S12 S7 and S11 91
S11 S8 or S9 or S10 3342
S10 TI vitamin* N5 c OR AB vitamin* N5 c 1762
S9 TI ascorb* OR AB ascorb* 586
S8 (MH "Ascorbic Acid") 2325
S7 S1 or S2 or S3 or S4 or S5 or S6 1767
S6 TI ((viral or virus*) N2 rhinit*) OR AB ((viral or virus*) N2 rhinit*) 5
S5 TI acute rhinitis OR AB acute rhinitis 30
S4 TI coryza OR AB coryza 23
S3 TI rhinovirus* OR AB rhinovirus* 153
S2 TI common cold* OR AB common cold* 501
S1 (MH "Common Cold") 1400

Appendix 4. LILACS (BIREME) search strategy 2012

VHL > Search > (MH:"Common Cold" OR "Resfriado Común" OR "Resfriado Comum" OR "Coriza Aguda" OR catarro OR coryza OR rhinovir$ OR MH:rhinovirus OR "acute rhinitis" OR "viral rhinitis") AND (MH:"ascorbic acid" OR "Ácido Ascórbico" OR "Vitamin C" OR MH:D02.241.081.844.107$ OR MH:D02.241.511.902.107$ OR D09.811.100$ OR "Vitamina C")

Appendix 5. Web of Science (Thomson Reuters) search strategy 2012

Topic=("common cold" or "common colds" or rhinovir* or coryza or "acute rhinitis" or "viral rhinitis" or (virus* NEAR/2 rhinitis)) AND Topic=("ascorbic acid" or ascorb* or (vitamin* NEAR/5 c)) Refined by: Publication Years=(2011 OR 2010 OR 2012)
Timespan=1955-2012. Databases=SCI-EXPANDED, CPCI-S, CCR-EXPANDED, IC.
Lemmatization=On

Appendix 6. Trials Registers search strategy 2012

common cold AND vitamin c
ascorbic acid AND common cold

F E E D B A C K

Flaws in statistical analysis?

Summary

There appear to be several instances where there is considerable overlap between studies, but they are treated as independent studies as far as the meta-analysis is concerned. For example, the Anderson 1974, 1974a, 1974b studies seem to be treated as independent in graph (comparison 01, outcome 04), but the control groups seem identical, and 275 people in the treatment group seem the same in each study. The effect is to inflate the value of this study. Indeed, the difference between the treatment groups for Anderson 1974a, 1974b (33 new people, *all* apparently with one or more respiratory episodes) raises further issues.

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

David Wooff

Reply

In the new edition of the review we have avoided this problem described above by combining all trial arms that were compared with the one placebo group into one trial arm for purposes of the meta-analysis

Contributors

Reply supplied by the Authors of the review
Comment and reply posted 28 August 2004

Unit of analysis issues

Summary

Further to David Wooff's comment, I suspect there may be other statistical flaws in this review that could be placed under the heading, 'unit of analysis errors'.

At least one study (Lugviggson) appears to be a cluster randomised trial, yet there is no discussion of the possible over-weighting of this study when naively included in the meta-analyses.

At least two studies appear to be twin studies (Carr and Miller). Should the matching be taken into account in the analysis, in a similar way to a simple cross-over trial?

The particular meta-analysis for 'Mean symptom days per person' in the comparison 'Vitamin C 1G daily or more vs placebo' worries me considerably. Of the six studies (10 contributions) included in this analysis, I suspect that at most two are free of unit of analysis errors of various kinds. This makes it a wonderful teaching example, but for the wrong reasons.

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

Julian Higgins

Reply

Ludvigsson writes explicitly "Every class was divided at random into two groups." In our opinion this statement means that Ludvigsson was taking one class and he divided the participants of that one class into to two groups 'at random,' and then he went to another class and similarly randomised the second class. We disagree that cluster randomisation applied here.

