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

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ABSTRACT

Background
The role of vitamin C (ascorbic acid) in the prevention and treatment of the common cold has been a subject of controversy for 60 years, but is widely sold and used as both a preventive and therapeutic agent.

Objectives
To discover whether oral doses of 0.2 g or more daily of vitamin C reduces the incidence, duration or severity of the common cold when used either as continuous prophylaxis or after the onset of symptoms.

Search strategy
We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* Issue 4, 2006); MEDLINE (1966 to December 2006); and EMBASE (1990 to December 2006).

Selection criteria
Papers were excluded if a dose less than 0.2 g per day of vitamin C was used, or if there was no placebo comparison.

Data collection and analysis
Two review authors independently extracted data and assessed trial quality. '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
Thirty trial comparisons involving 11,350 study participants contributed to the meta-analysis on the relative risk (RR) of developing a cold whilst taking prophylactic vitamin C. The pooled RR was 0.96 (95% confidence intervals (CI) 0.92 to 1.00). A subgroup of six trials involving a total of 642 marathon runners, skiers, and soldiers on sub-arctic exercises reported a pooled RR of 0.50 (95% CI 0.38 to 0.66).

Thirty comparisons involving 9676 respiratory episodes contributed to a meta-analysis on common cold duration during prophylaxis. A consistent benefit was observed, representing a reduction in cold duration of 8% (95% CI 3% to 13%) for adults and 13.6% (95% CI 5% to 22%) for children.

Seven trial comparisons involving 3294 respiratory episodes contributed to the meta-analysis of cold duration during therapy with vitamin C initiated after the onset of symptoms. No significant differences from placebo were seen. Four trial comparisons involving 2753 respiratory episodes contributed to the meta-analysis of cold severity during therapy and no significant differences from placebo were seen.

Authors' conclusions

The failure of vitamin C supplementation to reduce the incidence of colds in the normal population indicates that routine mega-dose prophylaxis is not rationally justified for community use. But evidence suggests that it could be justified in people exposed to brief periods of severe physical exercise or cold environments.

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, and became particularly popular in the 1970s for the common cold when (Nobel Prize winner) Linus Pauling drew conclusions from earlier placebo-controlled trials of large dose vitamin C on the incidence of colds. New trials were undertaken.

This review is restricted to placebo-controlled trials testing at least 0.2 g per day of vitamin C. Thirty trials involving 11,350 participants suggest that regular ingestion of vitamin C has no effect on common cold incidence in the ordinary population. It reduced the duration and severity of common cold symptoms slightly, although the magnitude of the effect was so small its clinical usefulness is doubtful. Nevertheless, in six trials with participants exposed to short periods of extreme physical or cold stress or both (including marathon runners and skiers) vitamin C reduced the common cold risk by half.

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 symptoms. However, there were only a few therapeutic trials and their quality was variable. One large trial reported equivocal benefit from an 8 g therapeutic dose at the onset of symptoms, and two trials using five-day supplementation reported benefit. More therapeutic trials are necessary to settle the question, especially in children who have not entered these trials.

BACKGROUND

Numerous animal studies with different species have shown that vitamin C affects resistance to diverse infections by viruses and bacteria (Hemilä 2006a; Hemilä 1997c). It might therefore be expected that this vitamin would also play such a role in human beings, but its importance in this regard is unresolved. Since the early 1940s, a large number of controlled trials have been carried out to examine the possible effects of vitamin C on the common cold, a ubiquitous problem caused by a wide range of viral agents. The common cold causes enormous morbidity worldwide and the search for simple and effective preventive or therapeutic agents or both has been elusive.

In 1970, the publication of Pauling 1970a, a book for the general public entitled "Vitamin C and the Common Cold" generated huge public interest which persists today. Linus Pauling was a double Nobel Laureate in chemistry and peace. 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 decreases the 'incidence of colds' (P = 0.003). In 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 combining the P values by Fisher's method, led him to conclude that "the null hypothesis of equal effectiveness of ascorbic acid and placebo is rejected at the level P less than 0.001."

Ritzel 1961 had reported a brief randomised controlled trial of children at a ski school in the Swiss Alps in which he administered 1 g daily and found reduced incidence and duration of colds in the recipients of vitamin C. Pauling put much weight on the Ritzel trial and based his expectations of vitamin C benefits on it. Pauling 1970b and Pauling 1976 also presented other data suggesting that human diets might not provide sufficient intake of vitamin C for optimal health, and proposed that mega-dose supplementation might profoundly influence both the incidence and severity of the common cold.

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 often confusing (Anderson 1977), but generally failed to support Pauling's hope that vitamin C would be a panacea. Chalmers 1975 calculated an un-

weighted 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, and the incidence of colds in vitamin C groups was 0.09 ± 0.06 (SE) episodes less per year, neither of which is a statistically or clinically significant difference. In a qualitative review on vitamin C and the common cold published in the same year, Dykes 1975 also concluded that vitamin C had no effect on colds.

However, it has subsequently been claimed that the influential reviews by Chalmers 1975 and Dykes 1975 contain errors (Hemilä 1995; Hemilä 1996c; *see* p. 36-45 in Hemilä 2006a). 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 caused by the placebo effect. It has subsequently been argued that the placebo-explanation in the Karlowski paper (Karlowski 1975a; Karlowski 1975b; Karlowski 1975c) was not consistent with their own data (Chalmers 1996; Hemilä 1996a; Hemilä 1996d; *see* p. 21-5 in Hemilä 2006a).

Hemilä (Hemilä 1997b; Hemilä 2006a) claimed that the highly cited reviews of Chalmers 1975 and Dykes 1975 and the trial by Karlowski 1975a quelled interest in the 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 relative risk (RR) 0.99; 95% CI 0.93 to 1.04). However, four trials with UK males found moderate reduction in common cold incidence with vitamin C (pooled RR 0.70; 0.60 to 0.81). This was suggested to have been caused 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; 0.35 to 0.69) (Hemilä 1996b).

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).

In the first edition of this Cochrane review (Douglas 1998a), an analysis was made of the 30 published trials that had been selected for attention 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.

For the 2004 revised edition of this Cochrane review, 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. Twenty-five additional trials were 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. In this 2007 update, one new trial was identified (Sasazuki 2006).

The terms 'common cold' and 'coryza' are used loosely both generally and in these trials. Most investigators have used self report by participants of a widely agreed constellation of symptoms and the self-assessed duration and severity of those symptoms, to evaluate the impact of vitamin C supplementation.

Three distinct evaluative approaches are discernible in the trials which have been conducted.
(1) Laboratory trials in which volunteers were artificially exposed, in a laboratory setting, to known respiratory viruses, after preliminary dosage with vitamin C or placebo.
(2) Community prophylaxis trials in which volunteers took regular daily supplements of vitamin C or placebo over a study period ranging from weeks to months, in an effort to prevent the acquisition of colds and to ameliorate the effects of the colds that occurred. In some of these trials, medication was increased during the first few days of the colds that occurred.
(3) Community therapeutic trials which evaluated the therapeutic effects of vitamin C that was commenced only after naturally acquired cold symptoms had developed.

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/.

OBJECTIVES

The central question for the review is: does vitamin C in doses of 0.2 g daily or more, reduce the incidence, duration or severity of the common cold when used either as continuous prophylaxis or at the onset of cold symptoms.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Included studies were placebo-controlled trials of vitamin C to prevent or treat the common cold using oral doses of vitamin C of 0.2 g/day or more, and comparing outcomes with a placebo preparation. The description of the study must enable it to be methodologically assessed using the Jadad quality score (Jadad 1996) and provide statistical data that could be entered into one

or more of the five meta-analyses. These were the minimal criteria for inclusion of a trial in the review.

Types of participants

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

Types of intervention

The only interventions considered were comparisons of orally administered vitamin C of at least 0.2 g daily and a placebo. In a few instances the placebo included a low dose of vitamin C; Carr 1981a used 70 mg/day, whereas a few others used 50 mg/day or less. This has been done by some investigators to ensure that participants were not vitamin C 'deficient', recognising that regular dietary intake of vitamin C is highly variable in some groups.

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: days confined indoors, or off work or off school per episode and by 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 active and control groups.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Cochrane Acute Respiratory Infections Group methods used in reviews.

For the 2004 update, we 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). We ran the following search strings in combination with the search strategy developed by the Cochrane Collaboration for identifying randomised controlled trials (Dickersin 1994).

MEDLINE (OVID) and CENTRAL
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

EMBASE
1 exp Common Cold/
2 common cold$.mp.
3 exp Rhinovirus/
4 rhinovirus infection$.mp.
5 or/1-4
6 exp Ascorbic Acid/
7 vitamin c.mp.
8 or/6-7
9 5 and 8

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 strategies, *see* Kleijnen 1992) and the papers in those studies. One of the current review authors (HH) has a fifteen year research involvement 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 which appears in the figures, identified as the 'highest' lettered trial that it contained.

For this 2007 update, we searched CENTRAL (*The Cochrane Library* Issue 4, 2006); MEDLINE (2004 to December 2006); and EMBASE (1990 to December 2006). In this update, the

searches were repeated with a slightly modified EMBASE search string.

EMBASE (DataStar)
1 common adj cold$
2 rhinovirus$
3 ascorbic-acid#.de.
4 ascorb$
5 vitamin$ next c
6 1 or 2
7 3 or 4 or 5
8 6 and 7

In the period from June 2004 to December 2006 only one new trial conforming to our selection criteria was published (Sasazuki 2006).

METHODS OF THE REVIEW

The circumstances and results of three small laboratory trials were summarised in a separate table (Table 01) and were not included in the meta-analyses with the community trials.

