Vitamin C for preventing and treating the common cold (Review)

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[Intervention Review]

Vitamin C for preventing and treating the common cold

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ABSTRACT

Background

Vitamin C (ascorbic acid) in preventing and treating the common cold has been a subject of controversy for 60 years.

Objectives

To discover whether oral doses of 0.2 g per day or more of vitamin C reduce the incidence, duration or severity of the common cold when used as continuous prophylaxis (regularly every day) or as therapy after onset of symptoms.

Search strategy

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2010, issue 1) which contains the Acute Respiratory Infections Group's Specialised Register, MEDLINE (2006 to February 2010) and EMBASE (2006 to February 2010).

Selection criteria

We excluded trials if a dose less than 0.2 g per day of vitamin C was used, or if there was no placebo comparison. We did not restrict to randomised controlled trials (RCTs).

Data collection and analysis

Two reviewers independently extracted data. 'Incidence' of colds during prophylaxis was assessed as the proportion of participants experiencing one or more colds during the study period. 'Duration' was the mean days of illness of cold episodes.

Main results

Twenty-nine trial comparisons involving 11,306 participants contributed to the meta-analysis on the risk ratio (RR) of developing a cold whilst taking prophylactic vitamin C. In the general community trials, involving 10,708 participants, the pooled RR was 0.97 (95% confidence interval (CI) 0.94 to 1.00). Five trials involving a total of 598 marathon runners, skiers and soldiers on subarctic exercises yielded a pooled RR of 0.48 (95% CI 0.35 to 0.64).

Twenty-nine comparisons examined the effect of prophylactic vitamin C on common cold duration (9649 episodes). In adults the duration of colds was reduced by 8% (3% to 12%), and in children by 13% (6% to 21%). The severity of colds was significantly reduced in the prophylaxis trials.

Seven trial comparisons examined the effect of therapeutic vitamin C (3249 episodes). No consistent differences from the placebo group were seen in the duration or severity of colds.

Authors' conclusions

The failure of vitamin C supplementation to reduce the incidence of colds in the general population indicates that routine prophylaxis is not justified. Vitamin C could be useful for people exposed to brief periods of severe physical exercise. While the prophylaxis trials have consistently shown that vitamin C reduces the duration and alleviates the symptoms of colds, this was not replicated in the few therapeutic trials that have been carried out. Further therapeutic RCTs are warranted.

PLAIN LANGUAGE SUMMARY

Vitamin C for preventing and treating the common cold

The term 'the common cold' does not denote a precisely defined disease, yet the characteristics of this illness are familiar to most people. It is a major cause of visits to a doctor in Western countries and of absenteeism from work and school. It is usually caused by respiratory viruses for which antibiotics are useless. Other potential treatment options are of substantial public health interest.

Since vitamin C was isolated in the 1930s it has been proposed for respiratory infections. It became particularly popular in the 1970s when Nobel laureate Linus Pauling concluded from earlier placebo-controlled trials that vitamin C would prevent and alleviate the common cold. Over two dozen new trials were undertaken thereafter. Vitamin C has been widely sold and used as both a preventive and therapeutic agent.

This review is restricted to placebo-controlled trials testing 0.2 g per day or more of vitamin C. Regular ingestion of vitamin C had no effect on common cold incidence in the ordinary population. However, it had a modest but consistent effect in reducing the duration and severity of common cold symptoms. In five trials with participants exposed to short periods of extreme physical stress (including marathon runners and skiers) vitamin C halved the common cold risk.

Trials of high doses of vitamin C administered therapeutically, starting after the onset of symptoms, showed no consistent effect on either duration or severity of common cold symptoms. However, only a few therapeutic trials have been carried out, and none have examined children, although the effect of prophylactic vitamin C has been greater in children. One large trial with adults reported equivocal benefit from an 8 g therapeutic dose at the onset of symptoms, and two trials using five-day supplementation reported benefit. More trials are necessary to settle the possible role of therapeutic vitamin C, meaning administration immediately after the onset of symptoms.

BACKGROUND

Description of the condition

The term 'the common cold' does not denote any precisely defined disease, but this illness is familiar to practically everybody. Typically symptoms of the common cold consist of some combination of nasal discharge and obstruction, sore throat, cough, lethargy and malaise, with or without fever. The common cold is the leading cause of acute morbidity and of visits to a physician in Western countries, and a major cause of absenteeism from work and school.

The common cold is usually caused by respiratory viruses (rhino, corona, adeno, parainfluenza, influenza, respiratory syncytial), which overall have some 200 serotypes (Eccles 2005; Gwaltney 2005; Heikkinen 2003). Thus, the term 'the common cold' does not refer to a single entity but to a group of diseases caused by numerous unrelated aetiological agents. The most frequent agent causing the common cold is rhinovirus, which is found in 30% to 50% of sufferers. In a third of subjects with cold symptoms, the aetiology remains undefined even when extensive virological tests are used. It is not clear to what extent this latter group is explained by the low sensitivity of the tests, unidentified viruses, or similar symptoms arising from non-viral aetiology, such as allergic or mechanical irritation of the airways. Different respiratory viruses

have different symptom profiles, but the patterns are not consistent enough to validate aetiological conclusions from the patients' symptoms.

Although the great majority of common cold episodes are caused by the respiratory virus group, the symptom-based definition of the 'common cold' also covers some diseases caused by other viruses (varicella, measles, rubella, cytomegalo, Epstein-Barr) and some bacterial infections. For example, since streptococcal pharyngitis cannot be differentiated from viral pharyngitis on clinical grounds, it can also be included within the broad definition of the common cold. Symptoms of illnesses caused by *Mycoplasma pneumoniae (M. pneumoniae)* and *Chlamydia pneumoniae (C. pneumoniae)* may also be similar to the symptoms caused by the respiratory viruses. The manifestations of the common cold are so typical that usually the clinical diagnosis of the common cold can be made reliably by adult patients themselves. Allergic and vasomotor rhinitis can sometimes mimic the common cold, but usually these conditions can be easily differentiated (Heikkinen 2003).

In common cold trials an explicit definition of the common cold is used for logistic reasons; for example, based on the duration and the set of symptoms to yield an explicitly defined outcome. However, such limits are biologically arbitrary. There is no exact minimum duration or combination of symptoms which is meaningful when drawing a conclusion as to whether the symptoms should be explained by a viral infection, or by allergic or mechanical irritation of nasal airways or throat.

The use of antibiotics for a typical acute common cold episode is useless since the vast majority of colds are caused by viruses. Nevertheless, according to some surveys about 50% of common cold patients in the USA received antibiotics (Gonzales 1997; Mainous 1996). In this respect, the alternative treatment options for the common cold are of substantial public health interest.

Description of the intervention

Numerous animal studies with different species have shown that vitamin C affects resistance to diverse infections by viruses and bacteria (Hemilä 1997c; Hemilä 2006a). It might therefore be expected that this vitamin would also play such a role in infections in human beings. Since the early 1940s, a number of controlled trials have been carried out to examine the possible effects of vitamin C on the common cold.

In 1970, the publication of the book entitled *Vitamin C and the Common Cold* (Pauling 1970a) generated huge public interest which persists today. Linus Pauling had won Nobel Prizes in Chemistry (1954) and Peace (1962), and his book had a great influence. Pauling (Pauling 1971a) also carried out a meta-analysis in which he combined the P values derived from four placebo-controlled trials by Fisher's method and found that there was strong evidence that vitamin C decreased the 'incidence of colds' (P = 0.003). A second meta-analysis (Pauling 1971b) focused on 'days of illness per person' in the best two of the four trials (Cowan 1942; Ritzel 1961) and by combining the P values by Fisher's method led him to conclude that "the null hypothesis of equal effectiveness of ascorbic acid and placebo [on total morbidity] is rejected at the level P less than 0.001."

Ritzel (Ritzel 1961) had reported a brief randomised trial of children at a ski school in the Swiss Alps in which he administered 1 g of vitamin C daily and found reduced incidence and duration of colds in the recipients of vitamin C. Pauling (Pauling 1971a) put much weight on the Ritzel trial, based his expectations of vitamin C effects on it, and proposed that mega-dose supplementation might profoundly influence both the incidence and severity of the common cold over all the population. Pauling also presented data suggesting that human diets might not provide sufficient intake of vitamin C for optimal health (Pauling 1970b; Pauling 1976a). Pauling's advocacy of vitamin C led to numerous careful trials in different countries in the following decade, the largest of which were performed on healthy adult volunteers in Canada (Anderson 1972; Anderson 1974a; Anderson 1975a).

The evidence emerging from these trials was confusing (Anderson 1977), but generally failed to support Pauling's hope that vitamin C would be a panacea. Chalmers 1975 calculated an unweighted average of the treatment effect in seven placebo-controlled trials and found that colds in vitamin C groups were 0.11 ± 0.24 (standard error (SE)) days shorter which is not a statistically or clinically significant difference. In a qualitative review on vitamin C and the common cold published in the same year, Dykes also concluded that vitamin C had no effect on colds (Dykes 1975).

However, it has subsequently been claimed that the influential reviews by Chalmers 1975 and Dykes 1975 contain errors (Hemilä 1995; Hemilä 1996c; see also Hemilä 2006a). Hemilä 1995 showed that after extraction of correct data from the trial reports, correction of errors in calculations, and restriction to trials in which at least 1 g/day of vitamin C had been used, Chalmers 1975 should have calculated an eight times higher estimate of the vitamin C effect: 0.93 ± 0.22 (SE) days reduction in the duration of colds. Furthermore, both Chalmers 1975 and Dykes 1975 placed considerable weight on the double-blind, placebo-controlled trial carried out by Karlowski 1975a at the National Institutes of Health (NIH), which concluded that a statistically significant benefit of vitamin C supplementation was simply explained by the placebo effect. It has since been shown that the placebo explanation in the Karlowski 1975a paper was not consistent with their own data (Chalmers 1996; Hemilä 1996a; Hemilä 1996d; Hemilä 2006a; see also Hemilä 2006c).

Hemilä 1997b claimed that the highly cited reviews of Chalmers 1975 and Dykes 1975 and the trial by Karlowski 1975a quelled interest in real, but modest effects of vitamin C on the common cold after the mid-seventies. Hemilä 1997a pooled the results of the six largest trials and found no effect on common cold incidence using 1 g/day or more of vitamin C (pooled risk ratio (RR) 0.99; 95% CI 0.93 to 1.04), which refuted Pauling's proposal as to the effect of gram-dose vitamin C on common cold incidence.

However, four trials with UK males found a moderate reduction in common cold incidence with vitamin C (pooled RR 0.70; 95% CI 0.60 to 0.81), which was explained by the particularly low dietary vitamin C intake in the UK rather than high doses of supplements. Also, three trials with participants under heavy acute physical stress had reported reduced incidence of colds with vitamin C (pooled RR 0.50; 95% CI 0.35 to 0.69) (Hemilä 1996b). Thus, it is possible that vitamin C has an effect on common cold incidence in restricted subpopulations.

Although regular vitamin C supplementation at doses of 1 g/day or more has consistently decreased the duration or alleviated the symptoms of the common cold, there was substantial heterogeneity in the results (Hemilä 1994). A further meta-analysis found a trend for trials with children to show greater benefit than trials with adults, and another trend for trials with 2 g/day or more to show greater benefit than trials with 1 g/day, indicating dose-dependency (Hemilä 1999a).

How the intervention might work

Dozens of studies have found that vitamin C may affect, for example, phagocytosis and chemotaxis of leucocytes, replication of viruses, and production of interferon (Hemilä 1997c; Hemilä 2006a; Thomas 1978; Webb 2007). Vitamin C is an efficient water-soluble antioxidant and the effects on the immune system can be explained by the protection against oxidative stress generated during infections (Akaike 2001; Castro 2006; Hemilä 1992). Phagocytes have a specific transport system by which the oxidised form of vitamin C (dehydroascorbic acid) is imported into the cells, where the reduced form of vitamin C is regenerated (Nualart 2003; Wang 1997). If the major role of vitamin C in the immune system is that of a physiological antioxidant protecting various host cells against oxidative stress during an infection, it could have important effects in certain conditions even though the mechanisms are apparently non-specific. Furthermore, heavy physical stress also generates oxidative stress (Ji 1999) and the antioxidant role of vitamin C can thus also explain its effects on respiratory symptoms in physically stressed people. Dozens of animal studies found that vitamin C reduces the incidence and severity of bacterial and viral infections indicating that the vitamin has physiological effects on infections, and not just on laboratory measures of the immune system (Hemilä 2006a).

For brief notes on the history of this Cochrane Review, see Appendix 1. Links to the publications cited in this section, for which full-text versions are available, can be found at www.ltdk.helsinki.fi/users/hemila/CC/.

Why it is important to do this review

The common cold causes enormous morbidity worldwide and the search for simple and effective preventive or therapeutic agents has been elusive. Even if vitamin C might have modest effects in restricted population groups, that could be important from the public health point of view.

OBJECTIVES

To find out whether vitamin C reduces the incidence, the duration or severity of the common cold when used either as continuous prophylaxis or as therapy at the onset of cold symptoms.

METHODS

Criteria for considering studies for this review

Types of studies

We included placebo-controlled trials. We did not restrict to RCTs.

Types of participants

Trials of children and adults of either gender and any age were considered eligible.

Types of interventions

The intervention considered was orally administered vitamin C of at least 0.2 g daily for a single day or for a period. The limit of 0.2 g/day was selected as a choice of convenience. If a trial with a lower dose finds a negative result, the negative findings can be attributed to the low dose. Thus, trials with large doses are more critical for testing Pauling's proposal that gram doses of vitamin C would reduce morbidity due to common cold infections. On the other hand, under certain conditions vitamin C doses lower than 0.2 g/day might have effects (*see* Discussion: Possible role of marginal vitamin C deficiency). Thus, our selection criterion for dose does not mean that all excluded trials are irrelevant to the question of the effects of vitamin C.

In a few instances the placebo included a low dose of vitamin C; Carr 1981a used 70 mg/day, and a few others used 50 mg/day or less. This was done to ensure that participants were not 'vitamin C deficient', recognising that regular dietary intake of vitamin C is highly variable in some groups. Thus, the goal of these investigators was to test the effects of large doses for properly nourished participants.

Types of outcome measures

- 'Incidence' of colds during prophylaxis was assessed as the proportion of participants experiencing one or more colds during the study period.
- 'Duration' was the mean number of days of illness of cold episodes.
- 'Severity' of these episodes was assessed in two ways: a) days confined indoors, or off work or off school per episode and b) symptom severity scores.
- 'Evidence of possible medication side effects' was available from seven large prophylaxis studies, with the number of participants reporting possible medication side effects in the intervention and control groups.

Search methods for identification of studies

Electronic searches

For this 2010 update, we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2010, issue 1), which contains the Acute Respiratory Infections Group's Specialised Register, MEDLINE (2006 to February 2010) and EMBASE (2006 to February 2010).
See below the search strategy for MEDLINE. The EMBASE and CENTRAL searches were slightly modified to fit the databases (see Appendix 2 for EMBASE search strategy).

MEDLINE (OVID)

1 exp Common Cold/
2 common cold$.mp.
3 exp Rhinovirus/
4 rhinovir$.mp.
5 or/1-4
6 exp Ascorbic Acid/
7 ascorb$.mp.
8 (vitamin$ adj5 C).mp.
9 or/6-8
10 5 and 9
There were no language or publication restrictions in the literature searches.
For the search strategies of the previous versions of this review, see Appendix 1.

Searching other resources

The review authors screened the reference lists incorporated in two systematic reviews of the literature published by Briggs 1984 and Kleijnen 1989 (for the search strategy of the latter, *see* Kleijnen 1992) and the references in all identified studies. Furthermore, one of the review authors (HH) has a research involvement spanning two decades in this topic and has assembled a personal reference list of papers published in the grey literature or listed in indexing services that preceded electronic searching.

Data collection and analysis

Selection of studies

For the 2004 version of this review, HH and BD searched the literature and both independently assessed the titles and abstracts to identify potentially relevant articles (see Appendix 1). Full versions of all potentially eligible articles were obtained and scrutinised. When they disagreed on the relevance of an article, they discussed it until they reached a consensus. For the 2007 and 2009 updates, the first review author (HH) searched the literature and assessed the titles and abstracts to identify potentially relevant articles. Trials failing to meet the inclusion criteria were excluded from the review.

Data extraction and management

Two review authors (HH, BD) independently extracted pertinent data from the articles selected and entered data into the Review Manager program (see Appendix 1) for the 2004 version of this review (Douglas 2004). They sought consensus when they differed in the interpretation of study findings. Only one new trial satisfying the selection criteria (Sasazuki 2006) has been published since the first publication of this review and it was included in the 2007 update (Douglas 2007).

Assessment of risk of bias in included studies

We collected data for four methodological features of the identified studies:

1. allocation concealment;
2. double-blinding;
3. randomisation;
4. placebo indistinguishability.

Allocation concealment means that the participant and others directly involved in treatment do not know to which treatment group the participant had been allocated. This issue can be crucial in therapeutic trials in which the severity of a disease may affect allocation if it is not concealed. Even if the treatment cannot be blinded (for example, surgery), it is possible to carry out allocation as concealed. On the other hand, when the trial is double-blind that means that allocation must have been concealed, although the term allocation concealment is not used in the study reports. In our assessment of study quality, double-blind means that neither the participant nor the outcome assessor were aware of the identity of the treatment. In some studies, the participant was given a card to be filled in by herself or himself for reporting common cold

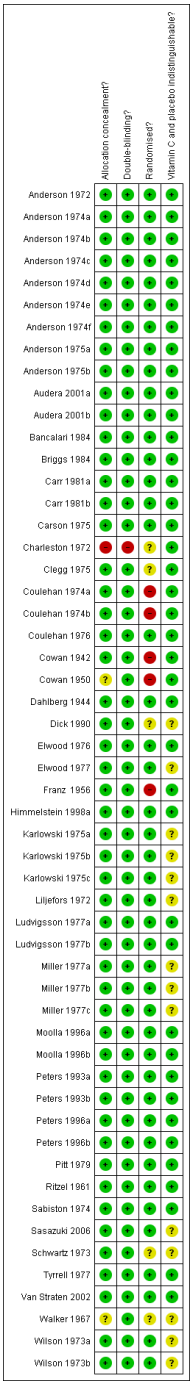
symptoms and in such cases we classify the study double-blind because the participant was also the assessor.