As to the two small twin trials: Miller 1977 explicitly stated that "analysis of the paired comparisons…" so we conclude their SE values in their main table are based on paired t-test, event though this is not explicitly stated in their methods; Carr 1981 explicitly stated "the results for the six summary cold variables of the paired analyses of variance between active and placebo groups are shown…" so we conclude their P-values refer to paired analyses. In any case, the mean difference between the groups is the same whether we calculate difference of means or mean of paired differences. Failure to take into account the pairing of data would mean that we would be over-conservative in our estimate of the precision of any effect, but it is unlikely that this issue would anyway have influenced our conclusions in a meaningful way.

In the current review we have not used as an outcome variable mean symptom days per person but have concentrated on mean symptom days per episode.

Contributors

Reply supplied by the Authors of the review
Comment and reply posted 28 August 2004

Doses too small

Summary

One gram daily is a small dose. Most mammals make 3 or more grams in their livers. Any practitioner of orthomolecular medicine knows that a minimum of several grams a day is needed to surely prevent a cold, and as much as 20 grams to cure one in progress. Not one trial in your RCT's qualifies.

I certify that I have no affiliations with or involvement in any organisation or entity with a direct financial interest in the subject matter of my criticisms

Reuven Gilmore

Reply

The practitioners of orthomolecular medicine have not to our knowledge published any controlled trial evidence on which this comment is based. As we have said in the review, there is no reasonable doubt that vitamin C supplementation plays some biological role in defence, and there is tantalising evidence from the Anderson 1974 study that a single therapeutic dose of 8 grams at commencement of a cold may have had a useful therapeutic effect.

We believe there is a case for rigorous evaluation of the possibility that very large doses (of the order of 8 g daily in adults for periods up to five days after the onset of symptoms) could produce benefits that were not seen at lower doses.

In view of the greater propensity of children to catch colds and the greater benefits observed in the child prophylaxis studies, this may be the group in which to explore this approach (with an appropriately pro-rated dose for weight). We add however a caution. Although studies in which doses of 1 or 2 g daily of vitamin C have been used for several months have not produced convincing evidence of adverse effects to the volunteers, dosage of the kind discussed here needs to be carefully monitored for adverse effects - especially in children.

Contributors

Reply supplied by the Authors of the review
Comment and reply posted 28 August 2004

Vitamin C for preventing and treating the colds, 10 July 2005

Summary

This paper by Hemila and Douglas is highly misleading. Two fundamental scientific errors invalidate the conclusions of their review.

Their first error is the dose range: the doses employed are too small. Treatment of disease requires pharmacological doses of vitamin C, in the range 10 to 200 g per day [Cathcart, Medical Hypotheses, 7, 1359-76]. Prevention of disease requires a minimum of 2.5 g per day, in divided doses, to establish a dynamic flow through the body. In defending their review, Hemila and Douglas cite Levine [Levine et al. JAMA, 1999, 281,1415-23] as showing that the body is saturated by a dose of 0.5 g per day: this finding has been discredited. A more recent paper by Levine and colleagues shows that the body is not saturated by doses up to 18 g per day. [Padayatty et al, Ann Intern Med, 2004, 140, 533-7]. This discrepancy has been explained in a recent book [Hickey and Roberts, Ascorbate, 2004, Lulu press].

The second error concerns the dose frequency. Since high doses of vitamin C have a half-life of about 30 minutes, single or twice daily doses do not increase plasma levels for more than a few hours [Levine et al. JAMA 1999, 281,1415-23]. Such doses provide a minimal protective effect. Given these infrequent doses, even a small positive effect implies a powerful therapeutic potential.

Douglas and Hemila have not shown that vitamin C is ineffective against the common cold, unless the doses used are both inadequate and inappropriate. They have, however, made clear that the previous 65 years of research has been based on a range of doses that are too small and too infrequent. Thus, the research to date may grossly underestimate the therapeutic value of vitamin C. Tests of appropriate dose levels and timing regimes are urgently required.

Steve Hickey PhD. Manchester Metropolitan University
Hilary Roberts PhD

Reply

Hickey and Roberts claim that the prophylactic and therapeutic trials that have been carried out to date have used a range of doses that are too small and too infrequent. They speculate, on the basis of pharmacodynamic studies, that prevention of disease would require a minimum of 2.5 g of vitamin C per day in divided doses. If they firmly believe in their reasoning (there are good grounds for debate), they or someone else need to undertake rigorous prophylactic trials at such dosage levels.