For the community trials, three outcomes were selected to compare vitamin C with placebo recipients, resulting in five meta-analyses; the number in parenthesis refers to the respective comparison figure in the analyses:

(Comparison 01) 'Incidence' - the proportion of participants who experienced one or more episodes of respiratory illness during prophylaxis;
(Comparison 02) and (Comparison 04) 'Duration' - mean days of cold symptoms per illness episode (episodes occurring in trials of prophylaxis and therapy were analysed separately); and
(Comparison 03) and (Comparison 05) 'Severity' - mean severity score for the illness episode (also applied separately to both prophylaxis and therapy trials). The severity index was a continuous variable measured in two ways in different trials: a) the number of days that the patient was absent from work or school or confined to bed; and b) a symptom severity score derived from patient kept records.

A meta-analysis was conducted using Review Manager (RevMan) software for each of these five outcomes.

A pooled relative risk (RR) of the probability of experiencing one or more colds while taking vitamin C was computed for the incidence data. Due to the heterogeneity observed in this outcome across the trials, a random-effects model in RevMan was applied to the pooled estimate. Heterogeneity was explored both qualitatively and using a sensitivity analysis.

The pooled mean difference (MD) in illness duration was computed to derive an estimate of the percentage of days of illness by which vitamin C reduced the average common cold. Since duration of cold episodes varied appreciably across trials, we standardised the mean values and standard deviations (SD) obtained in each trial group, against the mean of their placebo group. In this way, the placebo group gets value 100%, and the difference between the vitamin C and placebo group is directly the effect of treatment (in percentages). Because of the level of heterogeneity observed across trials, we applied a random-effects model to compute separate pooled estimates of the MD for two sub-groups; adults and children.

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 case of the Anderson 1972 and 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 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 the 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 SD-estimation 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.

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 method leads to quantitative results that cannot be directly interpreted. Rather the primary statistical result of the SMD method is the P value for the combined set.

Four factors were considered as possible explanations for the heterogeneity observed across the results of these trials. These were trial quality, vitamin C dosage, age of participants, and the particular life circumstances of the participants.

To explore the role of vitamin C dosage, each study comparison was categorised using the dose of vitamin C that active recipients were taking on the first day of development of respiratory illness:
(1) 0.2 g/day or more, and less than 1 g/day;
(2) 1 g/day or more, and less than 2 g/day;
(3) 2 g/day or more.

This variable was assigned to each meta-analytic study entry as a sorting variable in the RevMan software. It appears in the meta-analyses as the 'user defined' variable. If different study arms were combined in the analysis to compare with a single placebo group as part of our effort to avoid distortion of the pool estimate, the dose value assigned to the arm receiving the highest vitamin C dose was assigned to the combined group in the user defined variable. Doses for individual arms that are incorporated in a combined

arm comparison are presented in the 'Characteristics of included studies' table.

In the meta-analysis of duration while on prophylaxis, children and adults were considered as separate subgroups.

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 (*see* p. 20-1 in Hemilä 2006a) and was used when comparing groups with small numbers of cases. Two-tailed P values are used in this review. We do not repeat the '95% CI' in parentheses when the limits of the confidence interval are unambiguous in the context.

Assessing the role of study quality

To test the robustness of our conclusions regarding incidence and duration, we undertook a sensitivity analysis in which we excluded from the analysis all of the studies in which allocation concealment was judged to be 'inadequate'.

Unit of analysis issues

In the first edition of this review we were rightly criticised for the 'unit of analysis' problem, as we compared several arms of a trial to the same single placebo group, which meant that the same placebo group was counted several times in pooling. In the current version we have combined the respective treatment arms to a single treatment group so that there is no inflation of participants in the placebo groups. Miller and Carr studied twins, and this was pointed out by a comment on the previous version. Our current SD values used in the calculations are based on the SE and P values, respectively, of paired tests, so the two trials are getting proper weight in pooling.

DESCRIPTION OF STUDIES

Fifty-six separate comparative studies reported in 37 publications met the selection criteria. Twelve of these publications presented the results of two to six different study comparisons. Included in the selected papers are the four reports 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 of that group's first study which Pauling 1971a had available to him.
Links to the trial reports and translations can be found at www.ltdk.helsinki.fi/users/hemila/CC/.

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

The 56 included trials which have contributed data to this report fall into three distinct methodological groups.

(1) 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 small and qualitatively different from the community based trials, they have not been included in the meta-analyses but are presented in Table 01.
(2) Forty-two distinct community prophylaxis trials which evaluated the effects of daily supplementation with vitamin C on reducing the incidence or severity or both of naturally acquired colds.
(3) Eleven community therapeutic trials that evaluated the therapeutic effects of high dosage vitamin C after natural common cold symptoms had commenced.

Brief details of the circumstances, dosage, and quality assessment of the trials are available in the 'Characteristics of included studies' table.

METHODOLOGICAL QUALITY

Three indicators of study 'quality' were collected on all trials.
(1) Allocation concealment in which a series of judgements based on explicit criteria are made relating to the question whether the assigned treatment was adequately concealed prior to allocation. Three categories were used: A, Adequate; B, Unclear; C, Inadequate.
(2) The Jadad score (Jadad 1996) which requires allocation of points out of five relating to the methodological statements in the text about 'blinding' of participants and investigators and the process of randomisation as well as the reporting of trial 'drop outs'. The Jadad scores ranged from 0 to 5.
(3) Placebo distinguishability (PD) based on evidence presented in the publication as to the visual and taste characteristics and distinguishability between the test preparation of vitamin C (mostly ascorbic acid) and the placebo. The two categories were: I: placebo explicitly stated to be indistinguishable from vitamin C tablet, and ? : uncertain, no explicit comments.

Study quality was not used as an exclusion criterion, but we only included trials in the meta-analyses which were sufficiently well documented to enable us to assign values for each of the three measures of study quality. Allocation concealment was used to sort the meta-analyses when exploring possible reasons for study heterogeneity, and sensitivity analysis was carried out to test the robustness of the findings of the review when the meta-analyses were confined to studies in which allocation concealment was judged not to be inadequate.

Allocation concealment, Jadad scores and placebo distinguishability assessments are presented in the 'Characteristics of included studies' table.

RESULTS

1) Laboratory trials with artificially infected volunteers

Three laboratory trials were volunteer transmission studies which are summarised in Table 01. 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 treatment and placebo groups. Schwartz 1973 found reduced common cold severity in vitamin C group (P < 0.02 at day 4), but no effect on symptom duration, whereas Walker failed to report any benefit to those who took vitamin C.

2) Community prophylaxis trials: incidence of colds

Comparison 01 presents the meta-analysis of the relative risk of one or more colds developing while on prophylaxis. 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 30 entries in the figure represent 33 vitamin C arms in trials.

The studies summarised here represent 11,350 participants, of whom 6135 used vitamin C for periods ranging from two weeks to five years, and the RR of developing a cold while taking vitamin C prophylaxis in individual trials ranging from 0.39 to 1.36. The pooled RR for all trials using a random-effects model was 0.96 (95% CI 0.92 to 1.00).

Heterogeneity of results

Among all the 30 entries included in Comparison 01 there is substantial heterogeneity, as indicated by the chi-square test (P = 0.03) and the high I-square (I^2) value (36%).

Five of the 30 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). Five other trials recorded a non-significant RR $\leq$ 0.80 (Himmelstein 1998a; Moolla 1996a; Moolla 1996b; Peters 1996b; Sabiston 1974).

None of the 30 comparisons significantly favoured the placebo.

Of the nine relatively small trials with RR < 0.8, four were with marathon runners (Himmelstein 1998a; 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 in Comparison 01 in which the six studies which involved marathon runners, skiers, and Canadian soldiers in a subarctic exercise were moved to a separate subgroup: participants with heavy acute physical activity (RR 0.50; 95% CI 0.38 to 0.66). 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 chi-square test, and the zero values for the I^2s.

All of these six studies on physical or cold stresses or both, were randomised controlled trials. In three of them, vitamin C dose was less than 1 g/day so that the benefit in this subgroup is not explained by particularly high doses, but by the particular conditions.

To test the effect of study quality on the findings, we undertook sensitivity analysis in which we removed from the meta-analyses the seven study entries in which allocation concealment was judged inadequate. Total pooled RR was 0.97 (95% CI 0.94 to 1.01), with the pooled RR value for the physical or cold or both stress studies at 0.53 (0.37 to 0.76). Thus, the effect of study quality as assessed by allocation concealment did not appreciably change either the quantitative estimates of the pooled results, or the qualitative conclusions.

3) Community prophylaxis trials: duration of colds

The meta-analysis in Comparison 02 on duration of colds which developed while participants were taking prophylaxis was divided into two subgroups: adults and children. For adults there were 18 entries representing 22 trial arms (four separate trial arms in one entry for Anderson 1974a and two for Karlowski 1975a) and 7242 episodes of illness, and for children there were 12 trial comparisons including 2434 episodes of illness. The division into subgroups of child and adult trials was carried out for two reasons: a) children have 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.

Quite consistent benefit was seen in duration of colds, but the effect was greater in children. For children, the pooled effect was a 13.6% (95% CI 5.6% to 21.6%) reduction in common cold duration, and for adults, the pooled effect was an 8.0% (3.0% to 13.1%) reduction in duration. The chi-square test for trial heterogeneity was not statistically significant in either of the groups.

In four of the 30 trials (Carr 1981b; Charleston 1972; Ludvigsson 1977a; Ritzel 1961) the difference in episode duration was statistically significant within the trials themselves.

All but four of the 30 comparisons (Carr 1981a; Himmelstein 1998a; Peters 1993a; 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 Comparison 02. 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, for example, those living together might conceivably have exchanged or confused their tablets.

In contrast to all the other trials, Himmelstein 1998a recorded a statistically significant increase in common cold duration in marathon runners taking vitamin C (though incidence was decreased in the vitamin C takers, *see* Comparison 01). There was an extreme and divergent drop-out rate in the Himmelstein 1998a trial. They started with 52 marathon runners in two 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). The apparent increase in common cold duration might be related to biases caused by the high and significantly divergent drop-out rate. In a sensitivity analysis we excluded the Himmelstein 1998a trial from the adult subgroup, and there was a substantial reduction in the heterogeneity (P = 0.5 in the chi-square test; and I^2 = 0%), and the test for overall effect in this adult subgroup became even more significant (P = 0.0002), yet the difference in pooled effect for adults was minimally changed: 7.7% (3.7% to 11.8%).