Studies are classified as randomised on the basis of the study reports, but only a few studies described the actual method of randomisation.

Chalmers 1975 proposed that the benefits of vitamin C supplementation on the common cold might be caused by "the result of the power of suggestion." His proposal was based on the Karlowski 1975a trial, in which placebo consisted of lactose which is sweet and differs by taste from ascorbic acid which was used in the vitamin C capsules. Therefore, we collected data on the reported indistinguishability of vitamin C and placebo preparations.

When the methodological description was unambiguous, one review author (HH) entered the methodological description to the 'Risk of bias' tables in Characteristics of included studies. When the description of methods was ambiguous, the same review author discussed the issue with a co-author (EC) to reach a consensus. The methodological descriptions are summarised in Figure 1.

Figure 1. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Measures of treatment effect

For the community trials, three outcomes were selected to compare vitamin C with placebo groups, resulting in five tables.

Analysis 1.1: the measure of the treatment effect is risk ratio (RR) of 'incidence' of colds in vitamin C and placebo groups.

Analyses 2.1 and 4.1: the measure of treatment effect is the mean difference (MD) in common cold 'duration'. Since duration of cold episodes varied appreciably across trials, we standardised the mean values and standard deviations (SD) obtained in each vitamin C group against the mean of the respective placebo group. In this way, the placebo group of each trial gets a value of 100%, and therefore the difference between the vitamin C and placebo group is the effect of treatment in percentages.

Analyses 3.1 and 5.1: there are two measures of effect on 'severity': a) the difference in the mean number of days that the patient was absent from work or school or confined to bed; and b) the difference in the mean symptom severity score derived from patient kept records.

In analysing dichotomous data with only a few cases in the trial groups, the mid-P value is the most appropriate method to calculate the P values for the differences in the treatment groups (Hemilä 2006a) and was used when comparing groups with small numbers of cases. Two-tailed P values are used in this review.

Unit of analysis issues

In four of the trials (Anderson 1974a; Anderson 1975a; Audera 2001a; Karlowski 1975a) more than one actively treated group was compared with the same placebo treated group. Where multiple active arms were analysed in the same meta-analysis, the vitamin C arms were combined as one entry which appears in the figures, identified as the lowest lettered trial that the entry contained.

Miller 1977a and Carr 1981a studied twins and the comparison is paired. The SD values used in this meta-analysis are calculated from the SE and P values, respectively, of reported paired tests, so the two trials get proper weight in pooling.

Dealing with missing data

Some trials presented the mean duration or severity of colds, but not the respective SD. In some trials the P value for the difference of interest was reported and the SD was calculated from it. In the Anderson 1972, Anderson 1974a and Anderson 1975a trials, Fieller's theorem was used to estimate the SD for individual common cold episodes from the SD values presented in papers that were based on a per person experience. In the other trials with missing SD, we estimated SD as identical with the mean of the treatment group. This is based on our analysis that for trials reporting the SD the ratio of SD to mean is on average 0.7 so that our ratio of 1.0 used in the SD-imputation is somewhat conservative. The consequence of this is that we are putting slightly reduced weight on our estimates of effect on these trials with missing SD values, compared to the average.

Assessment of heterogeneity

We assessed heterogeneity using the χ^2 test and the I^2 statistic (Higgins 2003; Higgins 2009). The χ^2 test is known to be poor at detecting true heterogeneity among studies; while a statistically significant result indicates heterogeneity, a non-significant result is not evidence of no heterogeneity. The I^2 statistic examines the percentage of total variation across studies that is due to heterogeneity rather than chance. A value of I^2 about 50% indicates a moderate level of heterogeneity.

Data synthesis

We used the Review Manager (RevMan 2009) software to pool the results of the three outcomes of the included trials.

A pooled fixed-effect RR of the probability of experiencing one or more colds while taking vitamin C was computed for 'incidence'. A pooled fixed-effect MD in common cold 'duration' was computed to derive an estimate of the percentage of days of illness by which vitamin C reduced the average common cold.

The two different approaches to the assessment of severity were considered separately in the meta-analysis by treating the two sets of trials as separate subgroups. A standardised mean difference (SMD) was computed for each pool of results to enable us to derive a pooled estimate of the effect of vitamin C on cold severity across all trials for which severity data were available. The SMD calculation method leads to quantitative results but they do not have any direct clinical interpretation. Rather the primary statistical result of the SMD method is the P value for the combined set.

Subgroup analysis and investigation of heterogeneity

Three factors were considered as possible explanations for the heterogeneity observed across the results of these trials. These were vitamin C dosage, age of participants (children and adults), and the particular life circumstances of the participants.

Sensitivity analysis

To test the robustness of our conclusions regarding the methodological quality of the trials, we undertook sensitivity analyses in Analyses 1.1 and 2.1 in which we excluded all studies which were not randomised and double-blind.

In seven trials in Analysis 2.1 ('Duration of colds in prophylaxis trials') we imputed the SD values assuming that SD is equal to the mean of the group (Briggs 1984; Coulehan 1974a; Coulehan 1974b; Coulehan 1976; Peters 1996a; Peters 1996b; Pitt 1979). When we excluded these in a sensitivity analysis of Analysis 2.1, the pooled results indicated a slightly greater effect by vitamin C: adults, 8.6% (4.2% to 13.0%); children, 13.6% (6.2% to 21.1%). Thus, inclusion of the trials with imputed SD values in the Results section does not lead to an increase in the estimate of benefit, but to a slight reduction in the calculated benefit.

We also tested whether the exclusion of the Anderson 1974a trial might affect the estimates of Analysis 1.1 and Analysis 2.1. That trial had two placebo groups and we selected for our comparisons the placebo group number 4 which was close to the vitamin C groups on the basis of baseline data (see also Hemilä 2006a and Results section 4). Exclusion of the Anderson 1974a trial had minimal effects on the pooled estimates (not shown).

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search

The MEDLINE search retrieved 16 studies, the EMBASE search retrieved 99 studies and the CENTRAL search 58 studies. No new trials were identified in this update but we excluded the Himmelstein 1998b trial with marathon runners, because there were large and significantly divergent drop-out rates in the vitamin C and placebo arms.

Included studies

Fifty-four separate comparative studies reported in 36 publications met our selection criteria. Eleven of these publications presented the results of two to six different study comparisons. Included in the selected papers are the four trials identified originally by Pauling 1971a to justify his proposals for mega-dose prophylaxis and therapy (Cowan 1942; Franz 1956; Ritzel 1961; Wilson 1969). We have used the Wilson 1973a final report of his boarding school trials rather than the preliminary communication which Pauling 1971a had available to him.

In Anderson 1974a, Anderson 1975a, Audera 2001a and Karlowski 1975a more than one active arm is compared with a single placebo arm. This explains why the total number of participants presented in the summary analysis tables is less in the placebo groups than in the vitamin C groups.

The 55 included trials which have contributed data to this review fall into three distinct methodological groups.

1. Forty-one community prophylaxis trial arms which evaluated the effects of regular daily supplementation with vitamin C on reducing the incidence or severity or both of naturally acquired colds.
2. Ten community therapeutic trial arms that evaluated the therapeutic effects of high dosage vitamin C after natural common cold symptoms had commenced.
3. Three laboratory trials (Dick 1990; Schwartz 1973; Walker 1967) in which volunteers were intentionally exposed to known viruses after preliminary dosage with vitamin C or placebo. As they are qualitatively different from the community-based trials on natural common cold infections, they have not been included in the meta-analyses but are presented in Table 1.

Table 1. Three volunteer transmission studies

Study characteristics	Walker 1967	Schwartz 1973	Dick 1990
Number of participants	91 healthy volunteers; 47 vitamin C and 44 placebo	21 healthy male volunteers	Altogether 48 participants. Three separate transmission experiments each involving 16 healthy volunteers (8 vitamin C; 8 placebo) housed closely for one week with 8 volunteers actively infected with rhinovirus
Viruses used	Rhinovirus (3 strains); 29 vitamin C and 26 placebo Influenza B (8 / 8) B814 virus (10 / 10)	Rhinovirus 44; 11 vitamin C and 10 placebo	Rhinovirus 16; 24 vitamin C and 24 placebo

Table 1. Three volunteer transmission studies (*Continued*)

Transmission method	Nasal instillation	Nasal instillation	Close contact with infected volunteers over a period of a week
Intervention	1 g/d vitamin C for 3 days before and 6 days after inoculation	3 g/d vitamin C or placebo for 2 weeks before and 1 week after inoculation	2 g/d vitamin C for 3.5 weeks before exposure to infected volunteers
Incidence outcome	18 colds developed in each group	All in both groups developed colds	19/24 in vitamin C group and 22/24 in placebo group became infected
Duration outcome	Mean duration in each group 5 days	Both groups resolved by 6 to 7 days	Not provided
Severity outcome	Mean severity score 8 for vitamin C and 7 for placebo	Severity peaked earlier for vitamin C group and resolution more advanced by day 4 (P = 0.02). Overall mean severity scores not significantly different in the 2 groups	Mean cumulative severity score and mucus weights reduced in the vitamin C recipients (P = 0.03). Severity of colds reduced by 50% (P = 0.02; Dick 1990)
Comments	Not double-blind	Double-blind. Nasal virus shedding similar in the two groups	Double-blind. Viral shedding similar in these 2 groups. The studies are briefly described in a series of conference abstracts but no full published paper is available

Brief details of the circumstances, dosage and quality assessment of the trials are available in the Characteristics of included studies table. Links to the trial reports and translations can be found at www.ltdk.helsinki.fi/users/hemila/CC/.

Excluded studies

We excluded thirty-one studies. The major reasons for exclusion were lack of placebo control (13 trials), vitamin C dose lower than 0.2 g/day (in eight trials), and no data suitable for inclusion in our meta-analyses (in eight trials). For details, please see the Characteristics of excluded studies table.

Risk of bias in included studies

Allocation

Essentially all of the identified trials were randomised trials (Figure 1). Since double-blinding implies that allocation has to be concealed, all studies had allocation concealment because of the double-blinding (Figure 1).

Blinding

Essentially all of the identified trials were double-blind (Figure 1).

Incomplete outcome data

In many trials there were no drop-outs, and in those trials in which there were, the number of drop-outs was not great and not substantially different between the study groups. In this update we excluded the Himmelstein 1998b trial with marathon runners because of high and divergent drop-out rates (which has no effect on the conclusions).

Selective reporting

When there is one or are few trials with a positive finding on a poorly justified outcome, the possibility of publication bias is an

important concern. In our review we have two large groups of trials with the same well-justified outcomes: incidence and duration of colds (Analysis 1.1 and Analysis 2.1). We do not see any basis to speculate that the consistency in these two outcomes could be explained by selective reporting. There is no unambiguous definition for severity, and there might be more problems with selective reporting (Analysis 3.1), but that outcome has a lower priority in our review, and the findings are consistent with the effect on duration (Analysis 2.1).

Other potential sources of bias

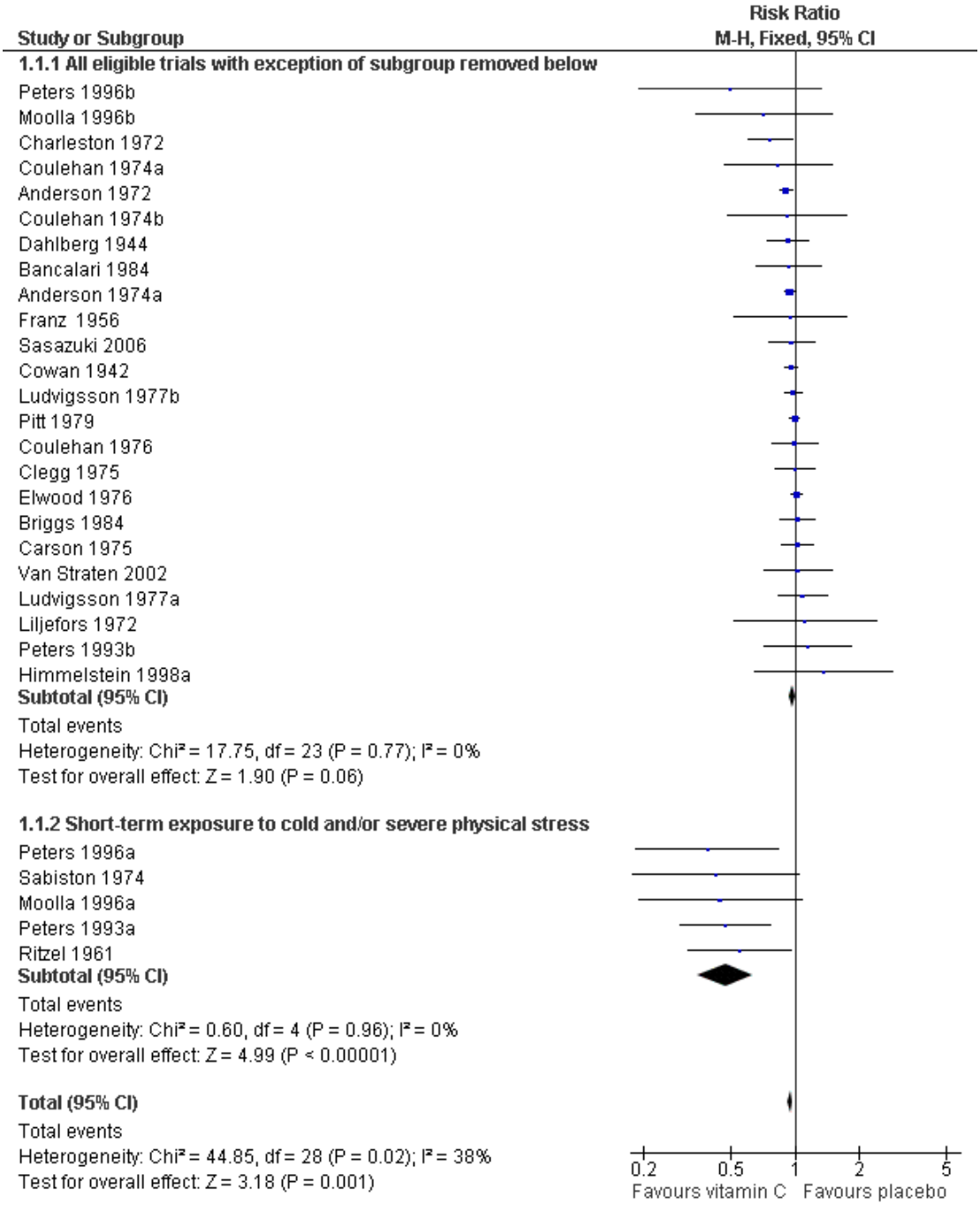
The great majority of the trials reported that vitamin C tablets (usually ascorbic acid) and placebo tablets (usually citric acid) were indistinguishable (Figure 1 and Characteristics of included studies table). Thus there is no reason to assume that difference in taste or appearance between the tablets could have generated substantial bias in the trials.

Effects of interventions

1. Community prophylaxis trials: incidence of colds

Analysis 1.1 presents the meta-analysis of the risk ratio of one or more colds developing while on prophylaxis (Figure 2). The entry in the meta-analysis for Anderson 1974a represents four separate trial arms (Anderson 1974a; Anderson 1974b; Anderson 1974c; Anderson 1974d) in which different vitamin C dosages ranging from 0.25 to 2 g/day were compared with one placebo group. Thus the 29 entries in the figure represent 32 vitamin C arms in trials.

Figure 2. Forest plot of comparison: 1 Development of colds while on vitamin C prophylaxis, outcome: 1.1 Proportions developing one or more cold episodes during prophylaxis.



The 29 entries represent 11,306 participants, of whom 6105 used vitamin C for periods ranging from two weeks to five years. The pooled RR for all trials was 0.95 (95% CI 0.92 to 0.98). Although the overall difference is statistically highly significant (P = 0.001) and indicates that vitamin C has an effect on common cold incidence, the narrow confidence interval precludes any clinically relevant effect over wide population groups.

Heterogeneity of results

Among all the studies included in Analysis 1.1 there is substantial heterogeneity, as indicated by the χ^2 test (P = 0.02) and the high I^2 statistic (38%). Heterogeneity indicates that the results are inconsistent with the notion that vitamin C has no effect on common cold incidence under any circumstances.

Five of the 29 comparisons recorded statistically significant (P < 0.05) protection favouring the vitamin C group: Peters 1996a (RR 0.39), Peters 1993a (RR 0.50), Ritzel 1961 (RR 0.55), Charleston 1972 (RR 0.77) and Anderson 1972 (RR 0.91). Four other trials recorded a non-significant RR < 0.80 (Moolla 1996a; Moolla 1996b; Peters 1996b; Sabiston 1974). None of the 29 comparisons significantly favoured the placebo.

Of the eight relatively small trials with RR < 0.8, three were with marathon runners (Moolla 1996a; Peters 1993a; Peters 1996a), two others were in sedentary controls for marathon runners (Moolla 1996b; Peters 1996b), one was with students in a skiing school in the Swiss Alps (Ritzel 1961), one with Canadian army troops on subarctic operations (Sabiston 1974), and one with staff and students at Glasgow University, UK (Charleston 1972).

A subgroup analysis is shown at the bottom of Analysis 1.1 in which the five studies which involved marathon runners, skiers and Canadian soldiers in a subarctic exercise were moved to a separate subgroup. This resulted in two distinct groups of trials which were significantly different from each other in their pooled estimates of effect. Furthermore, the two subgroups were homogeneous within the two pools, as indicated by the high P values in the χ^2 test, and the zero values for the I^2 statistic.

Subgroups: general community trials and heavy acute physical stress trials

Based on 24 entries with 10,708 participants from the general community who had no heavy physical stress, the narrow CI which is located close to the zero effect refutes the possibility that regular vitamin C supplementation would reduce the average incidence of colds in the general community: RR 0.97 (95% CI 0.94 to 1.00) (Figure 2 , Analysis 1.1.1).