Nevertheless, while stating that "prevention of disease requires a minimum of 2.5 g/day", Hickey and Roberts ignore our finding that in six trials with participants under heavy physical or cold stress or both, vitamin C halved the incidence of common cold type of symptoms (our Fig 01). This benefit was seen with doses of 0.25 to 1.0 g/day which is substantially less than those speculated as minimal by Hickey and Roberts. Thus in our Fig 01 the living conditions rather than the vitamin C dosage provided the explanation to the heterogeneous trial results.

Our review does not claim that the issue is closed. It acknowledges that vitamin C plays some biological role in defence against respiratory infections but finds no evidence that at doses up to 1 to 2 g/day vitamin C would prevent colds in the general population or reduce common cold duration enough to justify regular supplementation.

Finally, we drew attention to one study in which an 8 g therapeutic dose seemed to be beneficial and underlined the fact that no therapeutic trials have been carried out in children even though the regular supplementation trials found greater effect in children.

Contributors

Harri Hemilä and Robert M Douglas
Comment and reply posted 16 November, 2005

Vitamin C doses in trial, 24 July 2007

Summary

Studies which find the effects of vitamin C on the common cold inconclusive invariably use less than 1 g of ascorbic acid a day. Proponents of Vitamin C therapy consistently use 3 or more grams a day. This debate will not be resolved until both camps start testing the same dosages. Since the ascorbic acid proponents acknowledge that < 1 g a day will have little therapeutic effect, it is incumbent on researchers to analyze the effect of megadoses.

I routinely dose to bowel tolerance. 0.5 g every hour for eight hours will reach bowel tolerance for me. When I begin to become ill, I have dosed as high as 0.5 g every 20 minutes without reaching bowel tolerance. I can significantly reduce the effect of a cold in this fashion, and once was the only one functioning in my office when everyone else was sick.

My rule of thumb is 35 mg per pound of body weight per day. This must be distributed throughout the day to prevent overloading the ability of the stomach to absorb it, and to provide continuous saturation, because of the rapid decomposition of ascorbic acid once it is no longer in crystalline form. This dose is consistent with the levels of ascorbic acid produced by the liver of other mammals.

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

Sean Emerson

Reply

Our review shows that the relation between vitamin C dosage and effect is not as simple as Sean Emerson suggests. We found statistically significant heterogeneity in the effect of vitamin C on common cold incidence. The heterogeneity was not explained by vitamin C dosage but by segregating trials with people under heavy acute physical stress to a separate group. In the latter subgroup, vitamin C halved the common cold risk, yet the doses in the trials were rather low, from 0.25 to 1 g/day. Prophylactic trials with the general population found no evidence that vitamin C would prevent colds, even though the highest prophylactic dose was 3 g/day (Karlowski 1975).

In the therapeutic trials, the dose-response is also complex. Several studies with 3 to 4 g/day failed to find therapeutic benefit (Cowan 1950, Elwood 1977, Tyrrell 1977, Audera 2001). Thus, the negative findings in therapeutic trials are not simply explained by the use of ascorbic acid in "doses less than 1 gram a day". On the other hand, Anderson 1975 found statistically significant 25% reduction in "days spent indoors per subject" with dosage of 1 to 1.5 g/day for five days. This benefit is not explained by the use of particularly high doses.

We pointed out that in the Karlowski 1975 trial 6 g/day was associated with a double benefit compared with 3 g/day. We also pointed out that Anderson 1974 reported that 8 g/day on the first day of the common cold appeared better than 4 g/day. Thus, there are scattered data suggesting dose dependency, but these findings are more relevant for planning further trials than for immediate conclusions to claim dose-dependency.

Based on the trials analysed in our review, we do not consider that regular supplementation of the ordinary people is justified. On the other hand, vitamin C is inexpensive and safe in doses of grams per day and, while waiting for new therapeutic trials, testing vitamin C for common cold treatment may be reasonable at an individual level. However, explicit evidence from well-conducted trials is required for broad recommendations to use vitamin C for treating the common cold, and such evidence is missing.

