Vitamin C for preventing and treating pneumonia (Review)

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[Intervention Review]

Vitamin C for preventing and treating pneumonia

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ABSTRACT

Background

Pneumonia is one of the most common, serious infections, causing two million deaths annually among young children in low-income countries. In high-income countries pneumonia is most significantly a problem of the elderly.

Objectives

To assess the prophylactic and therapeutic effects of vitamin C on pneumonia.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL 2011, Issue 1) which contains the Acute Respiratory Infections Group's Specialised Register, MEDLINE (1950 to January week 4, 2011), EMBASE (1974 to February 2011) and Web of Science (1945 to February 2011).

Selection criteria

To assess the therapeutic effects of vitamin C, we selected placebo-controlled trials. To assess prophylactic effects, we selected controlled trials with or without a placebo.

Data collection and analysis

Two review authors independently read the trial reports and extracted data.

Main results

We identified three prophylactic trials which recorded 37 cases of pneumonia in 2335 people. Only one was satisfactorily randomised, double-blind and placebo-controlled. Two trials examined military recruits and the third studied boys from "lower wage-earning classes" attending a boarding school in the UK during World War II. Each of these trials found a statistically significant (80% or greater) reduction in pneumonia incidence in the vitamin C group. We identified two therapeutic trials involving 197 pneumonia patients. Only one was satisfactorily randomised, double-blind and placebo-controlled. That trial studied elderly patients in the UK and found lower mortality and reduced respiratory symptom scores in the vitamin C group; however, the benefit was restricted to the most ill patients. The other therapeutic trial studied adults with a wide age range in the former Soviet Union and found a dose-dependent reduction in the time to recovery with two vitamin C doses.

Authors' conclusions

The prophylactic use of vitamin C to prevent pneumonia should be further investigated in populations who have high incidence of pneumonia, especially if dietary vitamin C intake is low. Similarly, the therapeutic effects of vitamin C should be studied, especially in patients with low plasma vitamin C levels. The current evidence is too weak to advocate widespread prophylactic use of vitamin C to prevent pneumonia in the general population. However, therapeutic vitamin C supplementation may be reasonable for pneumonia patients who have low vitamin C plasma levels because its cost and risks are low.

PLAIN LANGUAGE SUMMARY

Vitamin C for preventing and treating pneumonia

Pneumonia is an infection of the lungs caused by bacteria, viruses or other infectious agents. Its clinical diagnosis is sometimes difficult. Pneumonia is more common in young children and in the aged. In low-income countries it causes two million deaths annually among young children. In the USA it is the most common cause of death from infection.

Vitamin C was identified in the early 1900s and suggestions that one of its biological roles may be to resist infections are supported by numerous animal studies. We looked for studies in humans and found three trials with a total of 2335 participants that looked at whether vitamin C prevents pneumonia. Two of the preventive trials studied soldiers while the third studied boys in a UK boarding school in the 1940s. Two other trials with a total of 197 pneumonia patients looked at whether vitamin C might help to cure pneumonia. One studied patients aged 66 to 94 years in the UK with pneumonia and benefit was restricted to those who were most ill and had low vitamin C levels. The other trial was conducted in the former Soviet Union but the social and nutritional backgrounds of the patients were not described. None of the five trials reported noteworthy adverse effects of vitamin C.

Overall, the results of the five identified trials suggested vitamin C is beneficial in both preventing and treating pneumonia. However, these trials were carried out in such extraordinary conditions that the results may not apply to the general population. Therefore, more research is needed. In the meantime, supplementing pneumonia patients who have low plasma vitamin C levels may be reasonable because of its safety and low cost.

BACKGROUND

Description of the condition

Pneumonia is an infection of the lungs and can be caused by bacteria, viruses, Rickettsia, fungi or parasites. Nearly 100 species have been identified as aetiological agents (Donowitz 2005; File 2003; Ruuskanen 2011). Although the pathological definition of pneumonia is clear, the clinical diagnosis is sometimes ambiguous. The risk of pneumonia is increased in young children and the elderly. In low-income countries, pneumonia causes two million deaths annually among children under five years of age (Graham 1990; Jones 2003; Rudan 2004). In the USA, pneumonia is the sixth most common cause of death and the most common cause of infection-related death (Donowitz 2005).

Description of the intervention

Although vitamin C affects the immune system, it may only affect particular conditions. For example, it is possible that variation in vitamin C intake does not affect the immune system in the ordinary Western population because of their relatively high dietary intake levels. Vitamin C might, however, be a limiting factor in populations with low intakes. An extreme example is the high prevalence of frank vitamin C deficiency, apparent as scurvy, in refugee camps in the Horn of Africa; reported to be up to 44% (WHO 1999a). Vitamin C metabolism is affected in various infections, including pneumonia, as indicated by decreased levels in plasma, leucocytes and urine (Hemilä 1997a; Hemilä 1999; Hemilä 2006a). These changes in metabolism mean that vitamin C might have a treatment effect on pneumonia irrespective of dietary intake. In animal studies, vitamin C increased resistance to various viral and bacterial infections (Hemilä 2006a).