When the general community meta-analysis was restricted to 17 entries with vitamin C dose 1 g/day or more, the prophylactic benefit of vitamin C supplementation was also refuted (RR 0.98; 95% CI 0.95 to 1.01; based on 6661 participants). The largest vitamin C dose, 3 g/day, was used by Karlowski 1975a, which is not included in Analysis 1.1.1 because they did not report the number of participants who caught a cold during the trial. Nevertheless, vitamin C had no effect on the number of common cold episodes, with RR 0.93 (95% CI 0.73 to 1.20) (Hemilä 1997a).

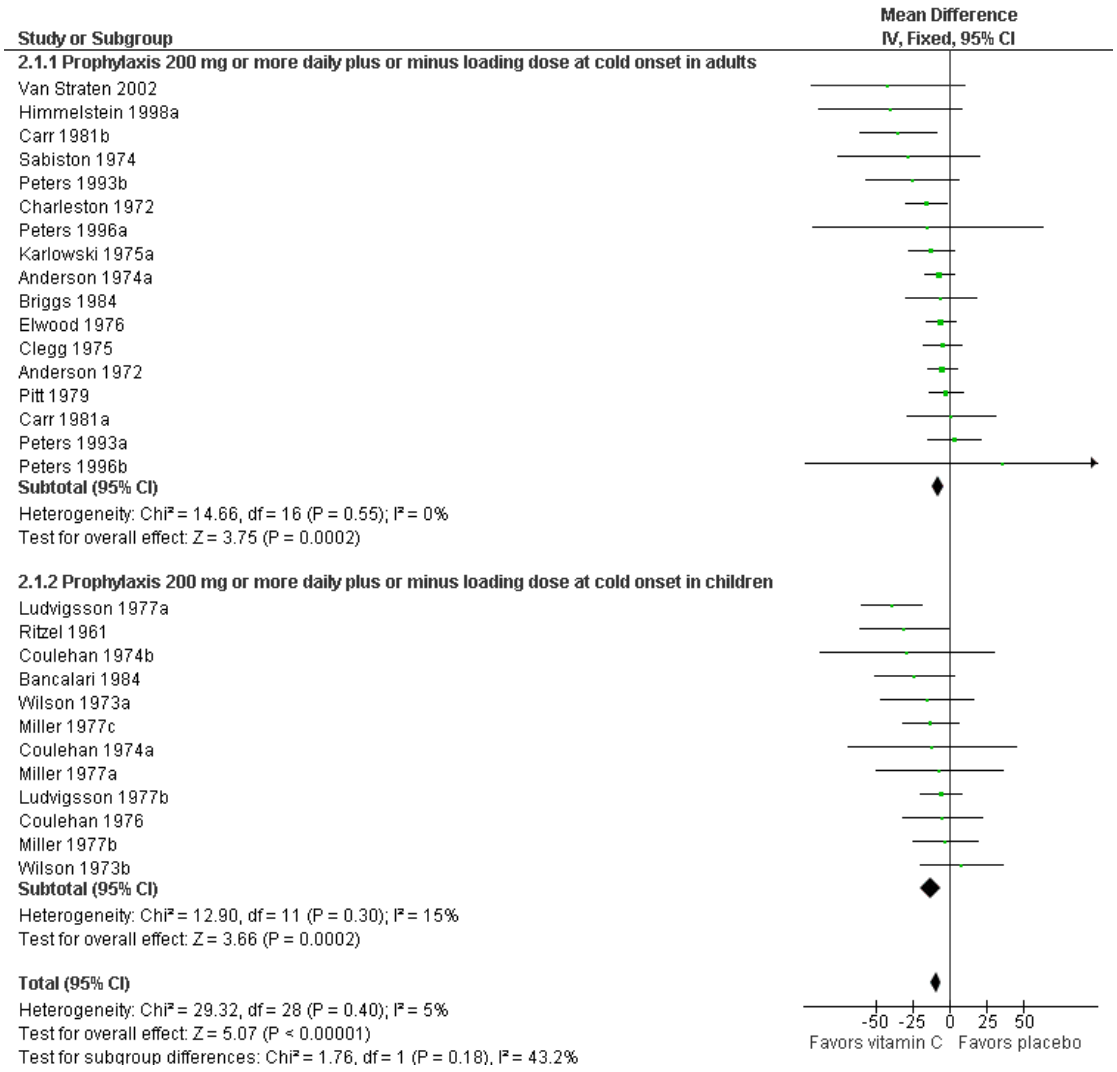
In five trials with participants undergoing heavy acute physical activity in the subgroup at the bottom of Analysis 1.1, vitamin C halved the incidence of colds: RR 0.48 (95% CI 0.35 to 0.64) (Figure 2 Analysis 1.1.2). All of these five studies were randomised and double-blind. In three of these studies, the vitamin C dose was less than 1 g/day so that the benefit in this subgroup is not explained by particularly high vitamin C doses, but by the particular conditions.

To test the effect of study quality on the findings in Analysis 1.1, we undertook a sensitivity analysis in which we removed five trials that were either not randomised or not double-blind from the general community meta-analyses and this had no effect on the estimate (RR 0.98; 95% CI 0.94 to 1.01). All trials with participants under heavy acute physical stress were randomised and double-blind. Thus, the effect of study quality as assessed by randomisation and double-blinding did not change the estimates of the pooled results.

2. Community prophylaxis trials: duration of colds

The meta-analysis in Analysis 2.1 on duration of colds which developed while participants were taking prophylaxis was divided into two subgroups: adults and children. The division into child and adult trials was carried out for two reasons: a) children have a substantially higher incidence of colds reflecting differences in immune system maturity, and b) children are on average smaller so that a fixed dose corresponds to a greater dose per weight (Figure 3).

Figure 3. Forest plot of comparison: 2 Duration of colds developing on vitamin C prophylaxis, outcome: 2.1 Duration of common cold symptoms (placebo group duration set as 100%).



For adults there were 17 entries representing 21 trial arms (four separate trial arms in Anderson 1974a and two in Karlowski 1975a) and 7215 episodes of illness, and for children there were 12 trial comparisons including 2434 episodes of illness.

A consistent benefit was seen in the duration of colds, but the effect was greater in children. For children, the pooled effect was a 13.2% (6.1% to 20.3%) reduction in common cold duration, and for adults the pooled effect was a 7.7% (3.7% to 11.8%) reduction in duration. The χ^2 test for trial heterogeneity was not significant in either of the subgroups.

In four of the 29 trials (Carr 1981b; Charleston 1972; Ludvigsson 1977a; Ritzel 1961) the difference in episode duration was statistically significant within the trials themselves.

All but three studies (Carr 1981a; Peters 1993a; Peters 1996b; Wilson 1973b) recorded a point estimate favouring the vitamin C group. Wilson 1973b used only 0.2 g/day vitamin C, which is the smallest dose in Analysis 2.1. Carr 1981a examined twins living together, whereas the Carr 1981b trial examined twins living apart; it is possible that the substantially divergent result in these twin groups is related to the living conditions - those living together might have exchanged or confused their tablets. The Peters 1996b trial was very small and the CI is wide and compatible also with a large benefit.

The great majority of the trials in Analysis 2.1 used 1 g/day of vitamin C and therefore a systematic examination of possible dose-dependency across the trials was not feasible. In the child subgroup, we used sensitivity analysis to test the possible role of low vitamin C doses in diluting the effect. When we removed the trials using less than 1 g/day of vitamin C (Miller 1977b; Miller 1977c; Wilson 1973a; Wilson 1973b), the pooled estimate of benefit was increased to a 17% (8% to 26%) reduction in the duration of colds of children.

In sensitivity analyses, we removed from the meta-analyses the studies which were not randomised and double-blind. Exclusion of two trials from the adult subgroup had no material effect on the estimated benefit of 7% (3% to 11%), and exclusion of two trials from the child subgroup similarly had no substantial effect on the estimated benefit of 13% (6% to 20%). Thus, excluding four trials with lower quality had no effect on conclusions.

In summary, this meta-analysis of duration of colds experienced while participants were on regular vitamin C supplementation demonstrated a modest but consistent and statistically significant benefit to the vitamin C supplemented participants which was greater in children than in adults.

3. Community prophylaxis trials: severity of colds

Two types of measures of the severity of illness were available.

Subgroup 1 in Analysis 3.1.1 consists of seven entries of 10 vitamin C study arms in which severity was measured by 'days confined to home' or 'days off work or school'. This included 5066 respiratory episodes in adults and children. The large-scale trials by Anderson 1972 and Ludvigsson 1977b reported statistically significant reductions in 'days confined to house per episode' with vitamin C supplementation. The pool as a whole found a quantitatively modest, but statistically highly significant reduction in common cold severity. This subgroup exhibited highly significant heterogeneity across the subgroup as measured by the χ^2 and I^2 statistic.

Subgroup 2 in Analysis 3.1.2 presents the results of symptom severity scores in seven trials. The large-scale trial by Pitt 1979 found a statistically significant, but small, 5% reduction in severity score. There is a statistically highly significant reduction in common cold severity also in this subgroup. There is no heterogeneity.

The measures of 'severity' that have been used in the trials are variable. We calculated the standardised mean difference (SMD) which normalises the difference between the vitamin C and placebo groups to the units of standard deviations. Therefore the pooled results of Analysis 3.1 are not practically useful, rather the significance level is of main importance in this analysis; P = 0.0004 for the studies that assessed days confined to home or off work or school, and P = 0.003 for studies which used severity scores, and P < 0.00001 when the two pools were combined.

Although the benefit with respect to days confined to home or off work or off school is statistically significant, it is modest in absolute terms which can be seen by viewing the values in Analysis 3.1.

4. Community therapeutic studies: duration of colds when treatment commenced after common cold symptoms began

The meta-analysis presented in Analysis 4.1 contains seven entries that incorporate data from 10 different trial arms involving 3249 cold episodes where participants initiated supplementation at the onset of cold symptoms. Audera 2001a, Anderson 1974e and Anderson 1975a contain two vitamin C arms.

The pooled result for these therapeutic trials did not exhibit a difference of vitamin C from placebo in the variety of therapeutic protocols that were used. The large trial by Anderson 1974e found a statistically significant but modest benefit on severity but this was counterbalanced by the negative results in other trials.

The Anderson 1974e entry combined two different dosage arms. Anderson 1974e administered 4 g/day and Anderson 1974f administered 8 g/day on the first day of illness only. The mean duration of illness episodes for those in the 4 g/day arm was 3.17 days, while that for 8 g/day arm was 2.86 days compared with the duration in the placebo group #4 of 3.52 days. However, this trial was bedeviled by the fact that the investigators originally intended to compare results with two separate placebo groups. One of the placebo groups (#6) had statistically significant baseline differences when compared with the six vitamin C groups. The comparisons presented here are with the placebo group #4 that was much closer to the vitamin C groups with respect to baseline data (see also Hemilä 2006a). If comparisons had been made with the placebo group #6 or a combination of the two placebo groups as the investigators had originally intended, the benefits would have been minimised as the mean episode duration for the placebo group #4 was 3.52, and for placebo group #6 was 2.83. Nevertheless, notwithstanding the placebo group problem, the proportion of 'short colds', that lasted for only one day was significantly larger in the 8 g/day group (46%; 222 out of 483) compared with the 4 g/day group (39%; 164 out of 417) (P = 0.046), consistent with the possibility of greater therapeutic benefit at the higher dose compared with the lower dose.

Tyrrell 1977, Elwood 1977 and Audera 2001a failed to show an effect on duration. Tyrrell evaluated males and females separately using a dosage of 4 g/day for the first 2.5 days of illness (total 10 g), Elwood evaluated males and females separately using a dosage of 3 g/day for the first 3.3 days of illness (total 10 g), and Audera evaluated 1 and 3 g/day over the first 3 days (total 3 and 9 g).

In summary, the data from the therapeutic trials do not provide consistent evidence that the duration of colds could be reduced with the protocols that have been tested in the vitamin C trials. The benefit from the use of an 8 g single dose immediately after the onset of cold symptoms is equivocal but suggests need for further research rather than practical conclusions.

5. Community therapeutic studies: severity of cold episodes when treatment commenced after common cold symptoms began

Analysis 5.1 has four entries which represent seven trial arms that included 2708 separate respiratory episodes for which cold severity was assessed. Audera 2001a, Anderson 1974e and Anderson 1975a contain two vitamin C arms.

As with the prophylaxis studies, we separated the measures of severity into two different subgroups: a) days confined to home, off work or school, and b) symptom severity scores, and analysed the subgroups separately and together.

In the first subgroup, the only comparison which revealed marginally significant benefit to those taking vitamin C was that for Anderson 1975a. In both vitamin C arms, participants took 1.5 g/day for the first day of the common cold and 1 g/day for the following four days (total 5.5 g). Anderson 1974e and Tyrrell 1977 found no meaningful difference between vitamin C and placebo. In the second subgroup, the Audera 2001a trial similarly found no meaningful difference between vitamin C and placebo groups.

6. Laboratory trials with artificially infected volunteers

Three laboratory trials were volunteer transmission studies which are summarised in Table 1.

Walker 1967 and Schwartz 1973 instilled virus into the noses of volunteers who had been pre-treated with vitamin C or placebo, whereas Dick 1990 used a more natural mechanism for transmission of a known rhinovirus. Their volunteers were housed for a week and worked closely with volunteers who had been previously infected by nasal instillation of rhinovirus.

In the Dick 1990 study, fewer vitamin C treated volunteers became infected and the cumulative symptom severity score and mucus weights were significantly less (P = 0.03), although the virus shedding was similar in both groups. Schwartz 1973 found reduced common cold severity in the vitamin C group (P < 0.02 at day 4), but no effect on symptom duration, whereas Walker 1967 did not observe any benefit to those who took vitamin C.

7. Adverse effects from high-dose vitamin C intake

Seven investigators of large prophylaxis trials recorded data on symptoms which participants attributed to the medication they were using.

Over the trials, data were recorded for a total of 2490 recipients who had used more than 1 g daily of vitamin C during prophylaxis compared with 2066 who took a placebo. Altogether 5.8% of the vitamin C recipients reported adverse symptoms which they attributed to the medication compared with 6.0% of those who were taking placebo (data not shown). No serious symptoms were reported.

DISCUSSION

Despite the variation in methodology and the substantial heterogeneity in results from this large number of trial results carried out over a 60-year period, certain rather strong conclusions can be drawn.

Effect on common cold incidence

Trials within the general community

An earlier meta-analysis pooled the results of the six largest trials in which 1 g/day or more of vitamin C had been administered regularly over the study period and found no effect of vitamin C on the incidence of colds with a narrow confidence interval (CI) (RR 0.99; 95% CI 0.93 to 1.04) (Hemilä 1997a). This earlier meta-analysis pooled the number of common cold episodes recorded during the study period, whereas this Cochrane meta-analysis used the number of participants catching a cold as the measure of common cold incidence. Nevertheless, this second outcome definition led to the same conclusion for the general community trials.

When the subgroup of marathon runners, skiers and soldiers on subarctic operations was excluded in this review, there was strong evidence that vitamin C supplementation has no effect on the number of people who catch the common cold during the supplementation period (RR 0.97; 95% CI 0.94 to 1.00). This estimate was based on trials in which the vitamin C dose was 0.2 g/day or more. However, the negative finding is not explained by the inclusion of a few trials in which the vitamin C dose was low: less than 1 g/day. When restricting to trials in which the vitamin C dose was 1 g/day or more, the estimate was essentially the same.

Trials with people under heavy acute physical stress

A previous meta-analysis identified three trials with participants under severe acute physical stress, and the pooling of results indicated significant benefit from vitamin C supplementation (Hemilä 1996b). Two later trials with marathon runners by Peters 1996a and Moolla 1996a have reinforced the findings of the earlier meta-analysis. It is noteworthy that all five trials in this group involved a brief exposure to high physical stress with or without cold stress. The doses of vitamin C were not particularly high, being between 0.25 and 1.0 g/day. Thus, the benefit in this subgroup cannot be explained by high doses. Similar doses in the general community have not affected the incidence of colds.

Furthermore, in the general community the acute respiratory symptoms usually have a viral cause, but it is not obvious that similar symptoms occurring after heavy exercise are caused by a viral infection because they can also result from exercise-induced bronchoconstriction (EIB), symptoms caused by an injury to the airways because of exceptional ventilatory exertion (Anderson 2008). In three trials, vitamin C supplementation reduced the decrease in

pulmonary function associated with EIB (Hemilä 2009c). Thus the common cold studies of physically stressed people might have been measuring, at least in part, the effects of vitamin C on EIB instead of viral infections. Nevertheless, although the aetiology of symptoms is not clear in the physically stressed subgroup, the beneficial effect of vitamin C on respiratory symptoms in this subgroup is firm.

Possible role of marginal vitamin C deficiency

One of the review authors (Hemilä 1997a) has also drawn attention to the possibility that some of the earlier benefits observed in low vitamin C dose studies, which were ruled ineligible for this review because of low doses (Baird 1979; Glazebrook 1942), might be a consequence of suboptimal dietary intakes in British males when the studies were carried out. This might also explain the significant benefit in the Charleston 1972 trial (Analysis 1.1), though participants in that study were single-blinded and not randomised. Few of the recent trials have estimated the dietary intakes of vitamin C. We cannot ignore the fact that vitamin C is an essential nutrient and all participants in the trials had regular intakes of this substance, some of them with lower levels than others. Four UK trials also found a reduction in the incidence of recurrent colds during the study period in males (pooled RR 0.54; 95% CI 0.40 to 0.74) but not in females (Hemilä 1997a). Nevertheless, a recent UK trial found a reduction in recurrent colds in a nine-week trial in both sexes (RR 0.13; 95% CI 0.03 to 0.53) (Van Straten 2002) (see also Hemilä 2006a). The most impressive trial in this UK group is the Baird 1979 study, which was a randomised, double-blind, placebo-controlled trial, but excluded from our analysis because of the low dose: 0.08 g/day. Methodological shortcomings do not explain the reduction in common cold incidence in males and the highly significant modification of vitamin C effect by sex (Hemilä 1997a; Hemilä 2008).

