

# VITAMIN C FOR PREVENTING AND TREATING THE COMMON COLD

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## A B S T R A C T

### 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.

### Objective

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.

### Criteria for considering studies for this review

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).

### 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.

## P L A I N L A N G U A G E S U M M A R Y

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.

## B A C K G R O U N D

### O B J E C T I V E S

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.

## M E T H O D S O F T H E R E V I E W

### C R I T E R I A F O R C O N S I D E R I N G S T U D I E S F O R T H I S R E V I E W

#### 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.

## S E A R C H M E T H O D S F O R I D E N T I F I C A T I O N O F S T U D I E S

### Search methods for identification of studies

#### Electronic searches

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). See [Appendix 1](#) for the EMBASE search strategy.

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. See [Appendix 2](#) for the EMBASE search strategy. In the period from June 2004 to December 2006 only one new trial conforming to our selection criteria was published ([Sasazuki 2006](#)).

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

## Searching other resources

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.

## DATA COLLECTION AND ANALYSIS

### Data collection and analysis

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.

## Selection of studies

The circumstances and results of three small laboratory trials were summarised in a separate table () 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.

## Data extraction and management

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.

## 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.

## Dealing with missing data

Some trials presented the mean duration or severity of colds, but not the respective SD. In some trials the P value for the difference of interest was reported and the SD was calculated from it. In 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.

## Assessment of heterogeneity

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.

## Sensitivity analysis

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'.

## M E T H O D O L O G I C A L   Q U A L I T Y

### R E S U L T S

## Results

### Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded 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/](http://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.

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 .

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.

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.

### Risk of bias in included studies

Three indicators of study 'quality' were collected on all trials.

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.

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.

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.

### Effects of interventions

#### 1) Laboratory trials with artificially infected volunteers

Three laboratory trials were volunteer transmission studies which are summarised in . [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<sup>2</sup>) 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<sup>2</sup>s.

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  $I^2$  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.

## Results

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

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

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

## DISCUSSION

### Discussion

## Summary of main results

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 sub-arctic 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 about 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.

## 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.

## A C K N O W L E D G E M E N T S

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## G R A P H S

### Graphs and Tables

To view a graph or table, click on the outcome title of the summary table below.

Development of colds while on vitamin C prophylaxis				
Outcome title	No. of studies	No. of participants	Statistical method	Effect size
<a href="#">1 Proportions developing one or more cold episodes during prophylaxis</a>	30	11350	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.92, 1.00]
<a href="#">1.1 All eligible trials with exception of subgroup removed below</a>	24	10708	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.95, 1.00]
<a href="#">1.2 Short term exposure to cold and/or severe physical stress</a>	6	642	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.38, 0.66]
Duration of colds developing on vitamin C prophylaxis				
Outcome title	No. of studies	No. of participants	Statistical method	Effect size
<a href="#">1 Duration of common cold symptoms (placebo group duration set as 100%)</a>	30	9676	Mean Difference (IV, Random, 95% CI)	-9.73 [-14.07, -5.39]
<a href="#">1.1 Prophylaxis 200 mg or more daily plus or minus loading dose at cold onset in adults</a>	18	7242	Mean Difference (IV, Random, 95% CI)	-8.02 [-13.08, -2.96]
<a href="#">1.2 Prophylaxis 200 mg or more daily plus or minus loading dose at cold onset in children</a>	12	2434	Mean Difference (IV, Random, 95% CI)	-13.62 [-21.63, -5.62]
Severity of colds developing on vitamin C prophylaxis				
Outcome title	No. of studies	No. of participants	Statistical method	Effect size
<a href="#">1 Indicators of severity of episodes experienced while on prophylaxis</a>	15	7045	Std. Mean Difference (IV, Random, 95% CI)	-0.13 [-0.21, -0.04]
<a href="#">1.1 Mean days indoors or off work or school per episode</a>	7	5066	Std. Mean Difference (IV, Random, 95% CI)	-0.14 [-0.27, -0.02]
<a href="#">1.2 Mean symptom severity score per episode</a>	8	1979	Std. Mean Difference (IV, Random, 95% CI)	-0.11 [-0.25, 0.04]
Duration of colds treated with vitamin C				
Outcome title	No. of studies	No. of participants	Statistical method	Effect size
<a href="#">1 Mean symptom days per episode standardised against control group</a>	7	3294	Mean Difference (IV, Random, 95% CI)	-2.54 [-10.09, 5.02]
Severity of colds treated with vitamin C				
Outcome title	No. of studies	No. of participants	Statistical method	Effect size
<a href="#">1 Indicators of severity of episodes for which vit C</a>	4	2753	Std. Mean Difference (IV,	-0.07 [-0.16,

<u>was used as therapy</u>			Random, 95% CI)	0.02]
<u>1.1 Mean days indoors or off work or school</u>	3	2569	Std. Mean Difference (IV, Random, 95% CI)	-0.08 [-0.18, 0.01]
<u>1.2 Mean symptom severity score per episode</u>	1	184	Std. Mean Difference (IV, Random, 95% CI)	0.10 [-0.24, 0.45]

**C O V E R   S H E E T**

**Vitamin C for preventing and treating the common cold**

**Reviewer(s)** Hemilä Harri, Chalker Elizabeth, Treacy Barbara, Douglas Bob

**Contribution of Reviewer(s)**

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**Date reviewers' conclusions section amended** Information not supplied by reviewer

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## COMMENTS AND CRITICISMS

### Flaws in statistical analysis?

#### Summary of comments and criticisms

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.

#### Reviewer's reply

#### Contributors to comment

David Wooff

Comment and reply posted 28/08/2004

#### Unit of analysis issues

#### Summary of comments and criticisms

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 (Lugvigsson) 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.

#### Reviewer's reply

#### **Contributors to comment**

Julian Higgins

Comment and reply posted 28/08/2004

#### **Doses too small**

#### **Summary of comments and criticisms**

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

#### **Reviewer's reply**

#### **Contributors to comment**

Reuven Gilmore

Comment and reply posted 28/08/2004

#### **Vitamin C for preventing and treating the colds**

#### **Summary of comments and criticisms**

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.

#### **Reviewer's reply**

#### **Contributors to comment**

Steve Hickey PhD. Manchester Metropolitan University

Hilary Roberts PhD

Comment and reply posted 16/11/2005

#### **Vitamin C doses in trial**

#### **Summary of comments and criticisms**

Studies which find the effects of vitamin C on the common cold inconclusive invariably use less than 1 g of ascorbic acid a day.

Proponents of Vitamin C therapy consistently use 3 or more grams a day. This debate will not be resolved until both camps start testing the same dosages. Since the Ascorbic acid proponents acknowledge that < 1 g a day will have little therapeutic effect, it is incumbent on researchers to analyze the effect of megadoses.

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

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

Submitter agrees with default conflict of interest statement:

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

#### Reviewer's reply

#### Contributors to comment

Sean Emerson  
Comment posted 24/07/2007

#### Vitamin C and the common cold, 2 May 2008

#### Summary of comments and criticisms

#### Reviewer's reply

#### Contributors to comment

Steve Hickey PhD and Hilary Roberts PhD  
Feedback and reply added 13 June 2008

### KEYWORDS

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### HISTORY

History

Protocol first published: Issue 1, 1998

Review first published: Issue 1, 1998

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

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