In the early 1900s, Alfred Hess carried out extensive studies of

scurvy and summarised a large series of autopsy findings: "pneumonia, lobular or lobar, is one of the most frequent complications [of scurvy] and causes of death" and "secondary pneumonias, usually broncho-pneumonic in type, are of common occurrence, and in many [scurvy] epidemics constitute the prevailing cause of death" (Hess 1920). He further commented, in a major medical journal a decade later, that in "infantile scurvy . . . a lack of the antiscorbutic factor [vitamin C] which leads to scurvy, at the same time predisposes to infections [particularly of the respiratory tract] . . . Similar susceptibility to infections goes hand in hand with adult scurvy" (Hess 1932). In the early 1900s, Casimir Funk, who coined the term 'vitamin', pointed out that an epidemic of pneumonia in the Sudan disappeared when antiscorbutic (vitamin C-containing) treatment was given to the numerous cases of scurvy which appeared at about the same time (Robertson 1934).

Since the 1930s, a few German and US physicians have proposed that vitamin C might be beneficial in the treatment of pneumonia (Bohnholtzer 1937; Hemilä 1999; Hochwald 1937). Gander and Niederberger concluded from a series of 15 cases that "the general condition is always favourably influenced [by vitamin C] to a noticeable extent, as is the convalescence, which proceeds better and more quickly than in cases of pneumonia which are not treated with vitamin C" (Gander 1936). Benefit from intravenous vitamin C was reported in a series of over 40 cases (Klenner 1948; Klenner 1951) and in three cases of viral pneumonia (Dalton 1962). A large dose of oral vitamin C was also claimed to be beneficial in patients with viral pneumonia (Cathcart 1981; Luberoff 1978).

The effect of vitamin C on the common cold has been studied extensively. A major finding from the trials is the heterogeneity in its effects. Although the largest trials found no effect on common cold incidence, the incidence was reduced in trials with participants under heavy acute physical stress and in British males, which was explained as the result of a diet low in vitamin C (Hemilä 1996; Hemilä 1997b; Hemilä 2006a; Hemilä 2010). Consequently, it is possible that the effects of vitamin C on other respiratory infections are also modified by various factors, such as physical stress and dietary vitamin C intake. Also, two large trials found considerable divergence in the effects of vitamin C depending on the type of cold. Vitamin C decreased the incidence of 'chest colds' (-18%; cough or other chest symptoms) but not of 'simple colds' (+1%; runny nose or sneezing) (Elwood 1976; Hemilä 1997b). Similarly, vitamin C decreased the incidence of 'throat colds' (-21%) but not 'nose colds' (-2%) (Anderson 1973; Hemilä 1997b). These two trials thus suggest that vitamin C might have a greater effect on infections affecting the lower respiratory tract.

In close parallel with vitamin C, lipid-soluble vitamin E is interesting as these two antioxidants interact; vitamin C reduces oxidised vitamin E levels (Hamilton 2000; Hemilä 2006a; Packer 1979). In a large-scale trial the effect of vitamin E on the risk of pneumonia was modified by the age at which participants began smoking, such that vitamin E reduced the risk in those who began smoking at a later age but increased the risk in those who began smoking at an early age (Hemilä 2004). Vitamin E reduced the risk of pneumonia by 50% in participants who exercised, also suggesting heterogeneous effects between population groups (Hemilä 2006a; Hemilä 2006b). Even though direct extrapolation of findings from vitamin E studies to vitamin C are unjustified, 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.

How the intervention might work

The major role of vitamin C in the immune system seems to be as a physiological antioxidant, protecting host cells against oxidative stress caused by infections. Its concentration in phagocytes and lymphocytes is very high. In various experimental settings vitamin C increased the functioning of phagocytes, the proliferation of T-lymphocytes and the production of interferon; and decreased replication of viruses (Beisel 1982; Hemilä 1997a; Hemilä 2003; Thomas 1978; Webb 2007).

Approximately 10 mg/day of vitamin C prevents scurvy but the safe dose range extends to grams per day. In the US nutritional recommendations, the 'tolerable upper intake level' is stated to be 2 g/day for adults. The basis for this upper limit is the appearance of diarrhoea (IOM 2000) which is, however, a trivial adverse effect that disappears quickly with a reduction in intake. Furthermore, it has been stated that patients with pneumonia can take 100 g/day of vitamin C without developing diarrhoea, possibly because of the changes in vitamin C metabolism (Cathcart 1981).

Why it is important to do this review

Pneumonia is a fairly common and severe infection and vitamin C is a safe and inexpensive essential nutrient. The possibility that vitamin C might affect susceptibility to pneumonia, even in restricted population groups, is worthy of examination. Similarly, the possibility that vitamin C treatment might affect the duration or severity of pneumonia, or both, is worthy of systematic consideration. One previous meta-analysis assessed the preventive effects of vitamin C on pneumonia (Hemilä 1997c) but the therapeutic effect on pneumonia has not so far been assessed systematically.

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/CP/.

OBJECTIVES

To analyse evidence regarding the effect of vitamin C supplementation on preventing and treating pneumonia.

METHODS

Criteria for considering studies for this review

Types of studies

For preventive trials of vitamin C supplementation we used controlled trials. The use of placebo was not required as it seems unlikely that being aware or not of taking vitamin C would affect the occurrence of a severe infection. Also, since a recent meta-analysis of trials comparing a placebo group with a no treatment group found no evidence of a placebo effect on binary outcomes (Hrobjartsson 2001; Hrobjartsson 2010), there is no empirical evidence indicating that the placebo effect might affect the occurrence of pneumonia.