The large, well-conducted trial by Anderson 1972 reported a statistically significant but quite small reduction in common cold incidence (RR 0.91; 95% CI 0.85 to 0.98). This trial was conducted during winter in Toronto, Canada, and participants were selected on the basis of having had problems with colds during previous winters. A cold Canadian winter might be a partial explanation for the benefit in this trial if it is true that cold as well as physical stress makes a prophylactic benefit for vitamin C more likely. Furthermore, as regards the possible interaction between vitamin C supplementation and the level of dietary vitamin C intake, the Anderson 1972 trial is interesting as the investigators found a 48% reduction in 'total days indoors' among participants in the vitamin C group who consumed < 3 oz of fruit juice (common dietary source of vitamin C), whereas vitamin C reduced total days indoors by only 22% among those who consumed more juice. A similar modifying effect with fruit juice was found in the therapeutic trial by Anderson (Anderson 1975a). See also Hemilä 2006a.

Effect on common cold duration and severity: prophylaxis trials

Both in adults and in children, regular vitamin C supplementation resulted in a statistically highly significant reduction in the duration of respiratory episodes that occurred during the prophylactic supplementation period. For children, the pooled estimate was 13.2% and for adults it was 7.7%.

Although these findings point to a definite physiological effect from prophylactic vitamin C on common cold duration, the practical significance of these findings is less convincing. It does not seem reasonable to ingest vitamin C regularly in the mega-dose range throughout the year if the anticipated benefit is to slightly shorten the duration of colds which occur for adults two or three times per year. Our pooled estimate suggests that long-term supplementation might result in an upper estimate average reduction of annual common cold morbidity from about 12 days (Douglas 1979) to about 11 days per year for adults. For children under 12, who experience colds more frequently (on average for this age, the upper estimate could be as high as 28 days of cold morbidity annually), our pooled estimate of benefit suggests that long-term prophylaxis might be associated with an average reduction in four symptom days from about 28 days to 24 days per year per child. Such a benefit is not trivial, but it would seem more fruitful to initiate therapeutic trials to test whether an equivalent benefit might be achieved in children through therapeutic supplementation alone.

In light of the consistent effect of vitamin C on the duration of colds, an obvious question is whether there might be dose dependency, as suggested in a previous overview (Hemilä 1999a). However, across the available pool of trials, duration would appear to be more determined by the nature of the participants than by dose. There are few trials that have used more than 1 g/day in the child and adult groups separately. Nevertheless, Karlowski 1975a and Coulehan 1974a used two different doses within the same trials, that is, with the same outcome definitions. Karlowski's paper shows 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 support the case for the examination of higher doses.

Regular vitamin C prophylaxis also led to some decrease in severity when measured as days indoors or days off work or school, and on severity score scales (Analysis 3.1).

On the issue of the severity of colds, the Pitt 1979 paper is of further interest. This was a randomised, placebo-controlled, double-blind trial with 674 marine recruits during an eight-week period using 2 g/day of vitamin C. There was no difference in common cold incidence and only a 2% reduction in duration of colds and a 5% reduction in severity (P = 0.023) for those in the vitamin C group. However, eight of the recruits developed pneumonia as a sequel to their colds and only one of these was in the vitamin

C group (P = 0.044; see Hemilä 2004a; Hemilä 2009a). Thus, in addition to the common cold, vitamin C might also affect other respiratory infections either independently of colds, or as complications of colds (Hemilä 1999b). It is also worth noting that, although the vitamin C tablets were shown to be indistinguishable from the placebo tablets, 6% (40 out of 674; P = 0.013) of Pitt 1979 participants correctly inferred vitamin C or placebo tablets on the basis of subjective observations (see also Hemilä 2006a).

Effect on common cold duration and severity: therapeutic trials

Since the prophylaxis trials have unambiguously shown that vitamin C affects duration and the severity of colds without changing their incidence in the general population, it would seem rational to administer vitamin C therapeutically, starting immediately after the first symptoms. However, the therapeutic trials have mostly been negative (Analysis 4.1 and Analysis 5.1). The pooled estimates for duration and severity do not find any difference between vitamin C and placebo.

Technically the therapeutic trials are in several ways more complicated than regular supplementation trials. If the timing of supplementation initiation, the duration of supplementation or the dosage affect the size of the benefit, false negative findings might result from inappropriate study protocols.

Cowan 1950 used a therapeutic dose of about 3 g/d in the first two days of illness with no effect on duration. Elwood 1977, Tyrrell 1977 and Audera 2001a used a three-day supplementation, and these three trials found no effect from vitamin C. However, in their therapeutic trial, Tyrrell 1977 found a 40% reduction (P = 0.04) in the incidence of recurrent colds in men during the trial (Hemilä 1997a). A five-day therapeutic trial by Anderson 1975a found a reduction in 'days spent indoors per subject' because of illness of 25% (P = 0.05) in the vitamin C group (1 to 1.5 g/day). Also, using a five-day therapeutic supplementation of 3 g/day in a 2 x 2 factorial design trial, Karlowski 1975c found that colds were 0.73 days shorter (P = 0.10; see also Hemilä 1996a). These findings are consistent with the possibility that three days might be too short a time for vitamin C to produce unambiguous benefits, and it seems that future therapeutic trials should use supplementation for longer than five days.

It is also possible that the rapidity of initiation of vitamin C supplementation may have an impact on the effect. Asfora 1977 gave the same participants either vitamin C (6 g/day for five days) or other medications (aspirin, etc.) during different common cold episodes, but not in a double-blinded fashion. When treatment started within 24 hours of the onset of symptoms, the mean duration of vitamin C treated colds was 3.6 days, whereas the duration was 6.9 days with the other medications (see Hemilä 2006a). However, if vitamin C supplementation was initiated later than 24 hours following the onset of symptoms, there was no meaningful benefit. Regnier 1968 also concluded from his therapeutic study that "the sooner the better" and "vitamin C administration is not effective when started on the third or fourth day or later in the viral infection." Anderson 1974f found a benefit from an 8 g vitamin C dose when administered only on the first day of illness, which is also consistent with the possibility that rapid initiation of supplementation may be essential.

In several therapeutic trials, tablets were given to participants to be taken at home so they could start taking them as soon as they experienced the first symptoms of what they anticipated would be a cold (Anderson 1975a; Audera 2001a; Cowan 1950; Elwood 1977; Tyrrell 1977). In the Karlowski 1975c trial "if a cold developed, the volunteers were instructed to return to have their symptoms and clinical observations recorded and to receive supplemental study drug to be taken" and thus there was an unknown delay between the onset of symptoms and the initiation of treatment. Tebrock 1956 carried out their trial "on participants reporting to several outpatient industrial clinics under the supervision of the physicians conducting the study" indicating delay between symptom onset and treatment. In the briefly described Abbott 1968 trial, it seems that the tablets were administered by the doctors taking part in the trial and the average time between symptom onset and treatment initiation remains unknown. Consequently, even though the time between symptom onset and treatment initiation may affect the benefit of vitamin C, the data on this factor are limited.

The possible larger effect observed using 8 g compared with 4 g as a single dose in the Anderson 1974f trial and the dose dependency in the Karlowski 1975a trial (Hemilä 1996a; Hemilä 1999a; see also Hemilä 2006a) suggest that future therapeutic trials with adults should use doses of at least 8 g per day. Similarly, the greater reported benefit of 2 g/day than 1 g/day in the prophylactic Coulehan 1974a trial suggests that therapeutic trials with children should use doses of at least 2 g per day.

None of the therapeutic trials examined the effect of vitamin C on children, although children have a substantially higher incidence of acute respiratory tract infections. Furthermore, the effect of prophylactic vitamin C on the duration of colds has been substantially greater in children, up to 18% reduction in duration by 1 to 2 g/day, compared with adults, which also motivates therapeutic trials with children. Finally, although a tablet is a practical and the most common form of administering vitamin C, it is worth noting that administering vitamin C powder directly into the nose has also been proposed (Gotzsche 1989).

Nevertheless, while the pooled results of our therapeutic trials do not justify routine vitamin C supplementation for the 'average' person as a therapy for the common cold, the regular supplementation trials have shown unambiguously that vitamin C has a physiological effect on the duration and severity of colds. Furthermore, the results of controlled trials and the pooled results of trials apply to the average of the groups. We expect different sizes of vitamin C effects in different people, some having greater and some having smaller benefits than the average. Thus, given that vitamin

C is safe and inexpensive, it does not seem unreasonable to test the effect of vitamin C on an individual basis as a therapy for the common cold soon after the onset of symptoms.

Laboratory studies

The three experimental studies, which differed in their method of exposing volunteers to the infecting virus, is instructive. The study by Dick 1990, which has only been reported in conference proceedings, paid careful attention to the severity of the colds experienced by those who acquired them from fellow volunteers, who had been inoculated with a known rhinovirus. They also found that in these more natural circumstances of acquiring the virus, fewer, but not significantly fewer, volunteers on vitamin C developed cold symptoms but demonstrated similar viral shedding to the placebo group. The tantalisingly fragmentary descriptions of the Dick studies indicate a biological effect of high-dose vitamin C on the nature and course of symptoms encountered. These findings appear consistent with the view from the community prophylaxis studies that the protective benefit from vitamin C comes into play after the virus has become established.

Heterogeneity in the effects of vitamin C

A major finding of Analysis 1.1 was heterogeneity in the effect of vitamin C supplementation on common cold incidence. Furthermore, Anderson 1972 found about an 8% increase in the proportion of participants who were 'not ill during the trial', 'not confined to the house' and 'not off work' in the vitamin C group. Accordingly, about one participant in 12 benefited from vitamin C supplementation in this particular setting (number needed to treat to benefit, NNTB 12; see also Hemilä 2006a). It is noteworthy, however, that participants in this Canadian trial were asked not to enrol in the trial unless they normally experienced at least one cold in the wintertime, and in this respect the participants do not represent the average population. Coulehan 1974a studied Navajo school children and found a 16% higher proportion of children in the vitamin C group who were 'never ill on active surveillance' by a medically trained clerk or the school nurse (NNTB 6; see also Hemilä 2006a). Thus, these two trials indicate that some individual participants may benefit, even though there is strong evidence that vitamin C supplementation does not affect the average incidence of colds in the general community.

In close parallel with vitamin C, lipid-soluble vitamin E is interesting as these two antioxidants interact. Vitamin C reduces the oxidised form of vitamin E in *in vitro* conditions (see also Hemilä 2006a) and modifies the effect of vitamin E on mortality of older males (Hemilä 2009b). Therefore heterogeneity in the effect of vitamin E supplementation on common cold incidence (Hemilä 2006b) and on pneumonia incidence (Hemilä 2004b) is also relevant when considering the plausible heterogeneity of vitamin C effects.

If the effects of vitamin C vary substantially between different subpopulations, the heterogeneity of the effect means a need for careful consideration of goals when planning new trials. Assuming heterogeneity, further trials should try to identify and characterise the population groups or living conditions in which vitamin C might be beneficial, rather than re-examining the effects on ordinary Western people for whom the trials already published have not found any substantial overall benefits from daily supplementation. Also, the notion that various factors may modify the effects of antioxidants is fundamentally important in restricting broad generalisations from individual trials, irrespective of whether the finding is positive or negative, and whether or not the trial is large and carefully conducted.

Potential for bias in the common cold trials

Even though shortcomings in the design and conduct of trials may lead to erroneous conclusions, a recent meta-analysis of 276 randomised controlled trials found that double-blinding and allocation concealment, two quality measures that are frequently used in meta-analyses, were not associated with treatment effects (Balk 2002). Furthermore, there is evidence that the importance of the placebo effect has been substantially exaggerated (Hrobjartsson 2001; Hrobjartsson 2003).

Nevertheless, we consider that given the expected small effects of vitamin C and the greatly subjective outcome definitions, only placebo-controlled trials can yield information of adequate rigour to meet the objectives of our study. Although we required only placebo-control as an inclusion criterion, essentially all of the trials we identified were double-blind RCTs (Figure 1). Sensitivity analyses showed that our conclusions were not affected by the few trials that were methodologically less satisfactory.

Chalmers 1975 proposed that the effect of vitamin C on the common cold might be explained by "the result of the power of suggestion." As a support to this proposal he referred to the Karlowski 1975a trial in which the placebo was made of lactose, which is sweet, and thus it could be distinguished by taste from ascorbic acid which was used in vitamin C capsules. However, it was shown that Karlowski's findings cannot be logically explained by the breaking of the blind code (Hemilä 1996a). Furthermore, in the great majority of other trials, placebo has contained citric acid which cannot be distinguished by taste from ascorbic acid and in most trials the indistinguishability of the vitamin C and placebo preparations was explicitly stated (Figure 1). Thus, Chalmers' proposal is refuted by the indistinguishability of vitamin C and placebo preparations in numerous double-blinded trials.

Some aspects of this Cochrane Review were commented on recently by two groups of commentators, to which Hemilä replied (Shamseer 2008).

Safety of vitamin C

None of the vitamin C common cold trials that reported on adverse effects found evidence that vitamin C might be harmful in doses that were tested.

In general, vitamin C is considered safe in doses up to several grams per day. Although there has been speculation about the potential harm of large doses, it has been shown to be unfounded (Dykes 1975; see also Hemilä 2006a). For example, while 0.01 g/day of vitamin C protects against scurvy, in a recent pharmacokinetic study participants were administered up to 100 g of vitamin C intravenously within a few hours without any reported adverse effects, indicating the safety of such a very large dose in healthy people (Padayatty 2004).

Bee 1980 proposed 10 to 15 g/day for treating colds and Cathcart 1981 reported that he had orally administered over 30 g/day vitamin C to common cold patients. Such reports indicate the safety of such high doses, even though uncontrolled observations do not provide valid evidence of benefit. There are few reports of severe harm caused by high-dose vitamin C administration, but they can usually be attributed to some other coinciding medical condition. For example, the death of a 68 year old African American man was not attributed to intravenous injection of 80 g of vitamin C on two consecutive days per se but to his coincident glucose-6-phosphate dehydrogenase deficiency (Campbell 1975).

Pauling's contribution

Among the four trials included in the Pauling 1971a meta-analysis, the largest dose, 1 g/day, was used by Ritzel 1961. Pauling based his optimistic quantitative expectations on this rather small and brief trial, which was randomised, double-blind and placebo-controlled. Ritzel found significant reduction in the incidence (- 45%) and duration (- 31%) of colds, and Pauling derived a combination of the duration and incidence, which he labelled 'integrated morbidity', referring to the total sickness days per person during the trial.

The 'integrated morbidity' was reduced by 61% in the Ritzel trial, and Pauling 1971a used this Ritzel finding to extrapolate the effect of vitamin C to a broader community. The present analysis suggests that 'integrated morbidity' is not a good outcome measure, since the effects on incidence and duration/severity seem to have quite different patterns, though in the case of the Ritzel study, they moved together.

Furthermore, Ritzel carried out his trial with school children in a skiing school in the Swiss Alps, and such children are not a representative selection of the general population. In our analysis, Ritzel's trial is included in the group of five trials with participants exposed to short physical stress which highlights the special character of this trial. Thus, it was not a misjudgement by Pauling 1971a to put the great weight on this randomised, double-blind, placebo-controlled trial, but his error was to extrapolate the findings to the general population (Hemilä 1997b; see Hemilä 2006a).

Pauling pointed out various errors in the influential review by Dykes 1975, but did not contribute thereafter to the vitamin C and common cold field (Pauling 1976b; Pauling 1976c).

Pauling's vigorous advocacy was undoubtedly the stimulus for a wave of methodologically good trials, which now enable us to understand better the rather confusing role that this substance plays in defence against the common cold. Significant uncertainties still persist, which further research could help to clarify.

AUTHORS' CONCLUSIONS

Implications for practice

The lack of effect of prophylactic vitamin C supplementation on the incidence of the common cold in the general population throws doubt on the usefulness of this practice. In special circumstances, where people are engaged in extreme physical exertion or exposed to significant cold stress, or both, vitamin C supplementation may have a beneficial effect, but caution should be exercised in generalising this finding.

The prophylaxis trials found a reduction in common cold duration of 8% in adults and 13% in children. The practical relevance of these findings is open. In our opinion, this level of benefit does not justify long-term prophylaxis in its own right. So far, therapeutic supplementation has not been shown to be effective. Nevertheless, given the consistent effect of vitamin C on duration and severity in the regular supplementation studies, and the low cost and safety, it may be worthwhile for common cold patients to test on an individual basis whether therapeutic vitamin C is beneficial for them.

Implications for research

It does not seem worthwhile to carry out further regular supplementation trials in the general population. However, the findings in marathon runners, skiers and soldiers operating in subarctic conditions warrant further research.

None of the therapeutic trials carried out so far have examined the effect of vitamin C on children, even though the regular supplementation trials have found substantially greater effect on cold duration in children than in adults. In view of the greater incidence of respiratory infections in children, such therapeutic trials are warranted.

The findings in the Anderson 1974 study on the greater benefit of 8 g than 4 g dose on the day of onset of respiratory symptoms suggest that doses in further therapeutic trials with adults should be at least 8 g/day.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Anderson 1972

Methods	Double-blind RCT. Prophylaxis trial. Duration 3 months
Participants	Canadian adults, both sexes. 407 vitamin C; 411 placebo. Recruitment specified previous cold proneness in the winter months
Interventions	1 g/d vitamin C and 3 g/d extra for the first 3 days of illness
Outcomes	Incidence (Analysis 1.1), duration (Analysis 2.1) and severity (Analysis 3.1)
Notes	-

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	
Double-blinding?	Yes	
Randomised?	Yes	
Vitamin C and placebo indistinguishable?	Yes	[Vitamin C tablets:] "The taste of this formulation was well matched by a placebo preparation...The effectiveness of the matching was established by asking 30 individuals to taste both tablets ..."