The great majority of the trials in Comparison 02 used 1 g/day of vitamin C and therefore a systematic examination of possible dose-dependency across the trials was not feasible. We used sensitivity analysis to test the possible role of low vitamin C doses in affecting the estimate of effect in the child subgroup. 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 18% (7% to 30%).

In seven 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, the pooled results indicated slightly greater effect by vitamin C supplementation: adults, 9.3% (3.0% to 15.6%); children, 14.3% (4.6% to 24.1%).

Furthermore, the Anderson 1974a trial used two placebo arms which were significantly discordant (Hemilä 2006a*see* p. 40). In this Cochrane review we used placebo arm #4 for which baseline data were close to the vitamin C arms. As a sensitivity analysis we excluded the Anderson 1974a, but the pooled effect for adults was minimally changed: 8.4% (2.6% to 14.2%).

Finally, to test the effect of study quality on the findings, we undertook sensitivity analysis in which we removed from the meta-analyses the studies in which allocation concealment was judged 'inadequate'. The total pooled benefit for adults was 7% (1% to 13%), and the pooled benefit for children was 13% (4% to 23%). Thus, the study quality as assessed by allocation concealment did not affect the conclusions.

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

4) Community prophylaxis trials: severity of colds

Two types of measures of the severity of illness were available. Seven entries in Comparison 03 present the results of 10 vitamin C study arms in which severity was measured by 'days confined to home' or 'days off work or school' (subgroup 1). This included 5066 respiratory episodes in adults and children. The large scale trial by Anderson 1972 reported a statistically significant protection by vitamin C. The pool as a whole found a modest, but significant reduction. This subgroup exhibited highly significant heterogeneity across the subgroup as measured by the chi-square and I^2 tests.

Subgroup 2 in Comparison 03 presents the results of symptom severity scores in eight trials. The large scale trial by Pitt 1979 found a statistically significant, but small, 5% reduction in severity score. Here too, the subgroup exhibited highly significant heterogeneity across the subgroup as measured by the chi-square and I-square tests. Himmelstein 1998a found substantially greater severity in vitamin C administered marathon runners, but as noted above, this trial had a particularly high and divergent drop-out rate, and the study groups may be biased. In a sensitivity analysis, excluding the Himmelstein 1998a trial substantially reduced the heterogeneity among the remaining seven trials (P = 0.5 in chi-square test, and I^2 = 0%), the overall effect significantly favouring vitamin C in this subgroup (P = 0.003).

The measures of 'severity' that have been used in the trials are highly variable and we used the standardised mean difference which normalises the results to standard deviations. Therefore the pooled results of Comparison 03 are not practically useful, rather, the significance level is of main importance in this case; P = 0.02 for the studies that assessed days confined to home or off work or school, and P = 0.16 for studies which used severity scores, and P = 0.004 when the two pools using different measures of severity were combined.

Sensitivity analysis using allocation concealment as the excluding variable failed to change appreciably the standardised mean difference that was estimated from the whole pool.

In summary, there was inconsistent evidence of the benefit of vitamin C on the severity of illness episodes that were experienced during prophylaxis. Such benefit with respect to days confined to home or off work or off school was statistically significant, but relatively slight in absolute terms which can be seen by viewing the original mean values in the figure.

5) Community therapeutic studies: duration of colds when treatment commenced after common cold symptoms began

The meta-analysis presented in Comparison 04 contains seven entries that incorporate data from 11 different trial arms involving 3294 cold episodes where participants initiated supplementation at the onset of cold symptoms. Audera 2001a contains three different vitamin C dosage arms, while Anderson 1974e and Anderson 1975a each contain two different vitamin C dosage arms. These are detailed in the 'Characteristics of included studies' table.

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

The statistically significant 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. This 1974 trial was bedeviled, however, by the fact that the investigators originally intended to compare results with two separate placebo groups. One of the placebo groups (#6) had substantial 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*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 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 therapeutic benefit at the higher dosage (*see* p. 42 in Hemilä 2006a).

Tyrrell 1977, Elwood 1977 and Audera 2001a, Audera 2001b, Audera 2001c 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 3 g/day over the first three days (total 9 g).

Sensitivity analysis in which allocation concealment was used as the excluding variable once again failed to change the conclusions of this meta-analysis.

In summary, the data from the therapeutic trials do not provide convincing evidence of reduced duration with the protocols that have been tested and the apparent benefits from the use of an 8 g single dose immediately after the onset of cold symptoms may be regarded as 'equivocal'.

6) Community therapeutic studies: severity of cold episodes when treatment commenced after common cold symptoms began

Comparison 05 has four entries which represent eight trial arms that included 2753 separate respiratory episodes for which cold severity was assessed. (Anderson 1974a and Anderson 1975a contain two vitamin C arms and Audera 2001a, Audera 2001b, Audera 2001c contains three different vitamin C arms). As with the prophylaxis studies, we have separated the measures of severity into two different subgroups (1) days confined to home, off work or school, and (2) 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 group, the Audera 2001a, Audera 2001b, Audera 2001c trial similarly found no meaningful difference between vitamin C and placebo groups.

Once again, the conclusions did not change when carrying out sensitivity analysis based on allocation concealment.

In summary, therapeutic vitamin C supplementation has shown no convincing effect on common cold severity with the protocols that have been used.

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.

Trials involving altogether 2490 recipients who had used more than 1 g daily of vitamin C during prophylaxis compared with 2066 who took a placebo recorded these data. 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

The term 'the common cold' does not denote a precisely defined disease, even though the illness is familiar to most of us. It is a complex of conditions caused by a broad range of viruses and occasionally bacteria. There is no unanimously accepted definition. Instead, various different operational definitions have been used, usually defining a minimum set of symptoms. This variation in

outcome definition could contribute to heterogeneity, although we are not able to explore this.

Although the importance of the placebo-effect has been challenged (Hrobjartsson 2001; Hrobjartsson 2005) we 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 to meet our study objectives. Most of the trials analysed in this review were reported to be double-blind, but that was not used as a selection criterion. Also we did not restrict the review to trials using random allocation and there are some trials included which used alternate allocation. Sensitivity analyses indicated that excluding trials which had inadequate allocation concealment did not alter our conclusions.

Despite the variation in methodology and the substantial heterogeneity in results from this large number of trial results carried out over a sixty year period, a rather coherent story emerged from the review.

Effect on common cold incidence

Consistent with earlier reviews (Hemilä 1997a; first version of this Cochrane Review (Douglas 1998a)) we found no convincing reduction in common cold incidence in the prophylaxis trials when the subgroup of marathon runners and skiers and soldiers on subarctic operations were excluded from the trial pool (RR 0.98; 95% CI 0.95 to 1.00).

A previous meta-analysis identified three trials with participants under severe acute physical stress which had found significant benefit from vitamin C supplementation (Hemilä 1996b). The more recent trials by Peters 1996a, Moolla 1996a and Himmelstein 1998a have reinforced and extended those observations. The small study reported by Sabiston 1974 which involved Canadian troops engaged in brief exercises in subarctic conditions, found a substantial reduction in common cold risk. It is noteworthy that all six studies in this group involved brief exposure to high physical or cold stress or both types of stress, and the doses of vitamin C were uniformly not particularly high.

One of the review authors (Hemilä 1997a) has also previously drawn attention to the possibility that some of the earlier benefits observed in low dose studies and controlled trials without a placebo, which were ruled ineligible for this review (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 though participants in that study were single-blinded and not randomised. Few of the recent trials have estimated the dietary intakes of vitamin C, but we cannot ignore the fact that vitamin C is an essential nutrient and all participants in the trials had regular intakes of this substance at some level, 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; 0.40 to 0.74) but not in females (Hemilä 1997a). A recent UK trial found reduction in recurrent colds in a nine week trial in both sexes (RR 0.13; 0.03 to 0.53) (*see* p. 47 in Hemilä 2006a; Van Straten 2002).

The large, well conducted trial by Anderson 1972 reported a statistically significant but quite small reduction in common cold incidence (RR 0.91; 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 supplementation and dietary vitamin C levels, this 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, 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 1975a (*see* p. 35 in 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 13.6%, and for adults it was 8.0%.

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 would not seem reasonable to ingest vitamin C regularly in the mega-dose range throughout the year if the only anticipated benefit is to rather 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 is it worth the cost of long term prophylaxis, and could an equivalent benefit perhaps 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) that might translate to a benefit when vitamin C is used therapeutically. 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 adult, 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 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, but the effect was not unambiguous on severity score scales (Comparison 03). These measures of severity are substantially more heterogeneous than the measures of symptom duration and the number of trials reporting data pertinent to 'severity' is small.

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 5% reduction in severity (P = 0.023). 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 2007). 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 on the basis of subjective observations, 6% (40 out of 674; P = 0.013) of Pitt 1979 participants correctly inferred vitamin C or placebo tablets even though the trial was double-blinded (*see* p. 26 in Hemilä 2006a).

Effect on common cold duration and severity: therapeutic trials

Since the prophylaxis trials have relatively consistently shown that vitamin C affects duration and, to some extent, the severity of the common cold without changing their incidence in the normal population, it might seem rational to administer vitamin C therapeutically, starting immediately after the first symptoms. But the therapeutic trials that have evaluated this have mostly been negative (Comparisons 04 and 05). 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 by 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* 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 three 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 (−48%; *see* p. 48 in 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 also is 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 supplementation, the data on this factor is limited and there are many other differences between the trials.

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) suggest that future therapeutic trials with adults should use doses larger

than 4 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 larger than 2 g per day.