For treatment trials of vitamin C on the severity and duration of pneumonia we used placebo-controlled trials since the outcome (for example, severity) may be affected by the awareness of the treatment by the patients. Also, the recent meta-analysis of trials comparing a placebo group with a no treatment group found evidence of a placebo effect in trials focusing on pain (Hrobjartsson 2001; Hrobjartsson 2010). A placebo control may, therefore, be crucial for the validity of treatment observations.

Types of participants

For prevention trials there was no age restriction in the participants.

For treatment trials we restricted trials to participants with pneumonia (both community-acquired and nosocomial pneumonia) with no age restrictions.

Types of interventions

Administration of vitamin C (ascorbic acid or its salts) to one trial group, either orally or intravenously. There were no restrictions on the dosage and frequency of administration of vitamin C and treatment trials with a single dose were also included. We excluded trials in which vitamin C was administered along with other substances, such as other vitamins.

Types of outcome measures

Primary outcomes

1. In assessing the preventive effect of vitamin C, the primary outcome was the occurrence of pneumonia during vitamin C supplementation.
2. In assessing the treatment effect of vitamin C, the primary outcomes of interest were the duration and severity of pneumonic episode, duration of hospital stay and death caused by pneumonia.

For our review pneumonia was defined operationally as the disease that the original trial authors classified as pneumonia. The basis of the diagnosis by the original authors is described in the 'Description of studies' section. We did not require that the pneumonia diagnosis was based on chest X-radiography (CXR) but we also accepted a clinical diagnosis of pneumonia (see Appendix 1 for details).

Secondary outcomes

We classified laboratory findings, such as C-reactive protein or erythrocyte sedimentation rate, as secondary outcomes. CXR changes and body temperature changes during treatment are classified as secondary outcomes.

Search methods for identification of studies

Electronic searches

For this 2011 update we searched the Cochrane Central Register of Controlled Trials (CENTRAL 2011, Issue 1) which contains the Acute Respiratory Infections Group's Specialised Register, MEDLINE (1950 to January week 4, 2011), EMBASE (1974 to February 2011) and Web of Science (1945 to February 2011). Details of the previous search are in Appendix 2.

We searched CENTRAL and MEDLINE using the following search strategy. We did not use a filter to identify randomised trials as there were too few results. We adapted the search for EMBASE (Appendix 3) and Web of Science (Appendix 4).

1 exp Pneumonia/
2 pneumon*.tw.
3 bronchopneumon*.tw.
4 exp Bronchitis/
5 bronchit*.tw.
6 or/1-5
7 exp Ascorbic Acid/
8 l-ascorb*.tw,nm.
9 ascorb*.tw,nm.
10 vitamin c.tw,nm.
11 vit c.tw,nm.
12 or/7-11
13 6 and 12

Searching other resources

Previously, Briggs 1984 carried out extensive searches of the literature and published a bibliography containing 413 references to papers related to vitamin C and infections. We perused the Briggs bibliography and other pertinent reviews and publications along

with the results of the database searches. Although our systematic review is focused on controlled trials, we also collected observational studies and trials of vitamin mixtures containing vitamin C. These were considered in the Discussion section if they were pertinent to the review. There were no language restrictions in the literature searches.

Data collection and analysis

Selection of studies

The contact author (HH) searched the literature and both review authors (HH, PL) independently assessed the extracted titles and abstracts to identify potentially relevant articles. We excluded trials failing to meet the inclusion criteria. When we disagreed on the relevance of an article, we discussed it until we reached a consensus.

Data extraction and management

Both review authors (HH, PL) independently extracted relevant data from the articles selected. When we differed in the interpretation of study findings we sought a consensus.

Assessment of risk of bias in included studies

We recorded the following quality features of the trials: allocation concealment, blinding, proportion of drop-outs and other relevant features that may limit the validity of the trial. We did not calculate any quality scores for the selected trials since "quality scores are at best useless and at worst misleading" (Greenland 1994). We agree with the Shapiro 1997 comment that quality is best evaluated qualitatively. The *Cochrane Handbook for Systematic Reviews of Interventions* also states that "The use of scales for assessing quality or risk of bias is explicitly discouraged in Cochrane reviews" (Higgins 2011).

Measures of treatment effect

We planned to calculate risk ratios (RR) for dichotomous outcome variables. However, in the identified prophylactic trials the number of pneumonia cases in the vitamin C groups was very low (zero to two cases) and, therefore, we decided to use the Peto method for calculating the odds ratio (OR), which does not need corrections for zero cell counts (Higgins 2011). Also, with only a few cases observed in the trial groups, the mid-P value is the most appropriate method to calculate the P values for the differences in the treatment groups (Hemilä 2006a) and was used when comparing groups with small numbers of cases. We used two-tailed P values in this review.

Unit of analysis issues

The Glazebrook 1942 study reported the number of pneumonia cases per seven administrative groups of the school. Thus, the unit of analysis is the group of schoolchildren in the administrative division. Glazebrook describes that "The youths of one division worked as a unit, and occupied certain tables in the dining hall. To some extent each division occupied particular dormitories, but this separation was not absolute, and there was a fair amount of mixing of divisions in the sleeping quarters. Sleeping and feeding conditions were, of course, the same for all divisions. Careful records had been kept of the incidence of all infections for 1½ years before the observations described here were begun. In the preceding year there had been an epidemic of tonsillitis, which had affected all the divisions uniformly, so that they could not be regarded as separate units within the larger population." Therefore, we consider that the schoolboys had a similar risk of pneumonia in each division and we carried out our primary analysis by the vitamin C and no vitamin C groups. However, as a sensitivity analysis, we also analysed the data by administrative units (see Results).
Other studies included in our analyses do not have unit of analysis concerns.