Anderson 1974a

Methods	Double-blind RCT. Duration 3 months. Four prophylaxis, 2 treatment and 2 placebo arms This entry reports a prophylaxis arm
Participants	Canadian adults, both sexes. Data for this arm include 277 vitamin C; 285 placebo
Interventions	1 g/d vitamin C and 4 g/d at onset of illness on the 1st day only
Outcomes	Incidence (Analysis 1.1), duration (Analysis 2.1) and severity (Analysis 3.1)
Notes	Problems with placebo group #6; see p 40 (Table 16) in Hemilä 2006a. Therefore comparison in this review is restricted to placebo group #4 which had close baseline values for "usual days indoors" and "usual days off work" and "contact with children" consistent with the baseline values in the 6 vitamin C groups

Anderson 1974a (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	
Double-blinding?	Yes	
Randomised?	Yes	
Vitamin C and placebo indistinguishable?	Yes	Tablets: "taste test carried out with the help of a number of colleagues demonstrated that they were reasonably well matched in flavour, texture and appearance"

Anderson 1974b

Methods	See Anderson 1974a. Prophylaxis arm
Participants	275 vitamin C
Interventions	1 g/d vitamin C
Outcomes	Incidence (Analysis 1.1), duration (Analysis 2.1) and severity (Analysis 3.1)
Notes	-

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	
Double-blinding?	Yes	
Randomised?	Yes	
Vitamin C and placebo indistinguishable?	Yes	

Anderson 1974c

Methods	See Anderson 1974a. Prophylaxis arm
Participants	308 vitamin C
Interventions	2 g/d vitamin C

Anderson 1974c (*Continued*)

Outcomes	Incidence (Analysis 1.1), duration (Analysis 2.1) and severity (Analysis 3.1)
Notes	-

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	
Double-blinding?	Yes	
Randomised?	Yes	
Vitamin C and placebo indistinguishable?	Yes	

Anderson 1974d

Methods	See Anderson 1974a. Prophylaxis arm
Participants	331 vitamin C
Interventions	0.25 g/d vitamin C
Outcomes	Incidence (Analysis 1.1), duration (Analysis 2.1) and severity (Analysis 3.1)
Notes	-

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	
Double-blinding?	Yes	
Randomised?	Yes	
Vitamin C and placebo indistinguishable?	Yes	

Anderson 1974e

Methods	See Anderson 1974a. Therapeutic arm
Participants	275 vitamin C
Interventions	4 g/d vitamin C on the 1st day of illness only
Outcomes	Duration (Analysis 4.1) and severity (Analysis 5.1)
Notes	-

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	
Double-blinding?	Yes	
Randomised?	Yes	
Vitamin C and placebo indistinguishable?	Yes	

Anderson 1974f

Methods	See for Anderson 1974a. Therapeutic arm
Participants	308 vitamin C
Interventions	8 g/d vitamin C on the 1st day of illness only
Outcomes	Duration (Analysis 4.1) and severity (Analysis 5.1)
Notes	-

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	
Double-blinding?	Yes	
Randomised?	Yes	
Vitamin C and placebo indistinguishable?	Yes	

Anderson 1975a

Methods	Double-blind RCT. Therapeutic trial. Duration 15 weeks. Two active and one placebo arm This arm used vitamin C tablets
Participants	Canadian adults, both sexes. 150 vitamin C; 146 placebo
Interventions	0.5 g weekly and 1.5 g/d on the 1st day of illness and 1 g/d for the next 4 days
Outcomes	Duration (Analysis 4.1) and severity (Analysis 5.1)
Notes	Indistinguishability of treatments: (p. 824) "three types of medication were used: a 500-mg tablet containing sodium and calcium ascorbate in an approximate 2:1 ratio, a placebo tablet of the same appearance and taste, and a capsule containing 500 mg of ascorbic acid in sustained-release form. ... It was not possible to obtain placebo capsules that were truly indistinguishable from the active sustained-release form because the contents of the capsules (ascorbic acid pellets) proved prohibitively expensive to imitate. The explanatory notes provided to the subjects were therefore deliberately phrased to give the impression that, as with the tablets, half of the capsules contained a placebo preparation. This subterfuge was successful ... "

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	
Double-blinding?	Yes	
Randomised?	Yes	
Vitamin C and placebo indistinguishable?	Yes	See notes above

Anderson 1975b

Methods	See Anderson 1975a. This arm used vitamin C capsules
Participants	152 vitamin C
Interventions	See Anderson 1975a
Outcomes	Duration (Analysis 4.1) and severity (Analysis 5.1)
Notes	-

Risk of bias

Item	Authors' judgement	Description

Anderson 1975b (*Continued*)

Allocation concealment?	Yes	
Double-blinding?	Yes	
Randomised?	Yes	
Vitamin C and placebo indistinguishable?	Yes	

Audera 2001a

Methods	Double-blind RCT. Therapeutic trial	
Participants	Australian adults of both sexes. 47 vitamin C; 42 placebo	
Interventions	1 g/d vitamin C for 3 days. Placebo group received 30 mg/d vitamin C daily for 3 days	
Outcomes	Duration (Analysis 4.1) and severity (Analysis 5.1)	
Notes	-	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	
Double-blinding?	Yes	
Randomised?	Yes	
Vitamin C and placebo indistinguishable?	Yes	"tablets with identical appearance and packaging"

Audera 2001b

Methods	See Audera 2001a	
Participants	50 vitamin C	
Interventions	3 g/d vitamin C for 3 days	
Outcomes	Duration (Analysis 4.1) and severity (Analysis 5.1)	
Notes	-	
Risk of bias		

Audera 2001b (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Yes	
Double-blinding?	Yes	
Randomised?	Yes	
Vitamin C and placebo indistinguishable?	Yes	

Bancalari 1984

Methods	Double-blind RCT. Prophylaxis trial. Duration 84 days
Participants	Chilean school children, male and female, age 10 to 12 years. 32 vitamin C; 30 placebo
Interventions	2 g/d vitamin C
Outcomes	Incidence (Analysis 1.1) and duration (Analysis 2.1)
Notes	-

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	
Double-blinding?	Yes	
Randomised?	Yes	
Vitamin C and placebo indistinguishable?	Yes	"vitamin C tablets and the placebo tablets were identical in color, taste, size and consistency"

Briggs 1984

Methods	Double-blind RCT. Prophylaxis trial. Over 8 winters for 3 or 6 months of commitment by each volunteer
Participants	Australian adults, male and female. 265 vitamin C; 263 placebo
Interventions	1 g/d vitamin C plus 4 g/d when respiratory symptoms occurred. Placebo group received 50 mg/d plus 200 mg/d when ill

Briggs 1984 (*Continued*)

Outcomes	Incidence (Analysis 1.1) and duration (Analysis 2.1)	
Notes	SD for duration was not published and it was estimated as SD = mean	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	
Double-blinding?	Yes	
Randomised?	Yes	
Vitamin C and placebo indistinguishable?	Yes	"identical opaque gelatin capsules (dark brown) and ... similar acidic taste, but lacking vitamin C activity. Citric acid was selected"

Carr 1981a

Methods	Double-blind RCT. Prophylaxis trial. Duration 100 days. Identical twins: one group living together and the other living apart. This deals with those living together	
Participants	Australian males and females age range 14 to 64 years (mean 25 years). 51 twin pairs living together	
Interventions	1 g/d vitamin C. Both groups received a multi-vitamin tablet containing 70 mg/d vitamin C	
Outcomes	Incidence (Analysis 1.1), duration (Analysis 2.1) and severity (Analysis 3.1)	
Notes	SD for duration was not published and the SD was calculated from the P value	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	
Double-blinding?	Yes	
Randomised?	Yes	
Vitamin C and placebo indistinguishable?	Yes	"matching of the active and placebo tablets was checked for both appearance and taste"

Carr 1981b

Methods	See Carr 1981a. This deals with those living apart	
Participants	44 twin pairs living apart	
Interventions	1 g/d vitamin C	
Outcomes	Incidence (Analysis 1.1), duration (Analysis 2.1) and severity (Analysis 3.1)	
Notes	-	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	
Double-blinding?	Yes	
Randomised?	Yes	
Vitamin C and placebo indistinguishable?	Yes	"matching of the active and placebo tablets was checked for both appearance and taste"

Carson 1975

Methods	Double-blind RCT. Prophylaxis trial. Duration 40 days	
Participants	UK adults. 121 vitamin C; 123 placebo	
Interventions	1 g/d vitamin C	
Outcomes	Incidence (Analysis 1.1)	
Notes	-	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	
Double-blinding?	Yes	
Randomised?	Yes	
Vitamin C and placebo indistinguishable?	Yes	"tablets or matching lactose dummies"

Charleston 1972

Methods	Single-blind, not randomised. Prophylaxis trial. Duration 15 weeks	
Participants	Staff and students of the University of Strathclyde, UK. 47 vitamin C; 43 placebo	
Interventions	1 g/d vitamin C	
Outcomes	Incidence (Analysis 1.1) and duration (Analysis 2.1)	
Notes	-	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	No	
Double-blinding?	No	
Randomised?	Unclear	?
Vitamin C and placebo indistinguishable?	Yes	"placebo similar in appearance but containing lactose and 5% citric acid"

Clegg 1975

Methods	Double-blind RCT. Prophylaxis trial. Duration 15 weeks	
Participants	Scottish students. 67 vitamin C; 70 placebo	
Interventions	1 g/d vitamin C	
Outcomes	Incidence (Analysis 1.1) and duration (Analysis 2.1)	
Notes	-	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	
Double-blinding?	Yes	
Randomised?	Unclear	?
Vitamin C and placebo indistinguishable?	Yes	"The placebo and ascorbic acid tablets were organoleptically indistinguishable"

Coulehan 1974a

Methods	Double-blind, alternate allocation. Prophylaxis trial. Duration 14 weeks
Participants	USA. Students at a Navajo Indian school. Older residential students. 131 vitamin C; 128 placebo
Interventions	2 g/d vitamin C
Outcomes	Incidence (Analysis 1.1) and duration (Analysis 2.1)
Notes	SD for duration was not published and it was estimated as SD = mean Personal communication (13 September 1995), about table 4: "... you are right, it is quite obvious that there is a typographical error. What I am referring to in those columns is the number of children without days of sickness, rather than the number of days as such. The title of Table 4 is correct, but the labeling of the columns is incorrect."

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	
Double-blinding?	Yes	
Randomised?	No	Allocation: was "alternatively, from an alphabetical listing by classroom to one of two study groups"
Vitamin C and placebo indistinguishable?	Yes	"Placebos were formulated from citric acid to be indistinguishable in taste and appearance from the vitamin C tablets"

Coulehan 1974b

Methods	See Coulehan 1974a
Participants	Younger residential students. 190 vitamin C; 192 placebo
Interventions	1 g/d vitamin C
Outcomes	Incidence (Analysis 1.1) and duration (Analysis 2.1)
Notes	SD for duration was not published and it was estimated as SD = mean

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	

Coulehan 1974b (*Continued*)

Double-blinding?	Yes	
Randomised?	No	Allocation: was "alternatively, from an alphabetical listing by classroom to one of two study groups"
Vitamin C and placebo indistinguishable?	Yes	"Placebos were formulated from citric acid to be indistinguishable in taste and appearance from the vitamin C tablets"

Coulehan 1976

Methods	Double-blind RCT. Prophylaxis trial. Duration 18 weeks in one school and 15 weeks in another
Participants	USA. Children at 2 Navajo Indian residential schools, age 6 to 15 years. Both sexes. 428 vitamin C; 428 placebo
Interventions	1 g/d vitamin C
Outcomes	Incidence (Analysis 1.1) and duration (Analysis 2.1)
Notes	SD for duration was not published and it was estimated as SD = mean

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	
Double-blinding?	Yes	
Randomised?	Yes	
Vitamin C and placebo indistinguishable?	Yes	"placebo tablets were formulated with citric acid to be identical in appearance and taste with ascorbic acid pills"

Cowan 1942

Methods	Placebo-controlled, allocation method not clear. Prophylaxis trial. Duration 28 weeks
Participants	US college students. 208 vitamin C; 155 placebo
Interventions	0.2 g/d vitamin C
Outcomes	Incidence (Analysis 1.1)

Cowan 1942 (*Continued*)

Notes	SD for duration was not published and it was estimated as SD = mean	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	
Double-blinding?	Yes	
Randomised?	No	"The students were assigned alternately and without selection to an experimental and to a control group." However, the discrepancy in the size of trial arms is not consistent with alternate allocation, see above (208 versus 155)
Vitamin C and placebo indistinguishable?	Yes	"... placebo tablets of the same size, shape, appearance and taste as the ascorbic acid tablets.These students, of course, did not know that they were serving as controls. "

Cowan 1950

Methods	Probably double-blind RCT. Alternate allocation. Therapeutic trial	
Participants	US college students. 76 vitamin C; 77 placebo	
Interventions	0.67 g of vitamin C for every 4 hours, with a maximum of 10 doses (total 6.7 grams); i.e. about 3 g/d for 2 days	
Outcomes	Duration (Analysis 4.1)	
Notes	-	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	?
Double-blinding?	Yes	
Randomised?	No	"The medicaments were given out in strict rotation to the students as they enrolled"

Cowan 1950 (*Continued*)

Vitamin C and placebo indistinguishable?	Yes	"Placebo (citric acid to simulate the taste of ascorbic acid, lactose, cornstarch, sugar, talc and stearic acid)"

Dahlberg 1944

Methods	Double-blind RCT. Prophylaxis trial. Duration 57 days	
Participants	Swedish army. 1259 vitamin C; 1266 placebo	
Interventions	0.2 g/d vitamin C during the first 24 days; 50 mg/d thereafter	
Outcomes	Incidence Analysis 1.1	
Notes	-	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	
Double-blinding?	Yes	
Randomised?	Yes	
Vitamin C and placebo indistinguishable?	Yes	"Control tablets, to which a suitable amount of citric acid had been added, to disguise any difference in taste"

Dick 1990

Methods	Brief abstract report of 3 experimental prophylaxis studies using intense exposure to infected volunteers	
Participants	USA, adult volunteers. 24 vitamin C; 24 placebo	
Interventions	2 g/d vitamin C	
Outcomes	Shown in Table 1. Not included in meta-analyses	
Notes	Three abstracts, no full paper	
Risk of bias		
Item	**Authors' judgement**	**Description**

Dick 1990 (*Continued*)

Allocation concealment?	Yes	
Double-blinding?	Yes	
Randomised?	Unclear	?
Vitamin C and placebo indistinguishable?	Unclear	?

Elwood 1976

Methods	Double-blind RCT. Prophylaxis trial
Participants	Wales, young mothers. 339 vitamin C; 349 placebo
Interventions	1 g/d vitamin C
Outcomes	Incidence (Analysis 1.1) and duration (Analysis 2.1)
Notes	-

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	
Double-blinding?	Yes	
Randomised?	Yes	
Vitamin C and placebo indistinguishable?	Yes	"tablets ... These contained either 1 g ascorbic acid in an effervescent base or a matching placebo"

Elwood 1977

Methods	Double-blind RCT. Therapeutic trial
Participants	Wales, young mothers. 145 colds treated with vitamin C and 119 treated with placebo
Interventions	4 g/d vitamin C daily for the first 2.5 days of illness
Outcomes	Duration (Analysis 2.1) Colds were classified either as simple or chest colds

Elwood 1977 (*Continued*)

Notes	If the chest colds lasting more than 20 days are included in the comparison the statistically significant difference favouring vitamin C disappears

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	
Double-blinding?	Yes	
Randomised?	Yes	
Vitamin C and placebo indistinguishable?	Unclear	?

Franz 1956

Methods	Double-blind. Prophylaxis study. 2 x 2 factorial: vitamin C and flavonoids. Duration 3 months
Participants	Medical students and student nurses. 44 vitamin C; 45 no-vitamin C
Interventions	0.2 g/d vitamin C
Outcomes	Incidence (Analysis 1.1)
Notes	In the vitamin C group 93% (13/14) of colds were cured or improved in 5 days versus 53% (8/15) in the no-vitamin C group (P = 0.03; see p. 14 Hemilä 2006a)

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	
Double-blinding?	Yes	
Randomised?	No	"Groups were assigned in rotation"
Vitamin C and placebo indistinguishable?	Yes	Tablets: "all looked and tasted the alike"

Himmelstein 1998a

Methods	Double-blind RCT. Prophylaxis trial. Duration 3 months
Participants	US sedentary people. 23 vitamin C; 25 placebo
Interventions	1 g/d vitamin C
Outcomes	Incidence (Analysis 1.1), duration (Analysis 2.1) and severity (Analysis 3.1)
Notes	A parallel trial with marathon runners is excluded from our analysis, because the dropout rate was very high and divergent in the trial arms (Himmelstein 1998b)

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	
Double-blinding?	Yes	
Randomised?	Yes	
Vitamin C and placebo indistinguishable?	Yes	"Placebo (similar looking and tasting tablets containing lactose)"

Karlowski 1975a

Methods	Double-blind RCT. 2 x 2 factorial: prophylaxis and therapeutic vitamin C. Duration 9 months. We compared 3 different arms with the placebo arm This is prophylaxis arm
Participants	USA, employees of the NIH. 44 vitamin C; 46 placebo
Interventions	3 g/d vitamin C
Outcomes	Duration (Analysis 2.1)
Notes	The authors believed that the benefits observed were attributable to the breaking of the patient blind: "we discovered that some of the volunteers had tasted the contents of their capsules and professed to know whether they were taking the ascorbic acid or the placebo" However, their interpretation was later shown to be erroneous, see Hemilä 1996a, Hemilä 2006a, Hemilä 2006c

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	

Karlowski 1975a (*Continued*)

Double-blinding?	Yes	
Randomised?	Yes	
Vitamin C and placebo indistinguishable?	Unclear	See Notes

Karlowski 1975b

Methods	See Karlowski 1975a. This is prophylaxis plus therapeutic arm	
Participants	57 vitamin C	
Interventions	3 g/d vitamin C and 3 g/d therapeutic from the onset of cold for 5 days	
Outcomes	Incidence (Analysis 1.1) and duration (Analysis 2.1)	
Notes	-	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	
Double-blinding?	Yes	
Randomised?	Yes	
Vitamin C and placebo indistinguishable?	Unclear	See Notes

Karlowski 1975c

Methods	See Karlowski 1975a. This is therapeutic only arm	
Participants	43 vitamin C	
Interventions	3 g/d therapeutic vitamin C from the onset of cold for 5 days	
Outcomes	Duration (Analysis 4.1)	
Notes	-	
Risk of bias		
Item	**Authors' judgement**	**Description**

Karlowski 1975c (*Continued*)

Allocation concealment?	Yes	
Double-blinding?	Yes	
Randomised?	Yes	
Vitamin C and placebo indistinguishable?	Unclear	See Notes

Liljefors 1972

Methods	Double-blind RCT. Cross-over prophylaxis trial. Duration 2 + 2 weeks. In the first 2 weeks 25 participants received vitamin C and 18 placebo. As participants became ill they were removed from the trial and 3 persons withdrew. In the second period, 18 received placebo and 8 vitamin C
Participants	Swedish army males. 33 vitamin C; 33 placebo
Interventions	2 g/d vitamin C for 2 weeks
Outcomes	Incidence (Analysis 1.1)
Notes	-

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	
Double-blinding?	Yes	
Randomised?	Yes	
Vitamin C and placebo indistinguishable?	Unclear	?