Finally, none of the therapeutic trials examined the effect of vitamin C on children, although the effect of prophylaxis on duration has been substantially greater in children compared with adults, and children have substantially higher incidence of acute respiratory tract infections. Furthermore, although a tablet is 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).

Laboratory studies

The summary evidence from 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, less, but not significantly less, 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. The findings appear to confirm 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 Comparison 01 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 1 participant in 12 benefited from vitamin C supplementation in this particular setting (number needed to treat to benefit (NNTB) 12). 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 in this particular setting; *see* p. 44 in Hemilä 2006a). Thus, these two trials suggest that some participants may benefit, even though there is no marked effect from vitamin C on the average common cold incidence. Furthermore, evidence of heterogeneity was also found in an analysis of the effect of vitamin C on pneumonia incidence (Hemilä 2007).

In close parallel with vitamin C, lipid-soluble vitamin E is interesting as these two antioxidants interact; vitamin C reduces oxidised vitamin E levels (*see* Hemilä 2006a). Therefore heterogeneity in the effect of vitamin E 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 daily vitamin C supplementation vary substantially between different subpopulations, the heterogeneity of the effect evidently means a need for a 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 available 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.

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 and although there has been speculation bout the potential harms of large doses it has been shown to be unfounded (Dykes 1975; Hemilä 2006a). For example 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 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, which indicates the safety of such high doses, although their uncontrolled observations do not provide valid evidence of benefit. There are few reports of severe harm caused by high-dose vitamin C administration and, 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. 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. Pauling 1971a used these Ritzel findings to extrapolate the effects

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, even though technically the trial was randomised, double-blinded and placebo-controlled. In our analysis, Ritzel's trial is included in the group of trials exposed to short lived severe acute physical stress or cold or both environmental stresses which highlight the special character of this trial. Thus, it was not a misjudgment by Pauling 1971a to put the greatest weight on this randomised double-blinded placebo-controlled trial, but his error was to extrapolate the findings to the general population (*see* p. 35-6 in Hemilä 2006a).

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

AUTHORS' CONCLUSIONS

Implications for practice

The lack of effect of prophylactic vitamin C supplementation on the incidence of the common cold in normal populations throws doubt on the utility of this wide practice. In special circumstances, where people are engaged in extreme physical exertion or exposed to significant cold stress or both the current evidence indicates that vitamin C supplementation may have a considerable beneficial effect, but caution should be exercised in generalising this finding that is mainly based on marathon runners.

The prophylaxis trials found an 8% reduction in common cold duration in adults, and a 13.6% reduction in children, but the practical relevance of these findings is open, since the therapeutic trials carried out so far have not found benefits and this level of benefit probably does not justify long term prophylaxis in its own right.

In summary, on the basis of our analysis, there seems no justification for routine mega-dose vitamin C supplementation in the normal population. Prophylaxis may be justified in those exposed to severe physical exercise or cold stress or both. So far, therapeutic supplementation has not been shown to be beneficial.

Implications for research

Considering the findings from our analyses, it does not seem worthwhile to carry out further regular prophylaxis trials in the ordinary population. However, further research in people exposed to heavy exertion and cold stress could increase our understanding of the role of vitamin C. The findings in marathon runners, skiers and soldiers operating in sub-arctic 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 prophylaxis trials have found substantially greater effect on duration in children. In view of the greater incidence of respiratory infections in children, such therapeutic trials are warranted, especially where there is known to be sub-optimal dietary intake of vitamin C.

The findings in the Anderson 1974 studies on the therapeutic use of very high doses of 4 g and 8 g on the day of onset of respiratory symptoms are tantalising and deserve further assessment in light of the uncertainties raised by the problems with the placebo groups in that important study.

NOTES

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

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.

Author's 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

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 randomized 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.

Author's 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 randomized 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

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

Author's 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

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.

Author's 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.

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POTENTIAL CONFLICT OF INTEREST

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

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** Indicates the major publication for the study*

TABLES

Characteristics of included studies

Study	Anderson 1972
Methods	Double blind RCT. Prophylaxis trial. Duration 3 months
Participants	Canadian adults, both sexes. 407 vit C; 411 placebo. Recruitment specified previous cold proneness in the winter months
Interventions	1 g/d vit C and 3 g/d extra for the first 3 days of illness
Outcomes	Incidence (Comp 01) Duration (Comp 02) Severity (Comp 03)
Notes	Jadad 5 PD = I
Allocation concealment	A – Adequate

Characteristics of included studies (*Continued*)

Study	**Anderson 1974a**
Methods	Double blind RCT. Duration 3 months. Four prophylaxis, two treatment and two placebo arms. This entry reports a prophylaxis arm
Participants	Canadian adults, both sexes. Data for this arm includes 277 vit C; 285 placebo
Interventions	1 g/d vit C and 4 g/d at onset of illness on the 1st day only
Outcomes	Incidence (Comp 01) Duration (Comp 02) Severity (Comp 03)
Notes	Jadad 5 PD = I Problems with placebo group #6; see text
Allocation concealment	A – Adequate

Study	**Anderson 1974b**
Methods	See Anderson 1974a Prophylaxis arm
Participants	275 vit C
Interventions	1 g/d vit C
Outcomes	Incidence (Comp 01) Duration (Comp 02) Severity (Comp 03)
Notes	
Allocation concealment	A – Adequate

Study	**Anderson 1974c**
Methods	See Anderson 1974a. Prophylaxis arm
Participants	308 vit C
Interventions	2 g/d vit C
Outcomes	Incidence (Comp 01) Duration (Comp 02) Severity (Comp 03)
Notes	
Allocation concealment	A – Adequate

Study	**Anderson 1974d**
Methods	See Anderson 1974a. Prophylaxis arm
Participants	331 vit C
Interventions	0.25 g/d vit C
Outcomes	Incidence (Comp 01) Duration (Comp 02) Severity (Comp 03)
Notes	
Allocation concealment	A – Adequate

Study	**Anderson 1974e**
Methods	See Anderson 1974a. Therapeutic arm
Participants	275 vit C
Interventions	4 g/d vit C on the 1st day of illness only
Outcomes	Duration (Comp 04) Severity (Comp 05)
Notes	

Allocation concealment	A – Adequate

Study	**Anderson 1974f**
Methods	See for Anderson 1974a. Therapeutic arm
Participants	308 vit C
Interventions	8 g/d vit C on the 1st day of illness only
Outcomes	Duration (Comp 04) Severity (Comp 05)
Notes	
Allocation concealment	A – Adequate

Study	**Anderson 1975a**
Methods	Double blind RCT. Therapeutic trial. Duration 15 weeks. Two active and one placebo arm. This arm used vit C tablets
Participants	Canadian adults, both sexes. 150 vit C; 146 placebo
Interventions	0.5 g weekly and 1.5 g/d on the 1st day of illness and 1 g/d for next 4 days
Outcomes	Duration (Comp 04) Severity (Comp 05)
Notes	Jadad 5 PD = I
Allocation concealment	A – Adequate

Study	**Anderson 1975b**
Methods	See Anderson 1975a. This arm used vit C capsules
Participants	152 vit C
Interventions	See Anderson 1975a
Outcomes	Duration (Comp 04) Severity (Comp 05)
Notes	
Allocation concealment	A – Adequate

Study	**Audera 2001a**
Methods	Double-blind RCT. Therapeutic trial
Participants	Australian adults of both sexes. 47 vit C; 42 placebo
Interventions	1 g/d vit C for 3 days. Placebo group received 30 mg/d vit C daily for 3 days
Outcomes	Duration (Comp 04) Severity (Comp 05)
Notes	Jadad 4 PD = I
Allocation concealment	A – Adequate

Study	**Audera 2001b**
Methods	See Audera 2001a
Participants	50 vit C
Interventions	3 g/d vit C for 3 days
Outcomes	Duration (Comp 04) Severity (Comp 05)
Notes	

Allocation concealment	A – Adequate

Study	**Audera 2001c**
Methods	See Audera 2001a
Participants	45 vit C
Interventions	3 g/d vit C for 3 days with flavonoids
Outcomes	Duration (Comp 04) Severity (Comp 05)
Notes	
Allocation concealment	A – Adequate

Study	**Bancalari 1984**
Methods	Double-blind RCT. Prophylaxis trial. Duration 84 days
Participants	Chilean school children, male and female, age 10 to 12 years. 32 vit C; 30 placebo
Interventions	2 g/d vit C
Outcomes	Incidence (Comp 01) Duration (Comp 02)
Notes	Jadad 3 PD = I
Allocation concealment	B – Unclear

Study	**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 vit C; 263 placebo
Interventions	1 g/d vit C plus 4 g/d when respiratory symptoms occurred. Placebo group received 50 mg/d plus 200 mg/d when ill
Outcomes	Incidence (Comp 01) Duration (Comp 02)
Notes	Jadad 3 PD = I SD for duration was not published and it was estimated as SD = mean
Allocation concealment	A – Adequate

Study	**Carr 1981a**
Methods	Double blind RCT. Prophylaxis trial. Identical twins: one group living together and the other living apart. This deals with those living together. Duration 100 days
Participants	Australian males and females age range 14 to 64 years (mean 25 years). 51 twin pairs living together
Interventions	1 g/d vit C. Both groups received a multi vitamin tablet that contained 70 mg/d vit C
Outcomes	Incidence (Comp 01) Duration (Comp 02) Severity (Comp 03)
Notes	Jadad 4 PD = I SD for duration was not published and the SD was calculated from the P value
Allocation concealment	A – Adequate

Study	**Carr 1981b**
Methods	See Carr 1981a. This deals with those living apart

Characteristics of included studies (*Continued*)

Participants	44 twin pairs living apart
Interventions	1 g/d vit C
Outcomes	Incidence (Comp 01) Duration (Comp 02) Severity (Comp 03)
Notes	Jadad 4 PD = I
Allocation concealment	A – Adequate