Dealing with missing data

None of the trials had missing data that we needed to impute.

Assessment of heterogeneity

We assessed the heterogeneity of a trial in the same analysis by using the I^2 statistic (Higgins 2003). This examines the percentage of total variation across studies that is due to heterogeneity rather than chance. A value of I^2 statistic greater than about 70% indicates a high level of heterogeneity. We also used the Chi^2 test to calculate the probability that the observed heterogeneity was caused by chance.

Assessment of reporting biases

We did not construct funnel plots as we do not consider them to be a useful tool when deciding whether there is publication bias or not (Ioannidis 2007; Lau 2006).

Data synthesis

We planned that if a number of trials were available with sufficient uniformity in settings and outcome definitions, we would pool the data; but, if the trials were heterogeneous, either statistically or clinically, we would present them separately. There is no statistical heterogeneity in Analysis 1.1 but the studies are clinically so divergent that we considered pooling was inappropriate.

Subgroup analysis and investigation of heterogeneity

We included both community-acquired and nosocomial pneumonia in this review. However, due to their substantial clinical differences, we planned to analyse them separately. We did not identify any trials on nosocomial pneumonia.

We did not use poor descriptions of the definition of pneumonia as a basis to exclude a trial from the review. However, we planned to carry out subgroup analyses based on the rigour of our outcome definition (CXR or not) and on the level of blinding of outcome assessments. Given the trials we identified, this did not differ from the sensitivity analysis based on the methodological quality of the trials.

We did not set limits on the vitamin C doses for the inclusion of trials but we planned to carry out subgroup analyses based on dosage. In the preventive trials, we decided to set the limit of subgroup analysis to 100 mg/day, since it is close to the dosage leading to maximum vitamin C plasma levels in healthy people. In the treatment trials, we decided to set the limit of subgroup analysis to 1000 mg/day, since there is evidence of changes in vitamin C metabolism in infections and larger doses might, therefore, be needed for significant effects. We did not find suitable variation in the doses that would make subgroup analysis by dose reasonable, except in the within-study variation in the Mochalkin 1970 trial (Table 1).

Sensitivity analysis

Two of the identified trials were double-blind, placebo-controlled, randomised controlled trials (RCTs) (Hunt 1994; Pitt 1979) whereas three studies were methodologically less satisfactory (Glazebrook 1942; Kimbarowski 1967; Mochalkin 1970). We carried out sensitivity analysis by excluding the latter three methodologically poorer quality trials.

Glazebrook 1942 had a unit of observation of an administrative group in a boarding school. We analysed their data assuming a similar risk for each participant in each administrative unit, but as a sensitivity analysis we also analysed their data by the administrative groups.

RESULTS

Description of studies

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

Results of the search

We identified no new trials for inclusion in the 2011 update searches (out of 99 records recovered). The MEDLINE search in 2009 retrieved 86 publications; the EMBASE search retrieved 308; the Web of Science search 67; and the CENTRAL search 13 publications. From these search results we found three controlled trials which provided data pertinent to the prevention of pneumonia with vitamin C supplementation and two trials which provided data on the therapeutic effect of vitamin C.

The main features of the included trials are summarised in the 'Characteristics of included studies' table. The methods are described here in more detail, largely using direct excerpts of the original papers as these show the strengths and weaknesses of the trials in the words of the original trial authors.

Included studies

The Glazebrook 1942 trial was the oldest trial identified. The structure of the paper is quite different from more modern trial reports: "In a large training school under our observation there were some 1500 youths aged 15-20 years. For the most part they were drawn from the lower wage-earning classes . . . The food distribution [at the school] was badly managed. . . Often 8 hr. elapsed between the time the food was cooked and its arrival on the dining tables . . .The total intake of vitamin C varied from about 10 to 15 mg per student per day" (pages 4 to 5). "Pure ascorbic acid powder was added to . . . the morning cocoa, and an evening glass of milk. The mixing was done in bulk in the kitchens before issue. The powder dissolved quickly and easily, and did not alter the appearance or taste of the vehicle" (page 7). We consider that the trial corresponds functionally to a placebo-controlled trial because the participants were unable to identify the treatment, although no inactive powder was added to the food of the control group. "The establishment was divided into seven groups or divisions for administrative purposes. The youths of one division worked as a unit, and occupied certain tables in the dining hall. To some extent each division occupied particular dormitories, but this separation was not absolute, and there was a fair amount of mixing of divisions in the sleeping quarters. Sleeping and feeding conditions were, of course, the same for all divisions. Careful records had been kept of the incidence of all infections for 1½ years before the observations described here were begun. In the preceding year there had been an epidemic of tonsillitis, which had affected all the divisions uniformly, so that they could not be regarded as separate units within the larger populations" (page 12). "The observations were made by supplying vitamin C in the form of pure ascorbic acid to one or more divisions. This was considered to be the only practical method of carrying out the observations without introducing unnecessary complications. For example, it was not possible to choose boys at random as it would have been impossible to supply them with vitamin C-treated cocoa or milk in the dining room. With the method actually chosen, all that was necessary was to add vitamin C to the supplies of cocoa or milk serving the tables for the appropriate divisions" (page 12). "Moreover, all of the divisions had a population more or less the same as regards duration

of stay in the establishment ('institution age'). Infectious diseases were more common amongst those who had more recently joined the institution" (page 12). "When a youth felt ill he was admitted to Sick Quarters unless his complaint was very mild. . . The admission to and discharge from the hospital was not under our control " (pages 13 to 14). [As to pneumonia:] "These cases were subjected to special investigations by us (X-rays, etc.) to establish certain criteria for the diagnosis" (page 16). However, it was not stated whether the diagnosis of pneumonia was carried out by the trial authors of the paper or the physicians at the Sick Quarters. Although the method of diagnosing pneumonia was not described in detail in the paper, with the given descriptions and the severe pathological processes occurring in pneumonia it seems unlikely that vitamin C treatment would have substantially affected the diagnosis of pneumonia.