Contributors

Hemilä, Douglas and Liz Chalker
22 August, 2007

Vitamin C and the common cold, 2 April 2008

Summary

Introduction

The Cochrane review provides a meta-analysis of low-dose studies of vitamin C and the common cold. Unfortunately, its authors limit the range of intakes to values that are marginally effective, and exclude clinical data on higher doses, which have been shown to provide positive results.

The review fails to understand orthomolecular claims for vitamin C in prevention and treatment of the common cold, repeated over a period of at least 50 years.[i],[ii],[iii],[iv],[v],[vi] Orthomolecular nutrition and medicine are concerned with varying the concentrations of substances such as vitamin C, which are normally present in the body, to prevent or control disease; typically, this involves large doses of nutrients. The doses Douglas *et al*. refer to as “mega-dose vitamin C supplementation” range from 200 mg, once or twice daily. These are small doses.

To avoid misunderstanding, we state the orthomolecular claims for vitamin C:

Vitamin C given at frequent intervals (< 6 hourly) and sufficiently high doses (8+ grams per day) will prevent common colds in the majority of subjects (individual variation is high).

Vitamin C, given at short intervals and very high doses to a subject with the common cold, can eliminate the symptoms and may bring about a cure within hours [1,2,3,3,5, 6,7]. Cathcart suggests 30-150 grams per day, at intervals of one hour or less.[vii] The Vitamin C Foundation recommends 8 grams every 20 minutes, from the onset of symptoms.

The dose-response relationship for the treatment claim is described as a threshold effect; unless a minimum threshold dose is reached, little or no clinical response is achieved.[viii]

Review shortcomings

Methodology

1. If a reviewer is aware of author names, experimental details, and results, she can influence the outcome of the review by unfair selection; even honest experimenters are subject to unconscious effects. In this case, the reviewers had prior knowledge of the literature on vitamin C and the common cold, and specific knowledge of the papers under consideration. The researchers were aware that selection criteria would exclude ALL clinical reports of high (orthomolecular) doses. These problems have been communicated to the authors, though their response has been unsatisfactory. A clear and objective response might provide reassurance that the potential for bias was being addressed.

2. As described in another Cochrane review, the placebo effect is irrelevant in the case of definitive and objective clinical effects. The effects claimed for vitamin C are large, objective, and definitive [6]. Orthomolecular physicians report complete, dose-related, reversal of symptoms, or rapid cure. The review required placebo controls on the basis that the authors considered "that with the expected small effects of vitamin C, and the greatly subjective outcome definitions, only placebo-controlled trials could yield information of adequate rigour." Such an expectation is based on a misconception of the claims for vitamin C. The explanation is particularly inadequate, as it restricts the doses studied to outliers of the range claimed to be effective.

Results

3. The review does not include data for intakes of the order of magnitude described in the orthomolecular prevention or treatment claims. This objection was made by Hickey and Roberts, and Higgins, in response to an earlier version, later reinforced by Emerson. Douglas *et al.* responded tangentially and failed to explain how their data could be extrapolated to cover the doses claimed to be effective.

4. The review covers longer dose intervals than those claimed to be effective. Hickey and Roberts published this objection and again the response by Douglas and Hemilä did not indicate how their data could be extrapolated to more frequent doses.

5. The reviewers disregard the pharmacokinetics of vitamin C. The half-life for kidney excretion of high-dose vitamin C from plasma is about 30 minutes [6]. At the dose levels and intervals studied by Douglas *et al.*, there would be little, if any, consistent increase in plasma ascorbate levels or body content. The action of vitamin C depends on its ability to donate and transfer electrons: if the ascorbate has been excreted, it cannot exert this redox effect. A rigorous response is required, as this failure breaches basic principles of pharmacology.

