT TO DO NOW

Your review can be accessed by authors. Please apply changes as indicated, and insert response to editorial