Hunt 1994 described that "The patients enrolled into this . . . study were suffering from acute bronchitis (often acute exacerbation of chronic bronchitis) or bronchopneumonia. Patients suspected or known to be suffering from lung cancer were excluded from the study, as were those who were judged by the clinician to be at high risk of death within a day or two of admission" (page 213). Thus the patients were a mixture of bronchitis and pneumonia patients, whereas in our methods section our purpose was to focus on pneumonia. However, with the soft clinical definition of pneumonia, as discussed in the 'Background' and 'Types of outcome measures' sections and the high false negative proportion in CXR versus high-resolution computed tomography (HRCT) comparison (see above), we included this trial in our analysis. Nevertheless, the wider definition of lower respiratory tract infection in this trial needs to be considered when drawing conclusions. "The patients were enrolled over a period of three years and were admitted mainly in the winter months. . . acute respiratory infection had, in all cases, been the primary reason for hospitalization" (page 213). "For consistency all clinical assessments were performed by the same Associate Specialist. Three main diagnostic features of infective respiratory conditions, namely cough, breathlessness and radiographic evidence of chest infection were used. Each was scored by the clinician according to severity. . . Then for each person, at each assessment interval, his or her three main diagnostic feature scores were added to give the 'total respiratory score'. By this procedure, the worst score that could be achieved by the most severely ill patient (whilst still alive) was 9, whilst those who were completely well with regard to the respiratory condition would score 3. A score of 10 was given for subjects who died during the trial. . . Assessments were made on admission (0 weeks) and at 2 and 4 weeks after admission. If patients were discharged from hospital as 'well' before 4 weeks, therapy was discontinued and they were assumed to remain well for up to 4 weeks, for the purpose of clinical scoring (none of the patients discharged were readmitted during their 4 week assessment period)" (page 213). "The clinical score results were approximately normally distributed..." (page 214), which allowed us to use the t-test in the comparison of the clinical score values. "After the initial clinical assessment . . . the patients commenced placebo or vitamin C therapy to which they were allocated on a randomized 'double-blind' basis. This was in addition to their normal medication" (page 213). Thus, the test of vitamin C effects was "over and above those of normal medication (mainly antibiotics and cough medicines) to which all participants were exposed" (page 217). "The vitamin C and placebo tablets were indistinguishable from each other by look or taste" (page 213). "None of the subjects who died on the trial had any secondary diagnosis, including ischaemic heart disease, and death was attributed directly to respiratory infection in each case" (page 217). At baseline, the mean plasma vitamin C level was 23.3 μmol/L and 35% patients had a vitamin C level lower than 11.4 µmol/L (page 215). After four weeks, the vitamin C level was 94.9 μmol/L (+307%) in the vitamin C group but only 24.4 μmol/L (+5%) in the placebo group (page 215).

The Kimbarowski 1967 trial was poorly described. Although published in German, an English translation is available. The main focus of the trial was to examine a chemical test, which is not relevant to the current review. However, as a secondary issue, in their report the authors reported the number of bronchopneumonia cases in vitamin C and control groups after hospitalisation. The trial authors excluded the pneumonia cases from their further study (page 2414). For this review the pneumonia cases are relevant since they occurred after vitamin C supplementation was initiated. Although the pneumonia cases occurred after hospitalisation, they occurred within a week and thus did not fall into the category of nosocomial pneumonia. "The studies were conducted with the use of soldiers almost all of whom were of the same age and received the same diet . . . The diagnosis of influenza was based mainly on the clinical pictures and epidemiological data with serological confirmation in a series of cases involving the type A virus." The geographic location where the trial was carried out, the military institution(s), the hospital in which the trial was carried out and the characteristics of the soldiers were not described. The allocation method was not described but the study arms were of closely similar size (112 versus 114 in the control and vitamin C arms, respectively, before excluding the bronchopneumonia cases) so it is possible that allocation occurred sequentially to the two trial arms. The two arms were well-balanced for severity of the influenza. The number of severe cases was 64 versus 65, moderate cases 26 versus 32, and mild cases 12 versus 14 in the two arms respectively (page 2414); the pneumonia cases were not included in these figures. A placebo was not mentioned in the paper and apparently was not used. Blinding of outcome assessment was not described. However, since pneumonia was a secondary issue in the study, the trial authors did not have reason to compare the number of pneumonia cases between the trial arms. It seems improbable, therefore, that the trial authors had substantial bias in their diagnosis of pneumonia. CXR ("Röntgenoscopie") was explicitly mentioned in the paper as a method that was used. It is probable that the diagnosis of bronchopneumonia was based on the CXR,

however, this was not explicitly stated in the paper.