Conclusions

6. The reviewers dismiss the observations of Cathcart and others, on the grounds that "their uncontrolled observations do not provide valid evidence of benefit". Scientifically, such experimental results are more valid than large-scale clinical trials or epidemiological studies. The scientific method involves hypothesis and refutation.[i] Easily replicable experiments, as reported by internationally-known physicians, such as Cathcart, Klenner, Hoffer, Levy, Kalokerinos, and Brighthope, have great scientific validity. If these observations were in error then, over the last half century, any physician or scientist could have refuted the claims, with little effort or cost. No such refutation exists in the literature.[6]

7. The authors failed to identify the limitations of their review. Their results relate to low doses: approximately an order of magnitude less than those claimed to be effective. The review did not specify that its results and conclusions exclude orthomolecular and other clinical claims for the effectiveness of vitamin C.

8. Taken as a whole, the review and resultant media generalisations are misleading, as they deflect attention away from the actual claims for vitamin C's effectiveness. The authors have promoted their conclusions widely under the Cochrane name, resulting in generalisations that are out of proportion to a scientific interpretation of the data. A widely-quoted press release from Douglas' university begins "vitamin C has been proven ineffective in combating the common cold in most people." Douglas claims, "vitamin C has proven not to be a magic bullet to solve the common cold".[i] We can find no evidence in the Cochrane review to support such unscientific claims,[9] let alone provide anything close to "proof".[9] The hypothesis that appropriate doses of vitamin C can prevent or cure the common cold has not been refuted and we ask that this review be withdrawn [6].

[1] Klenner F.R. (1953) The Use of Vitamin C as an Antibiotic, The Journal of Applied Nutrition, 6, 274-278.

[2] Stone I. (1972) Vitamin C Against Disease: The Healing Factor, Perigree Books.

[3] Cathcart R.F. (1981) The Method of Determining Proper Doses of Vitamin C for the Treatment of Disease by Titrating to Bowel Tolerance, Orthomolecular Psychiatry, 10(2),125-132.

[4] Lewin S. (1976) Vitamin C: Its Molecular Biology and Medical Potential, Academic press.

[5] Levy T. (2002) Vitamin C, Infectious Diseases and Toxins, Xlibris Corp.

[6] Hickey S. Roberts H. (2004) Ascorbate: The Science of Vitamin C, Lulu press.

[7] Cathcart R. (1981) Vitamin C, titrating to bowel tolerance, anascorbemia, and acute induced scurvy, Medical Hypotheses, 7, 1359-1376.

[8] Cathcart R.F. (1985) Vitamin C: the non-toxic,nonrate-limited, antioxidant free radical scavenger, Medical Hypotheses, 18, 61-77.

[9] Popper K. (1963) Conjectures and Refutations: The Growth of Scientific Knowledge. Routledge.

[10] Amanda Morgan (2005) News from The Australian National University, Tuesday 28 June.

Steve Hickey PhD and Hilary Roberts PhD

The following response demonstrates the cultural divide between clinicians and researchers. Offering a placebo is unethical for a clinician and logical for a researcher.

Reply

Reply to Hickey and Roberts' comments, May 2008

Hickey and Roberts reiterate comments to which we have already replied. See the earlier discussions. Here we focus on fundamental issues related to the evaluation of medical interventions.

First, Hickey and Roberts criticise us for excluding uncontrolled observations from our systematic review. The importance of control groups in the evaluation of medical interventions is discussed in basic textbooks of clinical trials and epidemiology and also in the Cochrane Handbook (1). We do not repeat the arguments here. The Cochrane Collaboration focuses mainly on randomised controlled trials, but non-randomised controlled studies can be included when justified; however, the inclusion of uncontrolled observations is not an option (Ref. 1, Chapter 13). With their opinion that "uncontrolled observations are more valid than large-scale clinical trials or epidemiological studies", Hickey and Roberts challenge the whole Cochrane Collaboration and not just our review on the common cold.

Second, Hickey and Roberts state that "the placebo effect is irrelevant in the case of definitive and objective clinical effects." Even though the placebo effect has often been exaggerated, there is firm evidence of placebo effect on patient-reported continuous outcomes and on pain measured as a continuous outcome (2). Moreover, in their meta-analysis examining the role of methodology in controlled trials, Balk et al. (3) found that the lack of placebo control biased the treatment effects of paediatric trials that measured soft outcomes of respiratory diseases. Therefore, the absence of placebo leads to a high risk of bias in trials on the common cold, which is a short-lasting and non-severe disease with soft outcomes.