Study	**Carson 1975**
Methods	Double blind RCT. Prophylaxis trial. Duration 40 days
Participants	UK adults. 121 vit C; 123 placebo
Interventions	1 g/d vit C
Outcomes	Incidence (Comp 01)
Notes	Jadad 3 PD = ?
Allocation concealment	C – Inadequate

Study	**Charleston 1972**
Methods	Single blind not randomised. Prophylaxis trial. Duration 15 weeks
Participants	Staff and students of the University of Strathclyde UK. 47 vit C; 43 placebo
Interventions	1 g/d vit C
Outcomes	Incidence (Comp 01) Duration (Comp 02)
Notes	Jadad 0 PD = ?
Allocation concealment	C – Inadequate

Study	**Clegg 1975**
Methods	Double blind RCT. Prophylaxis trial. Duration 15 weeks
Participants	Scottish students. 67 vit C; 70 placebo
Interventions	1 g/d vit C
Outcomes	Incidence (Comp 01) Duration (Comp 02)
Notes	Jadad 2 PD = I
Allocation concealment	B – Unclear

Study	**Coulehan 1974a**
Methods	Double blind, alternate allocation. Prophylaxis trial. Duration 14 weeks
Participants	USA. Students at a Navajo Indian school. Older residential students. 131 vit C; 128 placebo
Interventions	2 g/d vit C
Outcomes	Incidence (Comp 01) Duration (Comp 02)
Notes	Jadad 4 PD = I SD for duration was not published and it was estimated as SD = mean
Allocation concealment	C – Inadequate

Characteristics of included studies (*Continued*)

Study	**Coulehan 1974b**
Methods	See Coulehan 1974a
Participants	Younger residential students. 190 vit C; 192 placebo
Interventions	1 g/d vit C
Outcomes	Incidence (Comp 01) Duration (Comp 02)
Notes	
Allocation concealment	C – Inadequate

Study	**Coulehan 1976**
Methods	Double blind RCT. Prophylaxis trial. Duration 18 weeks in one school and 15 weeks in another
Participants	USA. Children at two Navajo Indian residential schools, age 6 to 15 years. Both sexes. 428 vit C; 428 placebo
Interventions	1 g/d vit C
Outcomes	Incidence (Comp 01) Duration (Comp 02)
Notes	Jadad 4 PD = I SD for duration was not published and it was estimated as SD = mean
Allocation concealment	A – Adequate

Study	**Cowan 1942**
Methods	Placebo-controlled, allocation method not evident. Prophylaxis trial
Participants	US College students. 208 vit C; 155 placebo
Interventions	0.2 g/d vit C
Outcomes	Incidence (Comp 01)
Notes	Jadad 2 PD = ? SD for duration was not published and it was estimated as SD = mean
Allocation concealment	B – Unclear

Study	**Cowan 1950**
Methods	Probably double blind RCT. Therapeutic trial
Participants	US College students. 76 vit C; 77 placebo
Interventions	0.67 g of vit 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 (Comp 04)
Notes	Jadad 3 PD = ?
Allocation concealment	B – Unclear

Study	**Dahlberg 1944**
Methods	Double-blind RCT. Prophylaxis trial. Duration 57 days
Participants	Swedish army. 1259 vit C; 1266 placebo
Interventions	0.2 g/d vit C during the first 24 days; 50 mg/d thereafter
Outcomes	Incidence (Comp 01)
Notes	Jadad 3

	PD = ?
Allocation concealment	B – Unclear

Study	**Dick 1990**
Methods	Brief abstract report of three experimental prophylaxis studies using intense exposure to infected volunteers
Participants	USA, adult volunteers. 24 vit C; 24 placebo
Interventions	2 g/d vit C
Outcomes	Shown in Table 1. Not included in meta-analyses
Notes	Jadad 2 PD = ? Three abstracts, no full paper
Allocation concealment	B – Unclear

Study	**Elwood 1976**
Methods	Double-blind RCT. Prophylaxis trial
Participants	Wales, young mothers. 339 vit C; 349 placebo
Interventions	1 g/d vit C
Outcomes	Incidence (Comp 01) Duration (Comp 02)
Notes	Jadad 2 PD = ?
Allocation concealment	B – Unclear

Study	**Elwood 1977**
Methods	Double-blind RCT. Therapeutic trial
Participants	Wales, young mothers. 145 colds treated with vit C and 119 treated with placebo
Interventions	4 g/d vit C daily for the first 2.5 days of illness
Outcomes	Duration (Comp 02) Colds were classified either as simple or chest colds
Notes	Jadad 2 PD = ? If the chest colds lasting more than 20 days are included in the comparison the statistically significant difference favouring vit C disappears
Allocation concealment	B – Unclear

Study	**Franz 1956**
Methods	Single blind. Prophylaxis study. 2 x 2 factorial: vit C and flavonoids
Participants	German medical students and nurses. 44 vit C; 45 no-vit C
Interventions	0.2 g/d vit C
Outcomes	Incidence (Comp 01)
Notes	Jadad 4 PD = ? In vitamin C group 93%(13/14) of colds were cured or improved in 5 days versus 53% (8/15) in the placebo group (P = 0.024; Hemilä 2006a)
Allocation concealment	A – Adequate

Characteristics of included studies (*Continued*)

Study	**Himmelstein 1998a**
Methods	Double blind RCT. Prophylaxis trial. Duration 2 months before and 1 month after marathon race
Participants	USA. Marathon runners. 30 vit C; 14 placebo
Interventions	1 g/d vit C
Outcomes	Incidence (Comp 01) Duration (Comp 02) Severity (Comp 03)
Notes	Jadad 3 PD = I High and statistically significant differential dropout of placebo recipients; see text
Allocation concealment	A – Adequate

Study	**Himmelstein 1998b**
Methods	See Himmelstein 1998a. Sedentary controls for the marathon runners
Participants	US sedentary people. 23 vit C; 25 placebo
Interventions	1 g/d vit C
Outcomes	Incidence (Comp 01) Duration (Comp 02) Severity (Comp 03)
Notes	
Allocation concealment	A – Adequate

Study	**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 vit C; 46 placebo
Interventions	3 g/d vit C
Outcomes	Incidence (Comp 01) Duration (Comp 02)
Notes	Jadad 4 PD = ? The authors believed that the benefits observed were attributable to the breaking of the patient blind but see Hemilä 1996a, 2006a
Allocation concealment	B – Unclear

Study	**Karlowski 1975b**
Methods	See Karlowski 1975a. This is prophylaxis plus therapeutic arm
Participants	57 vit C
Interventions	3 g/d vit C and 3 g/d therapeutic from the onset of cold for 5 days
Outcomes	Incidence (Comp 01) Duration (Comp 02)
Notes	
Allocation concealment	B – Unclear

Study	**Karlowski 1975c**
Methods	See Karlowski 1975a. This is therapeutic only arm
Participants	43 vit C
Interventions	3 g/d therapeutic vit C from the onset of cold for 5 days
Outcomes	Duration (Comp 04)

Notes	
Allocation concealment	B – Unclear

Study	**Liljefors 1972**
Methods	Double blind RCT. Crossover prophylaxis trial. Duration 2 + 2 weeks. In the first 2 weeks 25 participants received vit 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 vit C; 33 placebo
Interventions	2 g/d vit C for two weeks
Outcomes	Incidence (Comp 01)
Notes	Jadad 3 PD = ?
Allocation concealment	A – Adequate

Study	**Ludvigsson 1977a**
Methods	Double blind RCT. Prophylaxis trial. Duration 7 weeks
Participants	Swedish school children. 80 vit C; 78 placebo
Interventions	1 g/d vit C. Placebo contained 30 mg/d vit C
Outcomes	Incidence (Comp 01) Duration (Comp 02) Severity (Comp 03)
Notes	Jadad 3 PD = I Pilot study to Ludviggson 1977b
Allocation concealment	B – Unclear

Study	**Ludvigsson 1977b**
Methods	Double blind RCT. Prophylaxis trial. Duration 3 months
Participants	Swedish school children. 304 vit C; 311 placebo
Interventions	1 g/d vit C. Placebo contained 10 mg/d vit C
Outcomes	Incidence (Comp 01) Duration (Comp 02) Severity (Comp 03)
Notes	Jadad 3 PD = I
Allocation concealment	B – Unclear

Study	**Miller 1977a**
Methods	Double blind RCT. Prophylaxis trial. Identical twins
Participants	US school children. 12 twin pairs “high body weight”
Interventions	1 g/d vit C. Placebo contained 50 mg/d vit C
Outcomes	Incidence (Comp 01) Duration (Comp 02) Severity (Comp 03)
Notes	Jadad 4 PD = I
Allocation concealment	B – Unclear

Study	**Miller 1977b**
Methods	See Miller 1977a

Characteristics of included studies (*Continued*)

Participants	12 twin pairs "medium body weight"
Interventions	0.75 g/d vit C
Outcomes	Incidence (Comp 01) Duration (Comp 02) Severity (Comp 03)
Notes	Jadad 4 PD = I
Allocation concealment	B – Unclear

Study	**Miller 1977c**
Methods	See Miller 1977a
Participants	20 twin pairs "low body weight"
Interventions	0.5 g/d vit C
Outcomes	Incidence (Comp 01) Duration (Comp 02) Severity (Comp 03)
Notes	Jadad 4 PD = I
Allocation concealment	B – Unclear

Study	**Moolla 1996a**
Methods	Double blind RCT. Prophylaxis trial. Ultra marathon runners. Duration 6 weeks before and 2 weeks after the race
Participants	South Africa. Ultramarathon runners. 13 vit C; 19 placebo
Interventions	0.25 g/d vit C
Outcomes	Incidence (Comp 01)
Notes	Jadad =3 PD = ? 1/4 of those who reported respiratory symptoms in vit C group and 8/13 in placebo group reported that their respiratory symptoms were severe (P = 0.08)
Allocation concealment	B – Unclear