The paper by Mochalkin 1970 is in Russian and a translation into English is available. The selection criteria for the participants were not described; neither were many other methodologically relevant aspects. Placebo was not mentioned and probably was not used in the control arm. However, participants in two other trial arms were administered different doses of vitamin C and the lower-dose arm was used as the reference group in the primary analysis of this review because it seems unlikely that the difference between these arms might be explained by the placebo effect. "The group of patients comprised 140 males diagnosed with acute pneumonia hospitalised during the first two days of onset of the disease [124 patients were 20 to 60 years of age, and 16 were over 60 years]. Depending on the mode of basic treatment, the patients were divided into three groups: Group I (70 patients) was treated with antibiotics without ascorbic acid (25 patients were treated with penicillin, 15 with streptomycin, 15 with penicillin and streptomycin, and 15 with tetracycline); Group II (39 patients) was treated with antibiotics combined with vitamin C (50 mg per 100,000 antibiotic units) (15, 8, 8, 8 patients in the antibiotic groups, respectively); Group III (31 patients) was treated with antibiotics combined with ascorbic acid (100 mg per 100,000 antibiotic units) (10, 7, 7, 7 patients in the antibiotic groups, respectively)" (page 18). Ascorbic acid powder was taken orally. Both antibiotics and ascorbic acid were used for 10 days . . . All patients were tested under equal conditions of placement, care, and nutrition, and were subjected to a complex therapy which included antibiotics . . . To monitor the effectiveness of the employed methods of treatment, we used the following parameters: dynamics of temperature normalisation, erythrocyte sedimentation rate, leucocyte quantity in the peripheral blood, timing of wet rattle disappearance, duration of roentgenologically-determined changes in the lungs, and the mean period of recovery" (page 18). At baseline, the mean plasma vitamin C level was 41 μmol/L. After 10 days treatment, the vitamin C level was 43 μmol/L (+7%) in the higher-dose vitamin C group but only 23 μmol/L (-44%) in the control group.

The authors of Pitt 1979 were primarily interested in the effect of vitamin C on the incidence of the common cold. However, other severe respiratory infections including pneumonia were also recorded. "The participants were male marine recruits who underwent 11 weeks of recruit training at Parris Island, South Carolina in October to December. . . Pill taking did not begin until the recruit's third week at Parris Island" (page 908). "These 862 recruits were assigned randomly to either the vitamin C or placebo group from a list of consecutive numbers randomized in pairs. Randomisation was carried out by individual recruits within each platoon" (page 908). "Of the 862 recruits who began taking the pills, 64 recruits (34, vitamin C; 30, placebo) were removed from their platoons by the US Marine Corps for further training or for discharge during the eight-week study period. An additional 123 recruits (64: vitamin C; 59: placebo) were excluded from the final analysis because they did not continue to take their pills for the eight-week study period. One additional recruit was eliminated from the vitamin C group because of recurrent urticaria related to taking the tablets" (page 909). "Before the initiation of pill taking, each recruit received adenovirus 4 and influenza vaccines and either intramuscular penicillin G benzathine or oral erythromycin estolate as streptococcal prophylaxis" (page 908). "Pill taking was supervised and observed by the drill instructors in each platoon. Neither the recruits or drill instructors nor the physicians and corpsmen who treated the recruits were aware of which pill any individual was taking" . . . "The placebo tablets were formulated from citric acid and were indistinguishable in appearance and taste from the vitamin C tablets" (page 908). "Pneumonia developed in eight recruits. . . Each of these eight recruits had typical roentgenographic and physical signs of pneumonia, although five recruits were febrile and only four recruits had elevated white blood cell counts. Pneumococci were isolated from the sputum in three recruits and seen intracellularly on Gram's stain in two other recruits. Two of these recruits also had four-fold increases in parainfluenza titers . . . Each of these recruits returned to his platoon after a mean Medical Dispensary stay of 4.4 days" (page 910). Pitt and Costrini did not estimate dietary vitamin C intake; however, their participants' mean vitamin C plasma level was rather high initially, 56 μmol/L (10 mg/L) (page 909), which would correspond to a dietary intake of 100 mg/day or more (Levine 1996). After six weeks, the vitamin C level was 77 μmol/L (+36%) in the vitamin C supplemented group and 52 μmol/L (-7%) in the placebo group (page 909).

Excluded studies

Five excluded studies are described in the 'Characteristics of excluded studies' table. Links to the trial reports and translations can be found at www.ltdk.helsinki.fi/users/hemila/CP/.

Risk of bias in included studies

Two of the trials were double-blinded, placebo-controlled RCTs without serious methodological defects and, from the descriptions, there was appropriate allocation concealment in these double-blind trials (Hunt 1994; Pitt 1979). Three other trials had methodological shortcomings of varying degrees, as described in the previous section (Glazebrook 1942; Kimbarowski 1967; Mochalkin 1970), and the possible role of these shortcomings in the interpretation of the study results is considered in the Discussion section. The risk of bias is summarised in Figure 1.

Figure 1. Risk of bias summary

Allocation

Pitt 1979 describes that marine recruits were assigned randomly to the groups from a list of consecutive numbers randomised in pairs. Randomisation was carried out by individual recruits within each platoon. Since the study was double-blind, allocation was concealed. Hunt 1994 describes that patients commenced placebo or vitamin C therapy to which they were allocated on a randomised double-blind basis, without giving further details. Since the study was double-blind, allocation was concealed. Glazebrook 1942 allocated schoolboys as administrative units of the boarding school. Thus, allocation was not concealed for the researchers, but it may have been concealed for the schoolboys since the researchers pointed out that vitamin C was added in the kitchen and it did not alter the appearance or taste of the vehicle (cocoa or milk). The number of participants in the vitamin C and placebo arms of the Kimbarowski 1967 was closely equal suggesting alternative allocation, but this is not explicitly stated. The report does not give any basis to assume allocation concealment by the researchers, while no conclusions can be drawn for the participants. Mochalkin 1970 has groups of quite different sizes indicating that it was not randomised. No description is given about the forming of the study groups.