Third, Hickey and Roberts are not consistent in their argumentations. They state that "even honest experimenters are subject to unconscious effects", yet they ignore this wisdom when they lean on the uncontrolled observations by vitamin C enthusiasts.

Our review was largely motivated by the work of Linus Pauling, who hypothesised in the early 1970s that grams of vitamin C per day would prevent colds. We found that trials in the general community do not support Pauling's hypothesis, whereas trials with individuals under heavy acute physical stress do. The statistically highly significant effect in the latter group of trials refutes Hickey and Roberts' argument that our "results relate to low doses: approximately an order of magnitude less than those claimed to be effective." The heterogeneity we found indicates that the characteristics and conditions of people are important in determining the effect of vitamin C, whereas we do not see basis to assume that doses that are an order of magnitude higher than those used in the prophylactic trials (up to 3 grams per day) would prevent colds in the general community.

The purpose of our systematic review was not to test Hickey and Roberts' orthomolecular claims and none of the identified controlled trials directly test them. With their belief that frequent high-dose vitamin C supplementation prevents colds in all people, and their note that testing vitamin C effects requires "little effort or cost", Hickey and Roberts should consider organizing by themselves a randomised controlled trial to examine their orthomolecular claims.

This response is irresponsible and obtuse.

1 Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.0 [updated February 2008]. The Cochrane Collaboration, 2008. Available at: http://www.cochrane.org/resources/handbook/

2 Hrobjartsson A, Gøtzsche PC. Placebo interventions for all clinical conditions. Cochrane Database Syst Rev 2004;(2): CD003974.

3 Balk EM, Bonis PAL, Moskowitz H, Schmid CH, Ioannidis JPA, Wang C, Lau J. Correlation of quality measures with estimates of treatment effect in meta-analyses of randomised controlled trials. JAMA 2002; 287: 2973-82.

Contributors

Harri Hemilä, Robert M Douglas, Elizabeth Chalker, Barbara Treacy
23 May, 2008

Vitamin C for preventing and treating the common cold, 25 November 2008

Summary

I would be interested in your results if you restricted studies to those using 1.0 grams or more.

Submitter agrees with default conflict of interest statement:

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

Roger Mann M.D.
Occupation Family Physician

Reply

We have previously replied to overlapping feedbacks on the dose-response issue (see the other comments). In this update, we calculated the effect of 1 g/day or more on common cold incidence in the general community trials and also with this restriction there is strong evidence that prophylactic vitamin C has no effect on the average incidence of colds. None of the five trials with physically stressed people used over 1 g/day and therefore the benefit in that group is not explained by particularly high dosage.

We note that Karlowski 1975 and Coulehan 1974 used two different doses within the same trials and with the same outcome definitions. Karlowski found that for adults, 6 g/day was associated with a double benefit compared with 3 g/day, and Coulehan found that for school children, 2 g/day caused about twice the benefit of 1 g/day (Hemilä 1996a; Hemilä 1999a). Although these findings do not establish dose dependency, they are interesting and support the case for examination of higher doses in therapeutic trials.

Contributors

Harri Hemila, Liz Chalker, Bob Douglas
13 November, 2009

Vitamin C for preventing and treating the common cold, 11 February 2013

Summary

Re review of studies about Vit C and prevention of urti. Linus Pauling recommended up to 16 gm /day. Were any of the studies using these doses?

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

Dr Robert McKillop
General Practitioner

Reply

As a short answer to the question, none of the studies in the review used doses as high as 16 g/day, but we will briefly summarize the question of doses.

In our review we acknowledge Linus Pauling's role in the 1970s in promoting publicity about the possible role of vitamin C against the common cold and in leading to the conduct of dozens of placebo-controlled trials on the topic. However, conclusions about reasonable vitamin C doses should not be based on what Pauling said or wrote, but should be based on empirical evidence.