Study	**Moolla 1996b**
Methods	See Moolla 1996a
Participants	Sedentary controls for runners. 11 vit C; 19 placebo
Interventions	0.25 g/d vit C
Outcomes	Incidence (Comp 01)
Notes	0/6 of those who reported respiratory symptoms in vit C group and 4/7 in placebo group reported that their respiratory symptoms were severe (P = 0.02)
Allocation concealment	B – Unclear

Study	**Peters 1993a**
Methods	Double blind RCT. Prophylaxis trial. Ultramarathon runners. Duration 3 weeks before and 2 weeks after the race
Participants	South Africa. Ultramarathon runners. 43 vit C; 41 placebo
Interventions	0.6 g/d vit C
Outcomes	Incidence (Comp 01) Duration (Comp 02)
Notes	Jadad 2

	PD = I
Allocation concealment	C – Inadequate

Study	**Peters 1993b**
Methods	See Peters 1993a. Sedentary controls for the runners
Participants	Sedentary controls. 34 vit C; 39 placebo
Interventions	0.6 g/d vit C
Outcomes	Incidence (Comp 01) Duration (Comp 02)
Notes	
Allocation concealment	C – Inadequate

Study	**Peters 1996a**
Methods	Double blind RCT. Prophylaxis trial. Ultramarathon runners. Duration 21 days prior to the race
Participants	South Africa. Ultramarathon runners. 44 vit C; 47 placebo
Interventions	0.5 g/d vit C
Outcomes	Incidence (Comp 01) Duration (Comp 02)
Notes	Jadad 3 PD = ? SD for duration was not published and it was estimated as SD = mean
Allocation concealment	B – Unclear

Study	**Peters 1996b**
Methods	See Peters 1966a. Family controls of runners
Participants	South Africa. Family controls for runners. 41 vit C; 45 placebo
Interventions	0.5 g/d vit C
Outcomes	Incidence (Comp 01) Duration (Comp 02)
Notes	
Allocation concealment	B – Unclear

Study	**Pitt 1979**
Methods	Double blind RCT. Prophylaxis trial. Duration 8 weeks
Participants	USA Marine recruits. 331 vit C; 343 placebo
Interventions	2 g/d vit C
Outcomes	Incidence (Comp 01) Duration (Comp 02) Severity (Comp 03)
Notes	Jadad 5 PD = I SD for duration was not published and it was estimated as SD = mean
Allocation concealment	A – Adequate

Study	**Ritzel 1961**
Methods	Double blind RCT. Prophylaxis trial. Duration 2 weeks
Participants	Children attending ski school in Swiss Alps. 139 vit C; 140 placebo

Characteristics of included studies (*Continued*)

Interventions	1 g/d vit C
Outcomes	Incidence (Comp 01) Duration (Comp 02)
Notes	Jadad 3 PD = I SD for duration was not published and the SD was calculated from the P value
Allocation concealment	A – Adequate

Study	**Sabiston 1974**
Methods	Double blind RCT. Prophylaxis trial. Duration about 2 to 3 weeks
Participants	Canadian male military recruits during subarctic winter exercises. 56 vit C; 56 placebo
Interventions	1 g/d vit C
Outcomes	Incidence (Comp 01) Duration (Comp 02)
Notes	Jadad 1 PD = I
Allocation concealment	C – Inadequate

Study	**Sasazuki 2006**
Methods	Double blind RCT. Prophylaxis trial. Duration 3.5 years
Participants	Japanese males and females, mean age 57 years. 140 vit C; 133 placebo
Interventions	0.5 g/d vit C. Placebo contained 50 mg/d vit C
Outcomes	Incidence (Comp 01) ITT results are shown
Notes	Jadad 5 PD = ? 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
Allocation concealment	A – Adequate

Study	**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 vit C; 10 placebo
Interventions	3 g/d vit C
Outcomes	Shown in Table 1 Not included in meta-analyses
Notes	Jadad 2 PD = ?
Allocation concealment	C – Inadequate

Study	**Tyrrell 1977**
Methods	Double blind RCT. Therapeutic trial
Participants	UK, both sexes. 274 episodes treated with vit C; 329 placebo
Interventions	4 g/d vit C for the first 2.5 days of illness

Characteristics of included studies (*Continued*)

Outcomes	Duration (Comp 04) Severity (Comp 05)
Notes	Jadad 4 PD = I
Allocation concealment	B – Unclear

Study	**Van Straten 2002**
Methods	Double-blind RCT. Prophylaxis trial. Duration 60 days
Participants	UK, both sexes. 84 vit C; 84 placebo
Interventions	1 g/d vit C. Esther-C ascorbate, a form that, according to authors, "allows cells to efficiently absorb and retain high levels of vitamin"
Outcomes	Incidence (Comp 01) Duration (Comp 02)
Notes	Jadad 4 PD = ?
Allocation concealment	A – Adequate

Study	**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 vit C; 44 placebo
Interventions	3 g/d vit C
Outcomes	Shown in Table 1 Not included in meta-analyses
Notes	Jadad 0 PD = I
Allocation concealment	C – Inadequate

Study	**Wilson 1973a**
Methods	Double blind RCT. Prophylaxis trial. Duration 9 months
Participants	UK boarding school girls. 70 vit C; 58 placebo
Interventions	0.2 g/d vit C
Outcomes	Incidence (Comp 01) Duration (Comp 02) Severity (Comp 03)
Notes	Jadad 4 PD = ? Complicated classification system makes comparison with other trials difficult
Allocation concealment	A – Adequate

Study	**Wilson 1973b**
Methods	See Wilson 1973a
Participants	UK boarding school boys. 88 vit C; 86 placebo
Interventions	0.2 g/d vit C
Outcomes	Incidence (Comp 01) Duration (Comp 02) Severity (Comp 03)
Notes	
Allocation concealment	A – Adequate

g/d: grams per day

mg/d: milligrams per day
PD: placebo distinguishability
SD: standard deviation
ITT: intention to treat
NIH: National Institutes for Health

Characteristics of excluded studies

Study	Reason for exclusion
Abbott 1968	Data not suitable for inclusion in our meta-analyses. This randomized 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 two 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
Asfora 1977	No placebo comparison. 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
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)
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 two 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
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
Boines 1956	No placebo comparison. Study of poliomyelitis sufferers
Brown 1945	No data that could be used in our meta-analyses. RCT comparison of US college students. Outcome was "Colds that did not develop" and benefit was claimed
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 three mountain parishes took vitamin C supplements up to 0.3 g/d
Dyllick 1967	No placebo comparison. Cohort workplace study involving 200 recipients of 1g/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. 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 vs. an undescribed placebo. Methodologically strong study but was excluded from the meta-analyses because there were three antioxidants in the active preparation which were each hypothesized 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 group, it may be assumed that the control drinks served functionally as a placebo. Colds were slightly less frequent in the vitamin C group (RR = 0.83; 95% CI: 0.64 to 1.07) (Hemilä 1997a; Hemilä 2004a)
Gormly 1977	No placebo comparison. Fourteen males of 29 members of a one year Antarctic expedition took 1 g/d vitamin C throughout their stay. Their health outcomes were compared with the remaining group who did not to take vitamin C, and no difference was observed between the two 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 in which the experience of 250 trainees who were given 3 g/d vitamin C during their 10 day course. 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!)
Hopfengärtner 1944	Low dose. Long term hospital baby study in which supplementation of 0.05 g/d vitamin C was used

Characteristics of excluded studies (*Continued*)

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 (Hemilä 2007)
Kimbarowski 1967	No placebo comparison, no data suitable for inclusion in our meta-analyses. 216 Russian soldiers were hospitalized 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 the trial found a lower incidence of complications of viral respiratory infection (Hemilä 2004a, Hemilä 2007)
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 Czeck 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 claimed
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 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 in 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 to 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 three 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

ADDITIONAL TABLES

Table 01. Three volunteer transmission studies

Study Characteristic	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
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 vit 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 two groups	Mean cumulative severity score and mucous weights reduced in the vit C recipients (P = 0.03). Severity of colds reduced by 50% (P = 0.02; Mink 1988)
Comments	Not double blind	Double blind. Nasal virus shedding similar in the two groups	Double blind. Virus shedding similar in these two groups . The studies are briefly described in a series of conference abstracts but no full published paper is available

ANALYSES

Comparison 01. Development of colds while on vitamin C prophylaxis

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Proportions developing one or more cold episodes during prophylaxis	30	11350	Relative Risk (Random) 95% CI	0.96 [0.92, 1.00]

Comparison 02. Duration of colds developing on vitamin C prophylaxis

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Duration of common cold symptoms (placebo group duration set as 100%)	30	9676	Weighted Mean Difference (Random) 95% CI	-9.73 [-14.07, -5.39]

Comparison 03. Severity of colds developing on vitamin C prophylaxis

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Indicators of severity of episodes experienced while on prophylaxis	15	7045	Standardised Mean Difference (Random) 95% CI	-0.13 [-0.21, -0.04]

Comparison 04. Duration of colds treated with vitamin C

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Mean symptom days per episode standardised against control group	7	3294	Weighted Mean Difference (Random) 95% CI	-2.54 [-10.09, 5.02]

Comparison 05. Severity of colds treated with vitamin C

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Indicators of severity of episodes for which vit C was used as therapy	4	2753	Standardised Mean Difference (Random) 95% CI	-0.07 [-0.16, 0.02]

INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Humans

COVER SHEET

Title Vitamin C for preventing and treating the common cold

Authors Douglas RM, Hemilä H, Chalker E, Treacy B

Contribution of author(s) 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, and wrote the review.
Harri Hemila (HH) carefully reviewed drafts of the second edition of the review (2004), assisted in paper retrieval, proposed alterations to data presentation, checked data entries

	and contributed significant input to the text. He has taken over responsibility for this, and future updates of this review. Elizabeth Chalker (EC) wrote the protocol of the first edition of the review, developed the initial search strategy, undertook the searches, organised retrieval of papers, screened papers against inclusion criteria and appraised the quality of papers for that edition. Barbara Treacy (BT) prepared overviews and summaries of published studies in preparation for the first version of the review (1998).
Issue protocol first published	1998/1
Review first published	1998/1
Date of most recent amendment	22 May 2007
Date of most recent SUBSTANTIVE amendment	14 May 2007
What's New	Updated January 2007: one new trial was identified. Conclusions were not changed from the 2004 update.
Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	21 December 2006
Date authors' conclusions section amended	12 June 2004
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GRAPHS AND OTHER TABLES

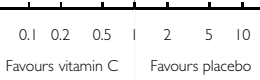
Analysis 01.01. Comparison 01 Development of colds while on vitamin C prophylaxis, Outcome 01 Proportions developing one or more cold episodes during prophylaxis

Review: Vitamin C for preventing and treating the common cold

Comparison: 01 Development of colds while on vitamin C prophylaxis

Outcome: 01 Proportions developing one or more cold episodes during prophylaxis

Study	Vitamin C n/N	Placebo n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 All eligible trials with exception of subgroup removed below					
Anderson 1972	302/407	335/411		10.6	0.91 [0.85, 0.98]
Anderson 1974a	922/1191	233/285		11.6	0.95 [0.89, 1.01]
Bancalari 1984	21/32	21/30		1.4	0.94 [0.67, 1.32]
Briggs 1984	125/265	121/263		4.0	1.03 [0.85, 1.23]
Carson 1975	85/121	84/123		4.5	1.03 [0.87, 1.22]
Charleston 1972	31/47	37/43		2.6	0.77 [0.60, 0.97]
Clegg 1975	48/67	50/70		3.2	1.00 [0.81, 1.24]
Coulehan 1974a	19/190	23/192		0.5	0.83 [0.47, 1.48]
Coulehan 1974b	16/131	17/128		0.4	0.92 [0.49, 1.74]
Coulehan 1976	98/428	98/428		2.5	1.00 [0.78, 1.28]
Cowan 1942	184/208	142/155		11.1	0.97 [0.90, 1.03]
Dahlberg 1944	131/1259	142/1266		2.9	0.93 [0.74, 1.16]
Elwood 1976	296/339	298/349		11.9	1.02 [0.96, 1.09]
Franz 1956	14/44	15/45		0.5	0.95 [0.52, 1.74]
Himmelstein 1998b	10/23	8/25		0.3	1.36 [0.65, 2.84]
Liljefors 1972	10/33	9/33		0.3	1.11 [0.52, 2.38]
Ludvigsson 1977a	49/80	44/78		2.2	1.09 [0.84, 1.41]
Ludvigsson 1977b	230/304	240/311		9.3	0.98 [0.90, 1.07]
Moolla 1996b	5/11	12/19		0.3	0.72 [0.35, 1.50]
Peters 1993b	18/34	18/39		0.8	1.15 [0.72, 1.82]
Peters 1996b	5/41	11/45		0.2	0.50 [0.19, 1.31]
Pitt 1979	298/331	309/343		12.8	1.00 [0.95, 1.05]
Sasazuki 2006	68/140	67/133		2.6	0.96 [0.76, 1.23]
Van Straten 2002	35/84	34/84		1.2	1.03 [0.72, 1.48]
Subtotal (95% CI)	5810	4898		97.7	0.98 [0.95, 1.00]
Total events: 3020 (Vitamin C), 2368 (Placebo)					



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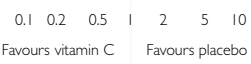
Study	Vitamin C n/N	Placebo n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Test for heterogeneity chi-square=17.75 df=23 p=0.77 I^2 =0.0%					
Test for overall effect z=1.92 p=0.05					
02 Short term exposure to cold and/or severe physical stress					
Himmelstein 1998a	10/30	6/14		0.3	0.78 [0.35, 1.71]
Moolla 1996a	4/13	13/19		0.2	0.45 [0.19, 1.07]
Peters 1993a	14/43	28/41		0.7	0.48 [0.30, 0.77]
Peters 1996a	7/44	19/47		0.3	0.39 [0.18, 0.84]
Ritzel 1961	17/139	31/140		0.6	0.55 [0.32, 0.95]
Sabiston 1974	6/56	14/56		0.2	0.43 [0.18, 1.04]
Subtotal (95% CI)	325	317		2.3	0.50 [0.38, 0.66]
Total events: 58 (Vitamin C), 111 (Placebo)					
Test for heterogeneity chi-square=1.93 df=5 p=0.86 I^2 =0.0%					
Test for overall effect z=4.98 p<0.00001					
Total (95% CI)	6135	5215		100.0	0.96 [0.92, 1.00]
Total events: 3078 (Vitamin C), 2479 (Placebo)					
Test for heterogeneity chi-square=45.26 df=29 p=0.03 I^2 =35.9%					
Test for overall effect z=2.02 p=0.04					



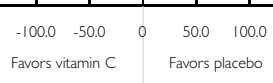
Analysis 02.01. Comparison 02 Duration of colds developing on vitamin C prophylaxis, Outcome 01 Duration of common cold symptoms (placebo group duration set as 100%)

Review: Vitamin C for preventing and treating the common cold

Comparison: 02 Duration of colds developing on vitamin C prophylaxis

Outcome: 01 Duration of common cold symptoms (placebo group duration set as 100%)

Study	Vitamin C N	Vitamin C Mean(SD)	Placebo N	Placebo Mean(SD)	Weighted Mean Difference (Random) 95% CI	Weight (%)	Weighted Mean Difference (Random) 95% CI
01 Prophylaxis 200 mg or more daily plus or minus loading dose at cold onset in adults							
Anderson 1972	561	95.00 (92.00)	609	100.00 (82.00)		9.3	-5.00 [-15.02, 5.02]
Anderson 1974a	1823	93.00 (102.00)	437	100.00 (99.00)		8.9	-7.00 [-17.40, 3.40]
Briggs 1984	125	94.00 (94.00)	121	100.00 (100.00)		2.7	-6.00 [-30.27, 18.27]
Carr 1981a	94	101.00 (96.00)	70	100.00 (96.00)		1.9	1.00 [-28.70, 30.70]
Carr 1981b	57	65.00 (75.00)	71	100.00 (75.00)		2.4	-35.00 [-61.14, -8.86]
Charleston 1972	44	84.00 (46.00)	80	100.00 (20.00)		6.1	-16.00 [-30.28, -1.72]
Clegg 1975	68	95.00 (41.00)	73	100.00 (39.00)		6.8	-5.00 [-18.23, 8.23]
Elwood 1976	627	94.00 (90.00)	690	100.00 (99.00)		9.1	-6.00 [-16.21, 4.21]
Himmelstein 1998a	15	200.00 (129.00)	12	100.00 (77.00)		0.3	100.00 [21.52, 178.48]
Himmelstein 1998b	14	60.00 (26.00)	12	100.00 (82.00)		0.8	-40.00 [-88.35, 8.35]
Karlowski 1975a	128	87.40 (51.50)	65	100.00 (52.00)		5.5	-12.60 [-28.07, 2.87]
Peters 1993a	14	103.00 (17.00)	28	100.00 (42.00)		4.4	3.00 [-14.93, 20.93]
Peters 1993b	18	75.00 (38.00)	18	100.00 (56.00)		1.7	-25.00 [-56.26, 6.26]
Peters 1996a	7	85.00 (85.00)	19	100.00 (100.00)		0.3	-15.00 [-92.37, 62.37]
Peters 1996b	5	136.00 (136.00)	11	100.00 (100.00)		0.1	36.00 [-97.05, 169.05]
Pitt 1979	600	97.40 (100.00)	619	100.00 (100.00)		8.2	-2.60 [-13.83, 8.63]
Sabiston 1974	6	72.00 (50.00)	14	100.00 (50.00)		0.8	-28.00 [-75.82, 19.82]
Van Straten 2002	37	58.00 (96.00)	50	100.00 (150.00)		0.7	-42.00 [-93.82, 9.82]
Subtotal (95% CI)	4243		2999			70.2	-8.02 [-13.08, -2.96]
Test for heterogeneity chi-square=21.88 df=17 p=0.19 I^2 =22.3%							
Test for overall effect z=3.11 p=0.002							
02 Prophylaxis 200 mg or more daily plus or minus loading dose at cold onset in children							
Bancalari 1984	38	76.00 (62.00)	46	100.00 (65.00)		2.2	-24.00 [-51.23, 3.23]
Coulehan 1974a	19	88.00 (88.00)	23	100.00 (100.00)		0.6	-12.00 [-68.88, 44.88]
Coulehan 1974b	16	71.00 (71.00)	17	100.00 (100.00)		0.5	-29.00 [-87.91, 29.91]
Coulehan 1976	98	95.00 (95.00)	98	100.00 (100.00)		2.2	-5.00 [-32.31, 22.31]



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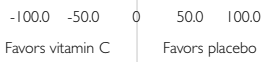
Study	Vitamin C N	Vitamin C Mean(SD)	Placebo N	Placebo Mean(SD)	Weighted Mean Difference (Random) 95% CI	Weight (%)	Weighted Mean Difference (Random) 95% CI
Ludvigsson 1977a	62	61.00 (41.00)	55	100.00 (67.00)		3.6	-39.00 [-59.44, -18.56]
Ludvigsson 1977b	423	94.00 (85.00)	398	100.00 (114.00)		6.4	-6.00 [-19.82, 7.82]
Miller 1977a	53	93.00 (105.00)	42	100.00 (105.00)		1.0	-7.00 [-49.51, 35.51]
Miller 1977b	42	97.00 (50.00)	40	100.00 (50.00)		3.3	-3.00 [-24.65, 18.65]
Miller 1977c	116	87.00 (73.00)	122	100.00 (73.00)		4.2	-13.00 [-31.55, 5.55]
Ritzel 1961	17	69.00 (51.00)	31	100.00 (51.00)		1.9	-31.00 [-61.17, -0.83]
Wilson 1973a	160	84.50 (131.00)	126	100.00 (134.00)		1.8	-15.50 [-46.48, 15.48]
Wilson 1973b	205	108.00 (150.00)	187	100.00 (132.00)		2.1	8.00 [-19.92, 35.92]
Subtotal (95% CI)	1249		1185			29.8	-13.62 [-21.63, -5.62]
Test for heterogeneity chi-square=12.90 df=11 p=0.30 I² =14.7%							
Test for overall effect z=3.34 p=0.0008							
Total (95% CI)	5492		4184			100.0	-9.73 [-14.07, -5.39]
Test for heterogeneity chi-square=36.73 df=29 p=0.15 I² =21.0%							
Test for overall effect z=4.40 p=0.00001							