Blinding

The Pitt 1979 and Hunt 1994 studies were double-blind. Glazebrook 1942 described that vitamin C was added in the kitchen and it did not alter the appearance or taste of the vehicle (cocoa or milk), indicating that the participants were blinded for vitamin C administration (see Included studies). Glazebrook's description further indicates that the diagnosis of pneumonia was made in the Sick Quarter by physicians who were not involved in the study so that they probably were blinded as to the treatment group (see Included studies). The level of blinding cannot be concluded for the Kimbarowski 1967 and Mochalkin 1970 trials.

Incomplete outcome data

The Glazebrook 1942 study was carried out in a boarding school and the report does not indicate that school children might have dropped out from the trial. Kimbarowski 1967 did not describe any drop-outs before pneumonia was diagnosed. Pitt 1979 described that 64 marine recruits (7.4% of the initial 862) were removed from their platoons and did not continue in the trial, but there was no difference between the study arms. An additional 123 recruits (14.3% of the initial 862) were excluded from the analysis because they did take their pills, but there was no difference between the study arms. One recruit was removed from the vitamin C group because of adverse effect. Thus, 22% of participants were not included in analysis, but there was no difference between the study arms. Hunt 1994 states that four patients were excluded because of "incomplete information" without further details and 57 remained for the analysis; the distribution of the excluded patients is not described. The Mochalkin 1970 study was carried out in a hospital in the former Soviet Union. No comment on drop-outs is given in the report, but it seems unlikely that many patients might have dropped out from the trial.

Selective reporting

Glazebrook 1942, Kimbarowski 1967 and Pitt 1979 considered pneumonia either of secondary interest or as a nuisance and therefore the findings for pneumonia were not selectively reported because of the findings. Hunt 1994 was specifically interested in the treatment of pneumonia and there are no indications in the paper that the reported outcomes would have been selected from a larger set. Mochalkin 1970 measured temperature, erythrocyte sedimentation rate, leukocyte level, time of wet rattle disappearance, time of normalisation of CXR and the mean period of recovery. All these outcomes were reported.

Other potential sources of bias

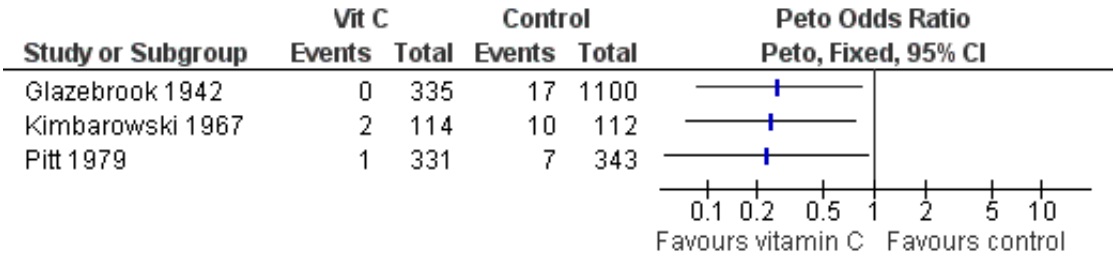
See the section Included studies above.

Effects of interventions

Preventing pneumonia

Three trials reported the number of pneumonia cases in vitamin C and control groups. All these trials found an 80% or greater decrease in the incidence of pneumonia in the vitamin C group (Analysis 1.1; Figure 2). Since the number of cases in the vitamin C groups was very low (zero to two cases in all of the trials) we used the Peto method for calculating the odds ratio (OR) as an approximation to the risk ratio (RR). The confidence intervals (CI) in the three trials were wide and overlapped substantially and there is no evidence of heterogeneity (Chi^2 test (2 df) = 0.03 and I^2 statistic = 0%) . However, the trials were clinically so heterogeneous that we did not calculate a pooled estimate of effect, because we did not consider that such a pooled estimate was meaningful. Nevertheless, all three trials tested the general question of whether vitamin C differs from placebo regarding susceptibility to pneumonia.

Figure 2. The prophylactic effect of vitamin C against pneumonia



The Peto OR method is suitable for calculating an estimate of OR and its CI. However, with only a few observed cases, the mid-P value was the more appropriate method to compare the study groups. In each of the three prophylactic trials, the mid-P value (2-t) for the comparison of trial arms was below 0.05 and the combined mid-P value (2-t) for the three trials was 0.00004 (Hemilä 1997c), indicating that the differences between the vitamin C and control arms in these three trials were unlikely to be explained by random variation.

Subgroup analysis by vitamin C dosage of less or more than 100 mg/day did not reveal any effect of the dose; however, the trials were clinically so heterogeneous and the number of cases so low so that we could not make any conclusions about dose-dependency.

All three trials mentioned the usage of the chest radiograph (CXR) but none of them provided a well-defined case definition of pneumonia. Thus we did not carry out a subgroup analysis by use of a CXR for diagnosis.