Doses of 3 g/day vitamin C have not prevented natural colds in ordinary people (Karlowski 1975) or laboratory colds (Walker 1967; Schwartz 1973). We do not see any basis to speculate that higher regular doses such as 16 g/day may have a different preventive effect for ordinary people. In our review we found a subgroup of five trials in which vitamin C halved the incidence of colds. However, the benefit was not explained by particularly high vitamin C dosage but by the special conditions of the participants: heavy acute physical stress.

The case for treating colds is different. The Karlowski 1975 study found significant dose dependency so that 6 g/day of vitamin C shortened colds in adults by twice as much as 3 g/day and Coulehan 1974 found that 2 g/day of vitamin C shortened colds of children twice as much as 1 g/day (Hemilä 1999a Table 2 and Fig. 2). Anderson 1974 found that a single dose of 8 grams of vitamin C was significantly more beneficial than a single dose of 4 grams at the beginning of the cold (Hemilä 2006a Table 19). Asfora 1977 found that 6 g/day caused such obvious clinical progress that it further led to the breakage of the double-blind code (this review Table 1).

We do not see any basis to assume that 6 or 8 g/day would lead to the maximal effect of vitamin C. Instead, linear extrapolation of the results of the Karlowski 1975 study, and of all adult trials, suggested that 18 g/day and 10 g/day, respectively, might decrease the duration of common cold episodes by half (Hemilä 1999a Figs. 1 and 2). Even though we must be cautious about simple linear extrapolation, if there is curvature in the dose dependency so that higher doses cause less than the assumed linear benefit, then the doses that halve the duration of colds would be even greater than those suggested by linear extrapolations.

Some clinicians have proposed 10 to 30 g/day vitamin C for treating colds on the basis of their personal empirical evidence with their patients (Bee 1980; Cathcart 1981). We do not know what the maximal therapeutic benefits are and the vitamin C doses leading to them. Nevertheless, as described in our review vitamin C is safe in high doses and we conclude that it may be worthwhile for common cold

patients to test on an individual basis whether therapeutic vitamin C is beneficial for them. Therapeutic trials explicitly testing dose dependency are needed.

Contributors

Harri Hemilä and Elizabeth Chalker
15 April, 2013

WHAT'S NEW

Date	Event	Description
17 April 2013	Feedback has been incorporated	Feedback comment and reply added to the review

HISTORY

Protocol first published: Issue 1, 1998
Review first published: Issue 1, 1998

Date	Event	Description
29 November 2012	New citation required but conclusions have not changed	Seven placebo-controlled trials, which were previously excluded because there were no data suitable for our meta-analyses, have been included (Table 1). Their exclusion was inconsistent with the Methods section. This change did not result in changes to our conclusions (Abbott 1968; Asfora 1977; Briggs 1984; Elliot 1973; Regnier 1968; Scheunert 1949; Tebrock 1956). In previous versions 'prophylactic' was used to indicate the trials in which vitamin C was administered every day. 'Prophylactic' is relevant when measuring the incidence of episodes. However, that term is confusing when measuring the duration of episodes that occur during the trial. Therefore, in the 2012 version, we changed to the term 'regular supplementation' to indicate trials in which vitamin C was administered every day.
29 November 2012	New search has been performed	Searches conducted. We included one new trial (Constantini 2011a; Constantini 2011b) and excluded two new trials (Maggini 2012; Schmidt 2011).
2 February 2010	New search has been performed	No new trials identified in this updated search. However, one trial with marathon runners was excluded because of the high level of drop-outs and severe bias in the drop-out rate between the study arms (Himmelstein 1998b). We excluded the Audera 2001c trial arm because flavonoids were administered in addition to vitamin C. We restricted the review to purely vitamin C comparisons. The conclusions remain unchanged since the last update (Douglas 2007).
13 November 2009	Feedback has been incorporated	Feedback comment and reply added.
13 June 2008	Feedback has been incorporated	Feedback comment and reply added.
12 June 2008	Amended	Converted to new review format.
23 July 2007	Feedback has been incorporated	Feedback added.