Ludvigsson 1977a

Methods	Double-blind RCT. Prophylaxis trial. Duration 7 weeks
Participants	Swedish school children. 80 vitamin C; 78 placebo
Interventions	1 g/d vitamin C. Placebo contained 30 mg/d vitamin C
Outcomes	Incidence (Analysis 1.1), duration (Analysis 2.1) and severity (Analysis 3.1)
Notes	Pilot study to Ludvigsson 1977b

Ludvigsson 1977a (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	
Double-blinding?	Yes	
Randomised?	Yes	
Vitamin C and placebo indistinguishable?	Yes	"fizzy tablet which contained 1000 mg vitamin C; in the other group the fizzy tablet looked and tasted the same"

Ludvigsson 1977b

Methods	Double-blind RCT. Prophylaxis trial. Duration 3 months
Participants	Swedish school children. 304 vitamin C; 311 placebo
Interventions	1 g/d vitamin C. Placebo contained 10 mg/d vitamin C
Outcomes	Incidence (Analysis 1.1), duration (Analysis 2.1) and severity (Analysis 3.1)
Notes	-

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	
Double-blinding?	Yes	
Randomised?	Yes	
Vitamin C and placebo indistinguishable?	Yes	"fizzy tablet which contained 1000 mg vitamin C; in the other group the fizzy tablet looked and tasted the same"

Miller 1977a

Methods	Double-blind RCT. Prophylaxis trial. Identical twins. Duration 5 months
Participants	US school children. 12 twin pairs "high body weight"
Interventions	1 g/d vitamin C. Placebo contained 50 mg/d vitamin C

Miller 1977a (*Continued*)

Outcomes	Incidence (Analysis 1.1), duration (Analysis 2.1) and severity (Analysis 3.1)	
Notes	-	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	
Double-blinding?	Yes	
Randomised?	Yes	
Vitamin C and placebo indistinguishable?	Unclear	?

Miller 1977b

Methods	See Miller 1977a	
Participants	12 twin pairs "medium body weight"	
Interventions	0.75 g/d vitamin C	
Outcomes	Incidence (Analysis 1.1), duration (Analysis 2.1) and severity (Analysis 3.1)	
Notes	-	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	
Double-blinding?	Yes	
Randomised?	Yes	
Vitamin C and placebo indistinguishable?	Unclear	?

Miller 1977c

Methods	See Miller 1977a
Participants	20 twin pairs "low body weight"
Interventions	0.5 g/d vitamin C
Outcomes	Incidence (Analysis 1.1), duration (Analysis 2.1) and severity (Analysis 3.1)
Notes	-

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	
Double-blinding?	Yes	
Randomised?	Yes	
Vitamin C and placebo indistinguishable?	Unclear	?

Moolla 1996a

Methods	Double-blind RCT. Prophylaxis trial. Duration 6 weeks before and 2 weeks after the race
Participants	South Africa. Ultra marathon runners. 13 vitamin C; 19 placebo
Interventions	0.25 g/d vitamin C
Outcomes	Incidence (Analysis 1.1)
Notes	1/4 of those who reported respiratory symptoms in the vitamin C group, and 8/13 of those who reported respiratory symptoms in the placebo group, reported that their respiratory symptoms were severe (P = 0.08)

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	
Double-blinding?	Yes	
Randomised?	Yes	

Moolla 1996a (*Continued*)

Vitamin C and placebo indistinguishable?	Yes	"placebo was identical in form to the ascorbic acid"

Moolla 1996b

Methods	See Moolla 1996a
Participants	Sedentary controls for marathon runners. 11 vitamin C; 19 placebo
Interventions	0.25 g/d vitamin C
Outcomes	Incidence (Analysis 1.1)
Notes	0/6 of those who reported respiratory symptoms in the vitamin C group and 4/7 of those who reported respiratory symptoms in the placebo group reported that their respiratory symptoms were severe (P = 0.02)

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	
Double-blinding?	Yes	
Randomised?	Yes	
Vitamin C and placebo indistinguishable?	Yes	"placebo was identical in form to the ascorbic acid"

Peters 1993a

Methods	Double-blind RCT. Prophylaxis trial. Duration 3 weeks before and 2 weeks after the race
Participants	South Africa. Ultra marathon runners. 43 vitamin C; 41 placebo
Interventions	0.6 g/d vitamin C
Outcomes	Incidence (Analysis 1.1) and duration (Analysis 2.1)
Notes	-

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	

Peters 1993a (*Continued*)

Double-blinding?	Yes	
Randomised?	Yes	
Vitamin C and placebo indistinguishable?	Yes	"identical looking and tasting placebo containing citric acid"

Peters 1993b

Methods	See Peters 1993a.
Participants	Sedentary controls for marathon runners. 34 vitamin C; 39 placebo
Interventions	0.6 g/d vitamin C
Outcomes	Incidence (Analysis 1.1) and duration (Analysis 2.1)
Notes	-

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	
Double-blinding?	Yes	
Randomised?	Yes	
Vitamin C and placebo indistinguishable?	Yes	"identical looking and tasting placebo containing citric acid"

Peters 1996a

Methods	Double-blind RCT. Prophylaxis trial. Duration 21 days prior to the race
Participants	South Africa. Ultra marathon runners. 44 vitamin C; 47 placebo
Interventions	0.5 g/d vitamin C
Outcomes	Incidence (Analysis 1.1) and duration (Analysis 2.1)
Notes	SD for duration was not published and it was estimated as SD = mean

Risk of bias

Item	Authors' judgement	Description

Peters 1996a (*Continued*)

Allocation concealment?	Yes	
Double-blinding?	Yes	
Randomised?	Yes	
Vitamin C and placebo indistinguishable?	Yes	"tablets of similar appearance"

Peters 1996b

Methods	See Peters 1996a.
Participants	South Africa. Family controls for marathon runners. 41 vitamin C; 45 placebo
Interventions	0.5 g/d vitamin C
Outcomes	Incidence (Analysis 1.1) and duration (Analysis 2.1)
Notes	-

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	
Double-blinding?	Yes	
Randomised?	Yes	
Vitamin C and placebo indistinguishable?	Yes	"tablets of similar appearance"

Pitt 1979

Methods	Double-blind RCT. Prophylaxis trial. Duration 8 weeks
Participants	USA marine recruits. 331 vitamin C; 343 placebo
Interventions	2 g/d vitamin C
Outcomes	Incidence (Analysis 1.1), duration (Analysis 2.1) and severity (Analysis 3.1)
Notes	SD for duration was not published and it was estimated as SD = mean

Risk of bias

Pitt 1979 (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Yes	
Double-blinding?	Yes	
Randomised?	Yes	
Vitamin C and placebo indistinguishable?	Yes	"the placebo tablets were formulated from citric acid and were indistinguishable in appearance and taste from the vitamin C tablets"

Ritzel 1961

Methods	Double-blind RCT. Prophylaxis trial. Duration 2 weeks
Participants	Children attending ski school in Swiss Alps. 139 vitamin C; 140 placebo
Interventions	1 g/d vitamin C
Outcomes	Incidence (Analysis 1.1) and duration (Analysis 2.1)
Notes	SD for duration was not published and the SD was calculated from the P value

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	
Double-blinding?	Yes	"Neither test subjects nor investigators knew whether the children got placebo or vitamin C"
Randomised?	Yes	
Vitamin C and placebo indistinguishable?	Yes	"The placebo was indistinguishable from the 1-gm ascorbic acid tablet"

Sabiston 1974

Methods	Double-blind RCT. Prophylaxis trial. Duration 2 to 3 weeks
Participants	Canadian male military recruits during subarctic winter exercises. 56 vitamin C; 56 placebo

Sabiston 1974 (*Continued*)

Interventions	1 g/d vitamin C	
Outcomes	Incidence (Analysis 1.1) and duration (Analysis 2.1)	
Notes	Personal communication from Manny Radomski (12 Sept 2009), see 'Risk of bias' table	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	
Double-blinding?	Yes	Personal communication (Radomski 12 Sept 2009): "Tent group commanders [who were responsible for distributing the pills and recording the distribution] did not know what was in the vials... We [the authors] collected the data by symptoms on T-scan cards. We did not 'break the code' until after all cards had been assessed."
Randomised?	Yes	
Vitamin C and placebo indistinguishable?	Yes	Personal communication (Radomski 12 Sept 2009): "Vitamin C and placebo were in identical capsules, so taste did not enter into the equation... In our pre-briefing to the troops, we believe that we told the troops that they would all be getting vitamin C but at different doses."

Sasazuki 2006

Methods	Double-blind RCT. Prophylaxis trial. Duration 3.5 years
Participants	Japanese males and females, mean age 57 years. 140 vitamin C; 133 placebo
Interventions	0.5 g/d vitamin C. Placebo contained 50 mg/d vitamin C
Outcomes	Incidence (Analysis 1.1) ITT results are shown
Notes	Additional data provided by authors Duration and severity of colds were reported, but they were recorded on the period after supplementation had been stopped, with no rationale described for such a comparison
Risk of bias	

Sasazuki 2006 (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Yes	
Double-blinding?	Yes	
Randomised?	Yes	
Vitamin C and placebo indistinguishable?	Unclear	?

Schwartz 1973

Methods	Double-blind experimental prophylaxis study with nasal instillation of virus after 2 weeks of pre-treatment
Participants	Male US prison volunteers. 11 vitamin C; 10 placebo
Interventions	3 g/d vitamin C
Outcomes	Shown in Table 1 Not included in meta-analyses
Notes	-

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	
Double-blinding?	Yes	
Randomised?	Unclear	?
Vitamin C and placebo indistinguishable?	Unclear	?

Tyrrell 1977

Methods	Double-blind RCT. Therapeutic trial
Participants	UK, both sexes. 274 episodes treated with vitamin C; 329 placebo
Interventions	4 g/d vitamin C for the first 2.5 days of illness
Outcomes	Duration (Analysis 4.1) and severity (Analysis 5.1)

Tyrrell 1977 (*Continued*)

Notes	-

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	
Double-blinding?	Yes	
Randomised?	Yes	
Vitamin C and placebo indistinguishable?	Yes	"the tubes with 'placebo treatment', contained inert substances of identical appearance and taste"

Van Straten 2002

Methods	Double-blind RCT. Prophylaxis trial. Duration 60 days
Participants	UK, both sexes. 84 vitamin C; 84 placebo
Interventions	1 g/d vitamin C. Ester-C ascorbate, a form that, according to authors, "allows cells to efficiently absorb and retain high levels of vitamin"
Outcomes	Incidence (Analysis 1.1) and duration (Analysis 2.1)
Notes	-

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	
Double-blinding?	Yes	
Randomised?	Yes	
Vitamin C and placebo indistinguishable?	Yes	Tablets: "ascorbate 500 mg or a matched placebo"

Walker 1967

Methods	Experimental prophylaxis study in which healthy volunteers were intranasally inoculated with viruses. Duration 3 days before and 6 days after nasal instillation of virus
Participants	UK adults both sexes. 47 vitamin C; 44 placebo
Interventions	3 g/d vitamin C
Outcomes	
Notes	-

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	?
Double-blinding?	Yes	
Randomised?	Unclear	?
Vitamin C and placebo indistinguishable?	Unclear	?

Wilson 1973a

Methods	Double-blind RCT. Prophylaxis trial. Duration 9 months
Participants	UK boarding school girls. 70 vitamin C; 58 placebo
Interventions	0.2 g/d vitamin C
Outcomes	Incidence (Analysis 1.1), duration (Analysis 2.1) and severity (Analysis 3.1)
Notes	Complicated classification system makes comparison with other trials difficult

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	
Double-blinding?	Yes	
Randomised?	Yes	
Vitamin C and placebo indistinguishable?	Unclear	?

Wilson 1973b

Methods	See Wilson 1973a	
Participants	UK boarding school boys. 88 vitamin C; 86 placebo	
Interventions	0.2 g/d vitamin C	
Outcomes	Incidence (Analysis 1.1), duration (Analysis 2.1) and severity (Analysis 3.1)	
Notes	-	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	
Double-blinding?	Yes	
Randomised?	Yes	
Vitamin C and placebo indistinguishable?	Unclear	?

g/d: grams per day
mg/d: milligrams per day
SD: standard deviation
ITT: intention-to-treat
NIH: National Institutes for Health
RCT: randomised controlled trial

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abbott 1968	Data not suitable for inclusion in our meta-analyses. This randomised, placebo-controlled therapeutic trial involved 270 family members of 78 UK general practitioners. Males and females were in equal numbers; 39% were 20 years or younger, 52% were from 21 to 50 years. 3 g/d vitamin C was used to treat 147 patients "continued as long as necessary, up to a total of fourteen days" and 133 received placebo. Clinical scores for a range of symptoms were computed and stated not to be different between the 2 groups: "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" (p 444). However, the only available data reports the severity of "sore throat in patients with a common cold" (Table 1 on p 443). Thus no usable data could be extracted from the paper to our meta-analyses. It is not clear how long a delay there was between the onset of symptoms and the initiation of treatment. "The doctors taking part in the trial were asked to treat families in order, as colds appeared during the course of the winter" (p 442), thus it seems that the doctor gave tablets only when he or she met the patient rather than patient keeping tablets ready at home for use when symptoms started

(*Continued*)

Asfora 1977	Placebo-controlled, double-blind trial with no suitable data, and a comparison without a placebo. A Brazilian study involving males and females aged between 14 and 89. The author describes: "a double-blind trial was conducted in which the preparations, numbered 1 and 8, were given to alternate patients as they presented themselves. .. 2 g three times per day for five consecutive days, or in other words 6 g per day or a total of 30 g. When 42 patients had received substance No. 1 and 41 patients had received No. 8, there was no longer any point in continuing the double-blind trial, since in view of the clinical progress of the patients there was not the slightest doubt that substance No. 1 was vitamin C and No. 8 was the placebo" (p 224). Thereafter the trial was continued as an open trial comparing vitamin C with other drugs. Rapid initiation of vitamin C supplementation (< 24 hours from the onset of symptoms) appeared beneficial, whereas late initiation (> 24 hours) did not. The paper suggests a bias of the investigator towards the therapeutic benefits of vitamin C
Audera 2001c	Vitamin C was administered with flavonoids. Thus the comparison was not on vitamin C specifically. There was no difference between placebo and 3 g/day vitamin C + flavonoid groups. Two other arms are included in our analyses (Audera 2001a and Audera 2001b)
Baird 1979	Low dose. 362 UK students aged 17 to 25 years were studied for 72 days in a double-blind RCT of prophylaxis. A daily drink contained either synthetic orange juice without ascorbic acid, synthetic juice with 0.08 g/d of ascorbic acid added, or natural orange juice with 0.08 g/d of ascorbic acid added. There was a highly significant reduction in common cold incidence among males (RR 0.63; 95% CI: 0.50 to 0.78) but not in females (RR 1.24; 0.95 to 1.61) (Hemilä 1997a; Hemilä 2006a). The heterogeneity between sexes was highly significant (Hemilä 2008). The benefit of low-dose vitamin C supplementation may be explained by low dietary vitamin C intake in the UK (Hemilä 1997a)
Barnes 1961	No placebo comparison. A trial in the USA. A multivitamin preparation that included 0.2 g/d vitamin C was given to 23 members (10 boys, 13 girls) of a basketball team for 7 weeks; medication being received from the coaches. The cold outcomes were compared with those of 16 people (8 boys, 8 girls) of the same age and background. The controls reported to the coaches daily. Days sick from cold were counted in each group. The study took place over 8 weeks during which the basketball players took medication on an average of 43 days. The only usable outcome was "mean days per person" in the vitamin C group 1.48 (SD 2.65) and in the control group 6.87 (SD 8.57). However, there are serious doubts about the comparability of the controls who were apparently not basketball players
Bartley 1953	Low dose. "The volunteers did not know to which group they belonged, nor did the physicians responsible for the clinical investigations. All the volunteers were given each day 7 supplementary tablets of identical taste and appearance, some containing vitamin C, others being dummies" (p 8). Three participants were administered 0.07 g/d vitamin C and a total of 14 cold episodes were recorded among them in the follow up, four participants were administered 0.01 g/d vitamin C (18 colds), and six persons were administered no vitamin C (30 colds). The geometric mean length of colds in vitamin C deprived subjects was 6.4 days, and in non-deprived subjects 3.3 days, and the authors concluded "such evidence as there is definitely confirms the hypothesis that the absence of vitamin C tended to cause colds to last longer" (p 43)
Bendel 1955	No placebo comparison and the control group was not parallel. 120 children at a summer camp for 2 weeks were given 0.2 g/d vitamin C daily and their cold experience was compared with that of participants in an earlier camp
Bergquist 1943	Low dose. A Swedish trial involving supplementation with only 0.03 g/d vitamin C