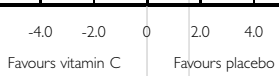
Analysis 03.01. Comparison 03 Severity of colds developing on vitamin C prophylaxis, Outcome 01 Indicators of severity of episodes experienced while on prophylaxis

Review: Vitamin C for preventing and treating the common cold

Comparison: 03 Severity of colds developing on vitamin C prophylaxis

Outcome: 01 Indicators of severity of episodes experienced while on prophylaxis

Study	Vitamin C N	Vitamin C Mean(SD)	Placebo N	Placebo Mean(SD)	Standardised Mean Difference (Random) 95% CI	Weight (%)	Standardised Mean Difference (Random) 95% CI
01 Mean days indoors or off work or school per episode							
Anderson 1972	561	1.04 (1.75)	609	1.32 (2.00)		13.2	-0.15 [-0.26, -0.03]
Anderson 1974a	1823	1.14 (1.71)	437	1.15 (1.52)		13.7	-0.01 [-0.11, 0.10]
Ludvigsson 1977a	62	0.95 (1.12)	55	1.90 (2.42)		4.2	-0.51 [-0.88, -0.14]
Ludvigsson 1977b	423	1.47 (1.27)	398	1.81 (1.79)		12.0	-0.22 [-0.36, -0.08]
Sabiston 1974	6	0.80 (0.80)	14	2.40 (2.10)		0.7	-0.84 [-1.83, 0.16]
Wilson 1973a	160	4.52 (6.32)	126	5.94 (6.28)		7.7	-0.22 [-0.46, 0.01]
Wilson 1973b	205	4.20 (4.44)	187	3.84 (4.51)		9.1	0.08 [-0.12, 0.28]



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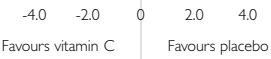
Study	Vitamin C N	Vitamin C Mean(SD)	Placebo N	Placebo Mean(SD)	Standardised Mean Difference (Random) 95% CI	Weight (%)	Standardised Mean Difference (Random) 95% CI
Subtotal (95% CI)	3240		1826			60.6	-0.14 [-0.27, -0.02]
Test for heterogeneity chi-square=17.73 df=6 p=0.007 I^2 =66.2%							
Test for overall effect z=2.32 p=0.02							
02 Mean symptom severity score per episode							
Carr 1981a	94	23.60 (33.57)	70	22.20 (33.57)		5.4	0.04 [-0.27, 0.35]
Carr 1981b	57	21.90 (33.57)	71	33.60 (33.57)		4.5	-0.35 [-0.70, 0.00]
Himmelstein 1998a	15	42.60 (28.66)	12	17.80 (25.98)		1.1	0.87 [0.07, 1.67]
Himmelstein 1998b	14	16.10 (14.59)	12	37.40 (52.65)		1.1	-0.55 [-1.34, 0.23]
Miller 1977a	53	22.50 (45.50)	42	27.30 (45.50)		3.7	-0.10 [-0.51, 0.30]
Miller 1977b	42	48.60 (22.60)	40	46.20 (22.60)		3.3	0.11 [-0.33, 0.54]
Miller 1977c	116	14.60 (20.00)	122	19.00 (20.00)		7.0	-0.22 [-0.47, 0.04]
Pitt 1979	600	1.87 (0.76)	619	1.97 (0.76)		13.3	-0.13 [-0.24, -0.02]
Subtotal (95% CI)	991		988			39.4	-0.11 [-0.25, 0.04]
Test for heterogeneity chi-square=11.40 df=7 p=0.12 I^2 =38.6%							
Test for overall effect z=1.41 p=0.2							
Total (95% CI)	4231		2814			100.0	-0.13 [-0.21, -0.04]
Test for heterogeneity chi-square=29.18 df=14 p=0.010 I^2 =52.0%							
Test for overall effect z=2.86 p=0.004							

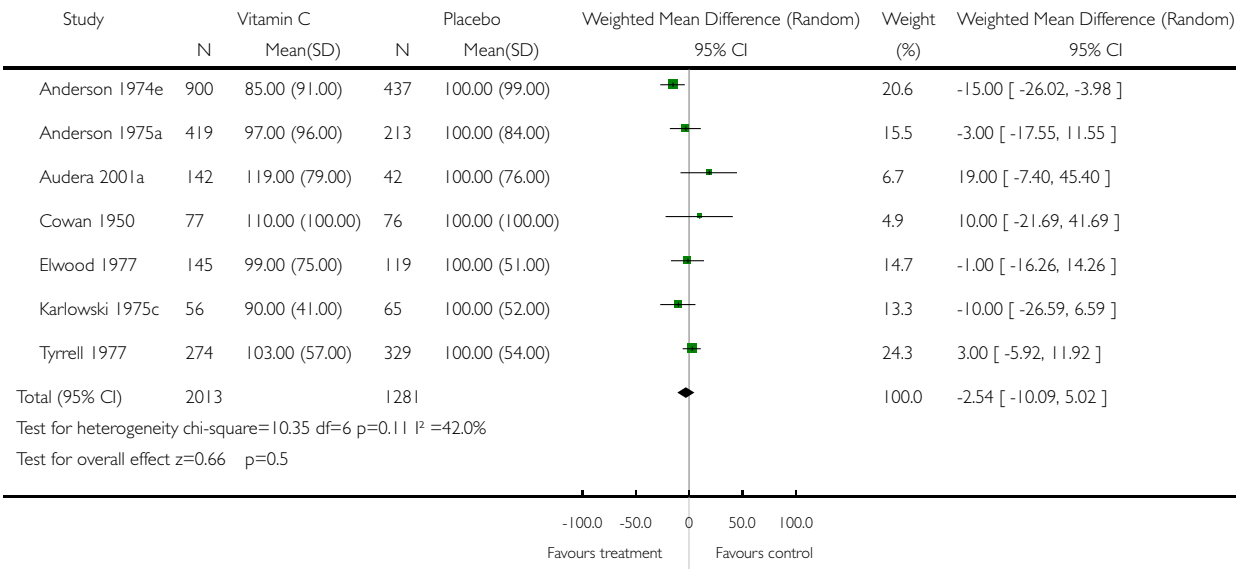


Analysis 04.01. Comparison 04 Duration of colds treated with vitamin C, Outcome 01 Mean symptom days per episode standardised against control group

Review: Vitamin C for preventing and treating the common cold

Comparison: 04 Duration of colds treated with vitamin C

Outcome: 01 Mean symptom days per episode standardised against control group

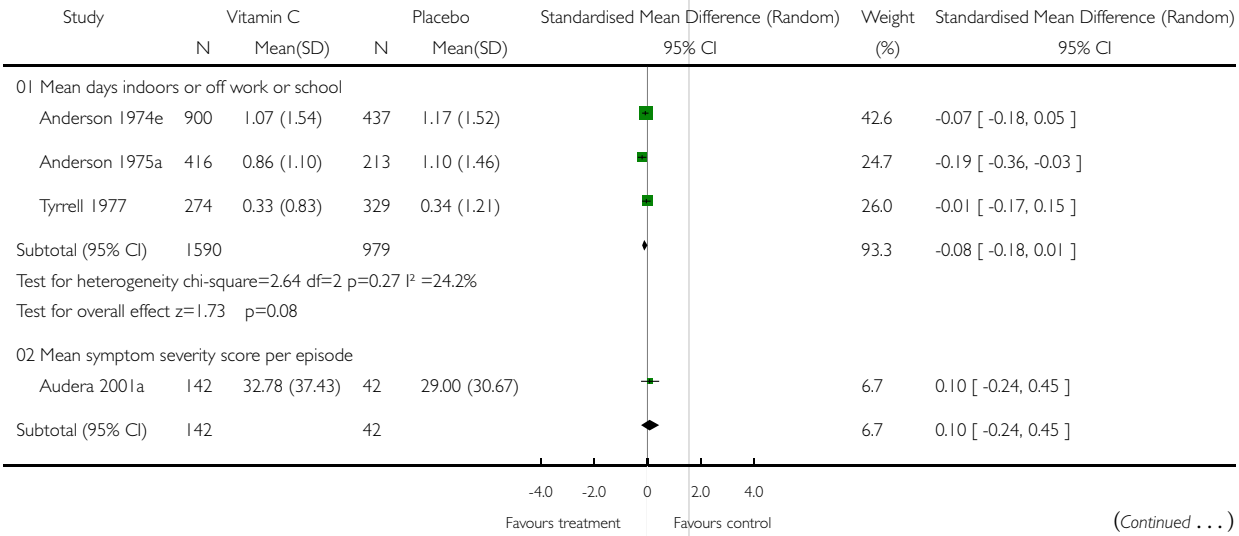


Analysis 05.01. Comparison 05 Severity of colds treated with vitamin C, Outcome 01 Indicators of severity of episodes for which vit C was used as therapy

Review: Vitamin C for preventing and treating the common cold

Comparison: 05 Severity of colds treated with vitamin C

Outcome: 01 Indicators of severity of episodes for which vit C was used as therapy



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