(*Continued*)

Bessel-Lorck 1958	No placebo comparison. Berlin school children in a skiing camp. Abridged summary: "26 subjects received 1 g of vitamin C daily during the first 9 days. Under this regimen only one student became sick. In 20 subjects the prophylaxis did not begin until the 9th day. At this point in time 9 students were already sick with upper respiratory infections; and 3 others became infected within the first 3 days after the trial began. All of those who were sick were treated with 2 g of vitamin C per day. Within just 24 hours a rapid improvement in the general condition was evident so that elevated physical demands were met without particular difficulty. All subjects displayed a significant increase in their capacity to perform physical activities while being treated with vitamin C." The Bessel-Lorck paper is available as a translation. This trial motivated Ritzel 1961 to carry out his trial (see Analysis 1.1.2)
Bibile 1966	This was cited by Kleijnen 1989, but we have been unable to retrieve a copy through a few library orders
Boines 1956	No placebo comparison. Study of poliomyelitis sufferers
Brown 1945	No data that could be used in our meta-analyses. Placebo-controlled RCT comparison of US college students. 1 g/d vitamin C. Outcome was "Colds that did not develop" and benefit was claimed. Methods: "... Those recommended for inclusion in the ascorbic acid study were then given either one gram of that substance, by mouth, in water, or an equivalent amount of citric acid as a placebo. The ascorbic acid and placebo were given alternately insofar as was practicable and without knowledge on the subjects' part that placebos were being given."
Chavance 1993	Low dose. Double-blind RCT of 0.09 g/d vitamin C in elderly participants. No benefit was demonstrated
Cuendet 1946	No placebo comparison. 200 children in 3 mountain parishes took vitamin C supplements up to 0.3 g/d
Dyllick 1967	No placebo comparison. Cohort workplace study involving 200 recipients of 1 g/d of vitamin C whose respiratory experience was compared with those not receiving vitamin C
Elliot 1973	Data not suitable for inclusion in our meta-analyses. Authors describe: "A double blind study was initiated on a Polaris submarine...0.5 g of ascorbic acid or a citric acid placebo would be taken four times a day [2 g/day]. Seventy of a 140 man crew volunteered and were randomly placed in treatment or placebo groups... Both ascorbic acid and placebo capsules looked identical and when opened the contents were similar in taste and appearance... at the end of the tenth week the study was terminated" (p 12). "There was no consistent difference between groups in the incidence of runny nose or sneezing. Man-days of morbidity for hoarseness, sore throats, non-productive coughs, and productive coughs was 36, 107, 42 and 72 in the placebo group with only 37%, 28%, 40% and 31% as much morbidity in the ascorbic acid group. The Wilcoxon Sequence Test with a one tailed test rejected the null hypothesis of equal effectiveness of ascorbic acid and placebo for sore throats and productive coughs (P = .0155 and .0327) but not for hoarseness or non-productive coughs" (p 12) (see Hemilä 2004a)
Fogelholm 1998	Vitamin C in combination with other antioxidants. Finnish study involving 75 athletes. RCT of 1 g/d vitamin C with 0.3 g/d vitamin E and 0.09 g/d ubiquinone versus an undescribed placebo. Methodologically strong study but was excluded from the meta-analyses because there were 3 antioxidants in the active preparation which were each hypothesised to be potentially beneficial
Glazebrook 1942	Low dose. 1500 boys of a UK boarding school during the World War II. The participants were allocated as administrative units and not on individual basis. Vitamin C (0.05 to 0.3 g/d) was added to cocoa and milk in the kitchen to a group of 335 boys. Although ineffective powder was not added to the drinks of the control

(*Continued*)

	group, the control drinks served functionally as a placebo. The number of participants who had colds was 17% lower in the vitamin C group (72/335 versus 286/1100; P = 0.10, Hemilä 2004a) and the number of participants admitted to hospital because of the common cold was 23% lower (59/335 versus 253/1100; P = 0.04, Hemilä 2004b)
Gormly 1977	No placebo comparison. Fourteen males of 29 members of a 1-year Antarctic expedition took 1 g/d vitamin C throughout their stay. Their health outcomes were compared with the remaining group who did not take vitamin C, and no difference was observed between the 2 groups
Gorton 1999	No placebo comparison and the control group not parallel. A technical training facility in Chile was the site of this cohort study with 250 trainees who were given 3 g/d vitamin C during their 10-day course. The vitamin C group was compared with a control group of 463 students who had been monitored in a somewhat similar way during the previous year (sic!)
Himmelstein 1998b	There was an extreme and divergent drop-out rate in the Himmelstein 1998b trial. They started with 52 marathon runners in 2 groups, but 42% (22 of 52) of the vitamin C group, and 75% (38 of 52) of the placebo group dropped out during the trial (P = 0.003)
Hopfengärtner 1944	Low dose. Long-term hospital baby study in which supplementation of 0.05 g/d vitamin C was used
Hunt 1994	Not focused on the common cold. Double-blind RCT. 57 elderly UK patients suffering from acute bronchitis or pneumonia who were admitted to hospital for treatment were administered 0.2 g/d of vitamin C (see Hemilä 2009a)
Kimbarowski 1967	No placebo comparison, no data suitable for inclusion in our meta-analyses. 216 Russian soldiers were hospitalised because of influenza A. 114 were administered 0.2 g/d vitamin C. There were 2 cases of pneumonia in the vitamin C group in comparison with 10 cases in the control group. Thus this trial found a lower incidence of complications of viral respiratory infection (see Hemilä 2004a; Hemilä 2009a)
Koytchev 2003	No placebo comparison. Double-blind RCT involving 1167 participants. Four arms, colds treated with 0.9 g/d vitamin C plus or minus antihistamine and antipyretics
Masek 1974	Low dose. Two large studies of Czech coal miners comparing 0.1 g/d vitamin C and placebo over a period of 4 or 8 weeks. Excluded both on the basis of low dose and inadequacy of data for inclusion in meta-analyses. The trials were neither randomised nor blind. Authors claimed benefits to the active recipients
Niemi 1951	Low dose and no placebo comparison. Finnish study with military recruits. 1036 people were observed during a 3-month period. 516 were administered 0.1 g/d vitamin C. No benefits of vitamin C
Peters 1940	No placebo comparison. Short-term baby supplementation study
Regnier 1968	No suitable data. The author describes: "I initiated a double-blind study using ascorbic acid alone, ascorbic acid plus bioflavonoids, flavonoids only and, fourthly, a lactose placebo with the two 'vitamins' present either alone or together in 0.2 g quantities. It was shortly obvious that there was no need to continue double-blind techniques. The continued studies were done by the single blind method... I limited myself to 22 subjects... The majority were adults whose ages ranged from 30 to 50, with the extremes being five children younger than 12 (p 949)." "The 22 subjects mentioned have been studied systematically and under conditions which were as controlled as is possible in a clinical investigation of an infection such as the common cold. Some

(*Continued*)

	acted as what are commonly termed their own controls... None of the subjects was studied for less than three years... (p 950)." "Within the first 24 hours of a typical infection which the patient recognizes as his usual early symptoms of a cold, and the sooner the better, the beginning dose of ascorbic acid or 0.6 or 0.625 g is taken every three hours" (p 950). The author reports that "in 50 colds the treatment consisted of ascorbic acid alone ... the colds were nicely suppressed in 45 [of the 50]... In 22 of 24 instances in which the lactose-filled capsules alone were taken the colds were seemingly untempered and ordinary" (p 952). The placebo-controlled observations thus suggest benefit, but there are no data suitable for inclusion in our meta-analyses
Scheunert 1949	Data not suitable for inclusion in our meta-analyses. Large study involving factory workers in Germany between November 1942 and June 1943. Pills were distributed by foremen and managers. Different doses of vitamin C were administered to four study groups (range 0.02 to 0.3 g/d) so that the lowest dose arm(s) might be used as the control group. The common cold [Erkältungskrankheiten] was one of the outcomes and "The percentual monthly duration of people sick with the common cold [Prozentualer Monatsdurchschnitt der erkrankten Personen]" was 7.3% in the 0.02 g/d group, 7.2% in the 0.05 g/d group, 1.95% in the 0.1 g/d group, and 1.93% in the 0.3 g/d group suggesting that there were more days sick with the common cold when vitamin C doses were low. However, the data are presented ambiguously and it is a combination of incidence and duration, and no data could be extracted for our meta-analyses
Tebrock 1956	Data not suitable for inclusion in our meta-analyses. 2000 adult subjects presenting with colds to industrial clinics were sequentially assigned to receive 0.2 g/d vitamin C and flavonoids in a 2 x 2 factorial design. All cases were again examined 3 days later by one of 3 physicians. The authors' conclusion from the extensively detailed tabulations is that "the overwhelming impression gained from the study is the singular lack of effect in altering the course of the common cold by either the bioflavonoids or the ascorbic acid". Recorded outcomes could not be used in this overview

RCT: randomised controlled trial

DATA AND ANALYSES

Comparison 1. Development of colds while on vitamin C prophylaxis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportions developing one or more cold episodes during prophylaxis	29	11306	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.92, 0.98]
1.1 All eligible trials with exception of subgroup removed below	24	10708	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.94, 1.00]
1.2 Short-term exposure to cold and/or severe physical stress	5	598	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.35, 0.64]

Comparison 2. Duration of colds developing on vitamin C prophylaxis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duration of common cold symptoms (placebo group duration set as 100%)	29	9649	Mean Difference (IV, Fixed, 95% CI)	-9.07 [-12.58, -5.57]
1.1 Prophylaxis 200 mg or more daily plus or minus loading dose at cold onset in adults	17	7215	Mean Difference (IV, Fixed, 95% CI)	-7.72 [-11.76, -3.69]
1.2 Prophylaxis 200 mg or more daily plus or minus loading dose at cold onset in children	12	2434	Mean Difference (IV, Fixed, 95% CI)	-13.24 [-20.32, -6.16]

Comparison 3. Severity of colds developing on vitamin C prophylaxis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Indicators of severity of episodes experienced while on prophylaxis	14	7018	Std. Mean Difference (IV, Fixed, 95% CI)	-0.12 [-0.17, -0.07]
1.1 Mean days indoors or off work or school per episode	7	5066	Std. Mean Difference (IV, Fixed, 95% CI)	-0.11 [-0.17, -0.05]

1.2 Mean symptom severity score per episode	7	1952	Std. Mean Difference (IV, Fixed, 95% CI)	-0.14 [-0.22, -0.05]

Comparison 4. Duration of colds treated with vitamin C

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean symptom days per episode standardised against control group	7	3249	Mean Difference (IV, Fixed, 95% CI)	-2.90 [-8.20, 2.39]

Comparison 5. Severity of colds treated with vitamin C

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Indicators of severity of episodes for which vitamin C was used as therapy	4	2708	Std. Mean Difference (IV, Fixed, 95% CI)	-0.07 [-0.15, 0.01]
1.1 Mean days indoors or off work or school	3	2569	Std. Mean Difference (IV, Fixed, 95% CI)	Not estimable
1.2 Mean symptom severity score per episode	1	139	Std. Mean Difference (IV, Fixed, 95% CI)	0.15 [-0.21, 0.51]

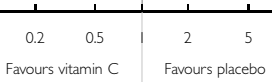
Analysis 1.1. Comparison 1 Development of colds while on vitamin C prophylaxis, Outcome 1 Proportions developing one or more cold episodes during prophylaxis.

Review: Vitamin C for preventing and treating the common cold

Comparison: 1 Development of colds while on vitamin C prophylaxis

Outcome: 1 Proportions developing one or more cold episodes during prophylaxis

Study or subgroup	Vitamin C n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 All eligible trials with exception of subgroup removed below					
Peters 1996b	5/41	11/45		0.4 %	0.50 [0.19, 1.31]
Moolla 1996b	5/11	12/19		0.3 %	0.72 [0.35, 1.50]
Charleston 1972	31/47	37/43		1.5 %	0.77 [0.60, 0.97]
Coulehan 1974a	19/190	23/192		0.9 %	0.83 [0.47, 1.48]
Anderson 1972	302/407	335/411		12.7 %	0.91 [0.85, 0.98]
Coulehan 1974b	16/131	17/128		0.7 %	0.92 [0.49, 1.74]
Dahlberg 1944	131/1259	142/1266		5.4 %	0.93 [0.74, 1.16]
Bancalari 1984	21/32	21/30		0.8 %	0.94 [0.67, 1.32]
Anderson 1974a	922/1191	233/285		14.4 %	0.95 [0.89, 1.01]
Franz 1956	14/44	15/45		0.6 %	0.95 [0.52, 1.74]
Sasazuki 2006	68/140	67/133		2.6 %	0.96 [0.76, 1.23]
Cowan 1942	184/208	142/155		6.2 %	0.97 [0.90, 1.03]
Ludvigsson 1977b	230/304	240/311		9.1 %	0.98 [0.90, 1.07]
Pitt 1979	298/331	309/343		11.6 %	1.00 [0.95, 1.05]
Coulehan 1976	98/428	98/428		3.7 %	1.00 [0.78, 1.28]
Clegg 1975	48/67	50/70		1.9 %	1.00 [0.81, 1.24]
Elwood 1976	296/339	298/349		11.2 %	1.02 [0.96, 1.09]
Briggs 1984	125/265	121/263		4.6 %	1.03 [0.85, 1.23]
Carson 1975	85/121	84/123		3.2 %	1.03 [0.87, 1.22]
Van Straten 2002	35/84	34/84		1.3 %	1.03 [0.72, 1.48]
Ludvigsson 1977a	49/80	44/78		1.7 %	1.09 [0.84, 1.41]
Liljefors 1972	10/33	9/33		0.3 %	1.11 [0.52, 2.38]
Peters 1993b	18/34	18/39		0.6 %	1.15 [0.72, 1.82]
Himmelstein 1998a	10/23	8/25		0.3 %	1.36 [0.65, 2.84]



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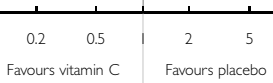
Study or subgroup	Vitamin C n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Subtotal (95% CI)	**5810**	**4898**		**96.1 %**	**0.97 [0.94, 1.00]**
Total events: 3020 (Vitamin C), 2368 (Placebo)					
Heterogeneity: Chi^2 = 17.75, df = 23 (P = 0.77); I^2 =0.0%					
Test for overall effect: Z = 1.90 (P = 0.057)					
2 Short-term exposure to cold and/or severe physical stress					
Peters 1996a	7/44	19/47		0.7 %	0.39 [0.18, 0.84]
Sabiston 1974	6/56	14/56		0.5 %	0.43 [0.18, 1.04]
Moolla 1996a	4/13	13/19		0.4 %	0.45 [0.19, 1.07]
Peters 1993a	14/43	28/41		1.1 %	0.48 [0.30, 0.77]
Ritzel 1961	17/139	31/140		1.2 %	0.55 [0.32, 0.95]
Subtotal (95% CI)	**295**	**303**		**3.9 %**	**0.48 [0.35, 0.64]**
Total events: 48 (Vitamin C), 105 (Placebo)					
Heterogeneity: Chi^2 = 0.60, df = 4 (P = 0.96); I^2 =0.0%					
Test for overall effect: Z = 4.99 (P < 0.00001)					
Total (95% CI)	**6105**	**5201**		**100.0 %**	**0.95 [0.92, 0.98]**
Total events: 3068 (Vitamin C), 2473 (Placebo)					
Heterogeneity: Chi^2 = 44.85, df = 28 (P = 0.02); I^2 =38%					
Test for overall effect: Z = 3.18 (P = 0.0015)					



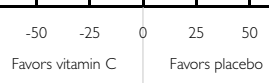
Analysis 2.1. Comparison 2 Duration of colds developing on vitamin C prophylaxis, Outcome 1 Duration of common cold symptoms (placebo group duration set as 100%).

Review: Vitamin C for preventing and treating the common cold

Comparison: 2 Duration of colds developing on vitamin C prophylaxis

Outcome: 1 Duration of common cold symptoms (placebo group duration set as 100%)

Study or subgroup	Vitamin C N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Prophylaxis 200 mg or more daily plus or minus loading dose at cold onset in adults							
Van Straten 2002	37	58 (96)	50	100 (150)		0.5 %	-42.00 [-93.82, 9.82]
Himmelstein 1998a	14	60 (26)	12	100 (82)		0.5 %	-40.00 [-88.35, 8.35]
Carr 1981b	57	65 (75)	71	100 (75)		1.8 %	-35.00 [-61.14, -8.86]
Sabiston 1974	6	72 (50)	14	100 (50)		0.5 %	-28.00 [-75.82, 19.82]
Peters 1993b	18	75 (38)	18	100 (56)		1.3 %	-25.00 [-56.26, 6.26]
Charleston 1972	44	84 (46)	80	100 (20)		6.0 %	-16.00 [-30.28, -1.72]
Peters 1996a	7	85 (85)	19	100 (100)		0.2 %	-15.00 [-92.37, 62.37]
Karlowski 1975a	128	87.4 (51.5)	65	100 (52)		5.1 %	-12.60 [-28.07, 2.87]
Anderson 1974a	1823	93 (102)	437	100 (99)		11.4 %	-7.00 [-17.40, 3.40]
Briggs 1984	125	94 (94)	121	100 (100)		2.1 %	-6.00 [-30.27, 18.27]
Elwood 1976	627	94 (90)	690	100 (99)		11.8 %	-6.00 [-16.21, 4.21]
Clegg 1975	68	95 (41)	73	100 (39)		7.0 %	-5.00 [-18.23, 8.23]
Anderson 1972	561	95 (92)	609	100 (82)		12.2 %	-5.00 [-15.02, 5.02]
Pitt 1979	600	97.4 (100)	619	100 (100)		9.7 %	-2.60 [-13.83, 8.63]
Carr 1981a	94	101 (96)	70	100 (96)		1.4 %	1.00 [-28.70, 30.70]
Peters 1993a	14	103 (17)	28	100 (42)		3.8 %	3.00 [-14.93, 20.93]
Peters 1996b	5	136 (136)	11	100 (100)		0.1 %	36.00 [-97.05, 169.05]
Subtotal (95% CI)	**4228**		**2987**			**75.5 %**	**-7.72 [-11.76, -3.69]**
Heterogeneity: Chi^2 = 14.66, df = 16 (P = 0.55); I^2 =0.0%							
Test for overall effect: Z = 3.75 (P = 0.00018)							
2 Prophylaxis 200 mg or more daily plus or minus loading dose at cold onset in children							
Ludvigsson 1977a	62	61 (41)	55	100 (67)		2.9 %	-39.00 [-59.44, -18.56]
Ritzel 1961	17	69 (51)	31	100 (51)		1.4 %	-31.00 [-61.17, -0.83]
Coulehan 1974b	16	71 (71)	17	100 (100)		0.4 %	-29.00 [-87.91, 29.91]
Bancalari 1984	38	76 (62)	46	100 (65)		1.7 %	-24.00 [-51.23, 3.23]



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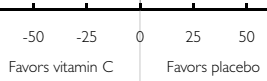
Study or subgroup	Vitamin C N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Wilson 1973a	160	84.5 (131)	126	100 (134)		1.3 %	-15.50 [-46.48, 15.48]
Miller 1977c	116	87 (73)	122	100 (73)		3.6 %	-13.00 [-31.55, 5.55]
Coulehan 1974a	19	88 (88)	23	100 (100)		0.4 %	-12.00 [-68.88, 44.88]
Miller 1977a	53	93 (105)	42	100 (105)		0.7 %	-7.00 [-49.51, 35.51]
Ludvigsson 1977b	423	94 (85)	398	100 (114)		6.4 %	-6.00 [-19.82, 7.82]
Coulehan 1976	98	95 (95)	98	100 (100)		1.6 %	-5.00 [-32.31, 22.31]
Miller 1977b	42	97 (50)	40	100 (50)		2.6 %	-3.00 [-24.65, 18.65]
Wilson 1973b	205	108 (150)	187	100 (132)		1.6 %	8.00 [-19.92, 35.92]
Subtotal (95% CI)	**1249**		**1185**			**24.5 %**	**-13.24 [-20.32, -6.16]**
Heterogeneity: Chi^2 = 12.90, df = 11 (P = 0.30); I^2 =15%							
Test for overall effect: Z = 3.66 (P = 0.00025)							
Total (95% CI)	**5477**		**4172**			**100.0 %**	**-9.07 [-12.58, -5.57]**
Heterogeneity: Chi^2 = 29.32, df = 28 (P = 0.40); I^2 =5%							
Test for overall effect: Z = 5.07 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 1.76, df = 1 (P = 0.18), I^2 =43%							



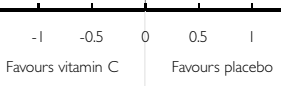
Analysis 3.1. Comparison 3 Severity of colds developing on vitamin C prophylaxis, Outcome 1 Indicators of severity of episodes experienced while on prophylaxis.

Review: Vitamin C for preventing and treating the common cold

Comparison: 3 Severity of colds developing on vitamin C prophylaxis

Outcome: 1 Indicators of severity of episodes experienced while on prophylaxis

Study or subgroup	Vitamin C N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
1 Mean days indoors or off work or school per episode							
Sabiston 1974	6	0.8 (0.8)	14	2.4 (2.1)		0.3 %	-0.84 [-1.83, 0.16]
Ludvigsson 1977a	62	0.95 (1.12)	55	1.9 (2.42)		1.8 %	-0.51 [-0.88, -0.14]
Wilson 1973a	160	4.52 (6.32)	126	5.94 (6.28)		4.6 %	-0.22 [-0.46, 0.01]
Ludvigsson 1977b	423	1.47 (1.27)	398	1.81 (1.79)		13.3 %	-0.22 [-0.36, -0.08]
Anderson 1972	561	1.04 (1.75)	609	1.32 (2)		19.0 %	-0.15 [-0.26, -0.03]
Anderson 1974a	1823	1.14 (1.71)	437	1.15 (1.52)		23.0 %	-0.01 [-0.11, 0.10]
Wilson 1973b	205	4.2 (4.44)	187	3.84 (4.51)		6.4 %	0.08 [-0.12, 0.28]
Subtotal (95% CI)	**3240**		**1826**			**68.4 %**	**-0.11 [-0.17, -0.05]**
Heterogeneity: Chi² = 17.73, df = 6 (P = 0.01); I² =66%							
Test for overall effect: Z = 3.58 (P = 0.00035)							
2 Mean symptom severity score per episode							
Himmelstein 1998a	14	16.1 (14.59)	12	37.4 (52.65)		0.4 %	-0.55 [-1.34, 0.23]
Carr 1981b	57	21.9 (33.57)	71	33.6 (33.57)		2.0 %	-0.35 [-0.70, 0.00]
Miller 1977c	116	14.6 (20)	122	19 (20)		3.9 %	-0.22 [-0.47, 0.04]
Pitt 1979	600	1.87 (0.76)	619	1.97 (0.76)		19.8 %	-0.13 [-0.24, -0.02]
Miller 1977a	53	22.5 (45.5)	42	27.3 (45.5)		1.5 %	-0.10 [-0.51, 0.30]
Carr 1981a	94	23.6 (33.57)	70	22.2 (33.57)		2.6 %	0.04 [-0.27, 0.35]
Miller 1977b	42	48.6 (22.6)	40	46.2 (22.6)		1.3 %	0.11 [-0.33, 0.54]
Subtotal (95% CI)	**976**		**976**			**31.6 %**	**-0.14 [-0.22, -0.05]**
Heterogeneity: Chi² = 5.35, df = 6 (P = 0.50); I² =0.0%							
Test for overall effect: Z = 2.99 (P = 0.0028)							
Total (95% CI)	**4216**		**2802**			**100.0 %**	**-0.12 [-0.17, -0.07]**
Heterogeneity: Chi² = 23.29, df = 13 (P = 0.04); I² =44%							
Test for overall effect: Z = 4.64 (P < 0.00001)							
Test for subgroup differences: Chi² = 0.21, df = 1 (P = 0.64), I² =0.0%							



Analysis 4.1. Comparison 4 Duration of colds treated with vitamin C, Outcome 1 Mean symptom days per episode standardised against control group.

Review: Vitamin C for preventing and treating the common cold

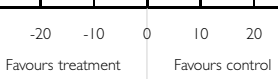
Comparison: 4 Duration of colds treated with vitamin C

Outcome: 1 Mean symptom days per episode standardised against control group

Study or subgroup	Vitamin C N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Anderson 1974e	900	85 (91)	437	100 (99)		23.0 %	-15.00 [-26.02, -3.98]
Karlowski 1975c	56	90 (41)	65	100 (52)		10.2 %	-10.00 [-26.59, 6.59]
Anderson 1975a	419	97 (96)	213	100 (84)		13.2 %	-3.00 [-17.55, 11.55]
Elwood 1977	145	99 (75)	119	100 (51)		12.0 %	-1.00 [-16.26, 14.26]
Tyrrell 1977	274	103 (57)	329	100 (54)		35.2 %	3.00 [-5.92, 11.92]
Cowan 1950	77	110 (100)	76	100 (100)		2.8 %	10.00 [-21.69, 41.69]
Audera 2001a	97	121 (80)	42	100 (76)		3.6 %	21.00 [-6.96, 48.96]
Total (95% CI)	**1968**		**1281**			**100.0 %**	**-2.90 [-8.20, 2.39]**

Heterogeneity: Chi^2 = 10.52, df = 6 (P = 0.10); I^2 =43%

Test for overall effect: Z = 1.08 (P = 0.28)

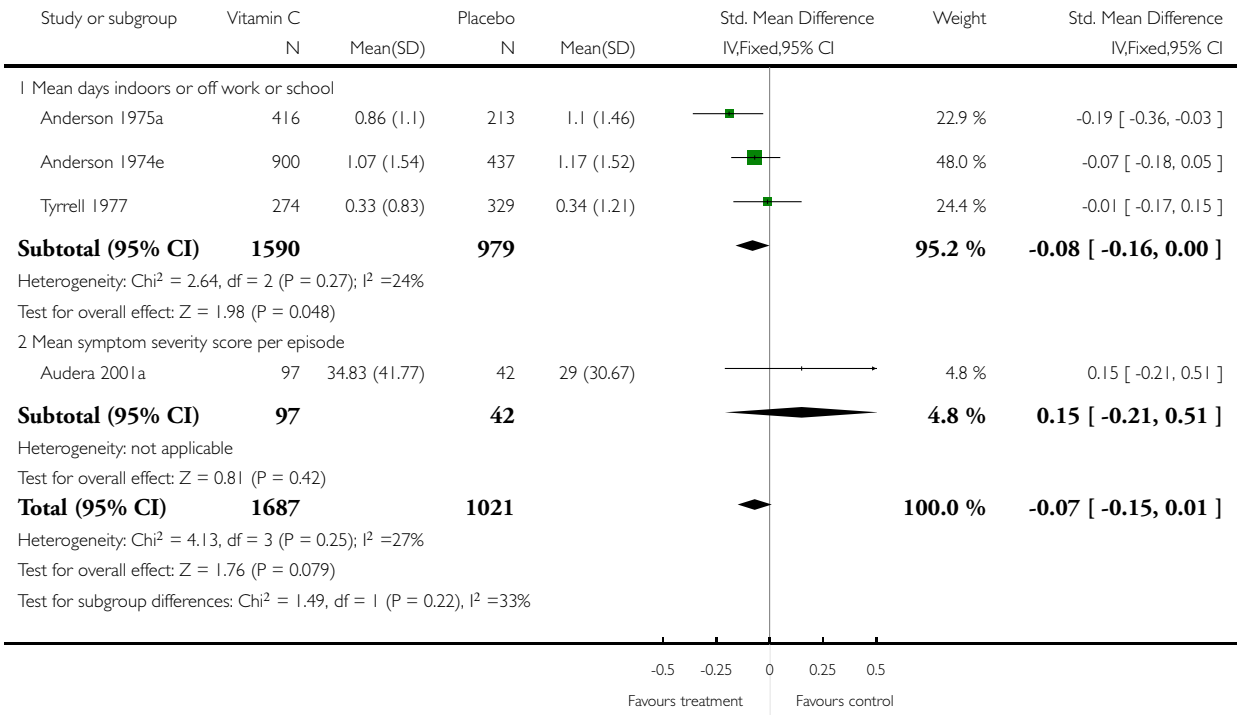


Analysis 5.1. Comparison 5 Severity of colds treated with vitamin C, Outcome 1 Indicators of severity of episodes for which vitamin C was used as therapy.

Review: Vitamin C for preventing and treating the common cold

Comparison: 5 Severity of colds treated with vitamin C

Outcome: 1 Indicators of severity of episodes for which vitamin C was used as therapy



APPENDICES

Appendix 1. History and previous search strategies

In the first **1998** edition of this Cochrane Review (Douglas 1998), an analysis was made of the 30 published trials that had been selected by two previous systematic reviewers, Hemilä 1992 and Kleijnen 1989. That selection of trials was one of convenience and was justified by the fact that all had been carried out post-Pauling in an era of relatively sophisticated trial methodology, and mainly using doses of vitamin C at the level recommended by Pauling (i.e. 1 g per day or more).

For the **2004** revised edition of this Cochrane Review (Douglas 2004), all known publications on the topic in the past 64 years were included. Some of these trials had been carried out since the original 1998 review, but also the controlled trials published before 1970 (pre-Pauling period) were added. We set the limit of daily vitamin C administration to 0.2 g/day, so that controlled trials with lower doses were not included in the review, but were listed and commented on in the excluded studies table.

Twenty-five additional trials were then added to the review, including a number of trials which evaluated the utility of vitamin C in the prevention of post-race colds among marathon runners and further explored the role of vitamin C as a therapy for colds.

For the 2004 update, we again searched the following electronic databases: the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* Issue 2, 2004); MEDLINE (January 1966 to June 2004) and EMBASE (1990 to June Week 23 2004). For the 2004 update, we also screened the reference lists incorporated in a series of systematic reviews of the literature published by Briggs 1984 and Kleijnen 1989 (for the search strategy of the latter, *see* Kleijnen 1992) and the references in those studies. One of the review authors (HH) has a research involvement spanning over a decade in this topic and has assembled a large personal reference list of papers published in the grey literature or listed in indexing services that preceded electronic searching. These were added to a primary database which was then systematically screened by two review authors (BD and Ron D'Souza - a previous review author) who worked together to exclude duplicate entries, preliminary reports of data more fully reported elsewhere, commentaries, editorials and other papers which did not contain unique reports of controlled or randomised clinical comparisons. These two review authors then separately reviewed hard copies or electronic abstract data on each of 84 papers, applying the selection criteria outlined above. A final list of 62 papers was selected, which contained unique data from one or more trials of vitamin C and the common cold. One of the papers (Bibile 1966 cited by Kleijnen 1989) remains unassessed as we have been unable to retrieve a copy through library orders. Twenty-six of the 61 remaining papers failed to meet the selection criteria.

This left us with 36 papers, of which 12 contained reports of two or more (up to six) unique study comparisons and an entry for each comparison was made into the 'Characteristics of included studies' table, using the letters a, b, c, d, e and f to identify different study comparisons within the one publication. The review in 2004 included data from 56 distinct trial comparisons, which was 25 more than in the original 1998 review. In four of the papers (Anderson 1974a; Anderson 1975a; Audera 2001a; Karlowski 1975a) more than one actively treated group was compared with the same placebo treated group. To avoid the 'unit of analysis problem' for which we were legitimately criticised in the original 1998 review, where multiple active arms were considered separately in the same meta-analysis, they were combined as one entry.

For the **2007** update (Douglas 2007), we searched CENTRAL (*The Cochrane Library* Issue 4, 2006); MEDLINE (2004 to December 2006) and EMBASE (1990 to December 2006). In the 2007 update, only one new trial was identified (Sasazuki 2006).

The 2007 MEDLINE search

1 exp Common Cold/
2 common cold$.mp.
3 exp RHINOVIRUS/
4 rhinovir$.mp.
5 or/1-4
6 exp Ascorbic Acid/
7 ascorbic acid.mp.
8 vitamin c.mp.
9 or/6-8
10 5 and 9

Appendix 2. Embase.com search strategy

EMBASE search run from 01 January 2006 to 03 February 2010

10. #5 AND #9
9. #6 OR #7 OR #8
8. ascorb*:ab,ti
7. (vitamin* NEAR/5 c):ab,ti
6. 'ascorbic acid'/exp
5. #1 OR #2 OR #3 OR #4
4. rhinovir*:ab,ti
3. 'human rhinovirus'/exp OR 'rhinovirus infection'/exp OR 'rhinovirus'/de
2. 'common cold':ab,ti OR 'common colds':ab,ti
1. 'common cold'/de OR 'common cold symptom'/de

FEEDBACK

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.

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
Reply supplied by the authors of the review.

Contributors

David Wooff
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.

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.
Reply supplied by the Authors of the review.

Contributors

Julian Higgins
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

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.
Reply supplied by the Authors of the review.

Contributors

Reuven Gilmore
Comment and reply posted 28 August 2004

Vitamin C for preventing and treating the colds

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.

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.
Harri Hemilä and Robert M Douglas

Contributors

Steve Hickey PhD. Manchester Metropolitan University
Hilary Roberts PhD
Comment and reply posted 16 November 2005

Vitamin C doses in trial

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.

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.

Reply by Hemilä, Douglas, Chalker (22 August 2007)

Contributors

Sean Emerson
Comment posted 24 July 2007

Vitamin C and the common cold, 2 May 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.

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.
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

Steve Hickey PhD and Hilary Roberts PhD
Feedback and reply added 13 June 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.

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

Contributors

Roger Mann M.D.

WHAT'S NEW

Last assessed as up-to-date: 1 February 2010.

Date	Event	Description
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.

HISTORY

Protocol first published: Issue 1, 1998

Review first published: Issue 1, 1998

Date	Event	Description
12 June 2008	Amended	Converted to new review format.
23 July 2007	Feedback has been incorporated	Feedback added.
15 November 2005	Feedback has been incorporated	Feedback added.
27 August 2004	Feedback has been incorporated	Feedback comment added.
11 June 2004	New citation required and conclusions have changed	Substantive amendment.

CONTRIBUTIONS OF AUTHORS

Harri Hemilä (HH) carefully reviewed drafts of the second edition of the review (Douglas 2004), assisted in paper retrieval, proposed alterations to data presentation, checked data entries and contributed significant input to the text. After the 2004 revision, he took over responsibility for future updates of this review.

Elizabeth Chalker (EC) wrote the protocol for the first edition of the review (Douglas 1998), developed the initial search strategy, undertook the searches, organised retrieval of papers, screened papers against inclusion criteria and appraised the quality of papers for the 1998 version. She has been involved in reviewing and rewriting the text for subsequent versions of this review.

Bob Douglas (BD) conceived the review, screened retrieved papers against inclusion criteria, appraised the quality of papers, abstracted data, entered data into RevMan, analysed and interpreted the data, wrote the first version of the review and has participated in updating. He accepted the 2009 update but did not actively participate in the update.

DECLARATIONS OF INTEREST

Professor Bob Douglas was co-ordinating investigator on the Audera 2001 study. None of the other review authors have any conflict of interest to declare in this review.

SOURCES OF SUPPORT

Internal sources

- Australian National University (until 2004), Australia.

External sources

- Commonwealth Department of Health and Ageing, Australia.

NOTES

Full-text versions of references which are available either free or at the publishers' databases can be accessed via the home page of the contact author, Harri Hemilä: www.ltdk.helsinki.fi/users/hemila/CC/.

In this 2009 update, we calculated meta-analyses using the fixed-effect model, whereas the earlier versions used the random-effects model. Conclusions remain unchanged from the 2007 update.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Oral; Ascorbic Acid [administration & dosage; *therapeutic use]; Common Cold [*drug therapy; *prevention & control]; Randomized Controlled Trials as Topic; Respiratory Tract Infections [drug therapy; prevention & control]

MeSH check words

Humans