We carried out sensitivity analysis in this set of prophylactic trials by excluding trials that did not use randomisation and placebo. This left Pitt 1979 as the only trial with high quality methodology. Nevertheless, the findings of the Pitt 1979 trial did not meaningfully differ from the other two trials. As noted above, the trials were clinically heterogeneous and we do not expect the same treatment effect in such variable conditions; however, there was no evident trend for the most positive findings to occur in methodologically less satisfactory trials.

In the Glazebrook 1942 trial, allocation to treatment groups was carried out by institute 'divisions' and not on the basis of individual boys. Therefore, we also analysed the Glazebrook 1942 trial using the 'division' as the unit of observation. Distribution of pneumonia cases in the five control divisions was 5, 3, 2, 4 and 3 (mean 3.4 cases per division) and in the two vitamin C divisions it was 0 and 0. We assumed that the mean of the control divisions was a suitable estimate for the Poisson distribution mean and used that assumption as a basis for statistical analysis. The size of the individual divisions was not stated in the paper but the two vitamin C divisions had on average 167 boys (335/2) and the five control divisions 220 boys (1100/5), thus the size of the vitamin C divisions was 0.76 times the size of the control divisions. We adjusted the mean incidence by this ratio, so that we expected 2.6 pneumonia cases per vitamin C division, assuming the same incidence as for the control divisions. With this Poisson mean, we calculated the probability that there was no case of pneumonia in one vitamin C division as P value = 0.074 and no case in two separate vitamin C divisions as having a P value = 0.006. Accordingly, using a 'division' as the unit of observation also revealed a significant difference between the vitamin C and control groups.

Treating pneumonia

Two trials examined the effect of vitamin C on patients with pneumonia (Mochalkin 1970), or pneumonia and bronchitis (Hunt 1994).

Hunt 1994 found 85% lower mortality in the vitamin C group compared with the placebo group, but this comparison was based on six cases only (Analysis 2.1). For this difference, the mid-P value = 0.12. In addition, Hunt examined the change in total respiratory score at four weeks and these data are presented in Table 2. There was statistically marginal significance of overall benefit on the respiratory score with vitamin C, but in a subgroup analysis based on the baseline severity of disease, the benefit was restricted to patients who were most severely ill when admitted to the hospital. These most severely ill patients had substantially lower vitamin C plasma levels compared with the less ill patients. In the less ill patients, there was no difference between the trial arms (Table 2). In their report, Hunt 1994 published the scores for all participants and for the most severely ill patients; for this review we calculated the scores for the less ill patients (see Table 2).

Mochalkin 1970 had three trial arms: control, low vitamin C and high vitamin C. The control arm was not administered a placebo and, therefore, we restricted our primary analysis to the comparison of the two vitamin C arms (Analysis 2.2). Their protocol meant that the mean vitamin C dose of the higher-dose arm was exactly double that of the lower-dose arm, although the dosage ranges within both vitamin C arms varied and overlapped (see 'Characteristics of included studies'). There was a statistically highly significant decrease in length of hospital stay in the higher

vitamin C dose arm compared with the lower-dose arm.

As a secondary analysis we present the results of the three arms of the Mochalkin 1970 trial in Table 1. Mochalkin reported the proportion of participants with no fever after seven days and with normalisation of the CXR in 10 days. For both outcomes, the vitamin C arms fared significantly better than the control arm. The number needed to treat (NNT) was around five for these two outcomes compared to the control group (Table 1).

We had planned a subgroup analysis of therapeutic trials by vitamin C dosage less and more than 1 g/day. Hunt 1994 used only 0.2 g/day. One of the Mochalkin 1970 arms was lower than the limit, but the other arm had a range over the limit and the planned subgroup analysis was thus not possible. However, the Mochalkin 1970 results suggest dose-dependency (Table 1). The duration of recovery was reduced from 23.7 days in the control group by 4.6 days (19%) in the low-dose vitamin C arm and by 8.6 days (36%) in the high-dose vitamin C arm. Since the mean vitamin C dose in the high vitamin C arm was exactly twice the mean of the lower vitamin C arm, the linearity in this response is striking (Table 1).

Sensitivity analysis based on the rejection of trials which were not randomised, left the Hunt 1994 trial as the only trial with high quality methodology. Thus, here too there was no evident trend to suggest that positive findings might be simply explained by methodological shortcomings of the trials.

Both therapeutic trials used CXR when evaluating patients, but neither provided a well-defined case definition of pneumonia; nor of lower respiratory tract infection in the Hunt 1994 trial. Mochalkin 1970 used normalisation of CXR as one of their outcomes, which implies that changes in CXR were included in their criteria to define pneumonia.

DISCUSSION

Summary of main results

We identified three prophylactic trials which recorded 37 cases of pneumonia in 2335 people and two therapeutic trials involving 197 pneumonia patients. All of these studies found benefit of vitamin C. One prophylactic and one therapeutic trial were satisfactorily randomised, double-blind and placebo-controlled and thus the benefits were not restricted to methodologically less satisfactory trials. However, the five trials were all carried out under conditions that are far from the ordinary life of people living in Western countries. Thus, even though the studies suggest a biological effect of vitamin C, no direct extrapolations should be made for the general population. None of the trials reported noteworthy adverse effects of vitamin C, and there is much additional literature indicating that vitamin C is safe (see section on Safety below).

Overall completeness and applicability of evidence

Although we consider that the findings of the analysed pneumonia trials are reliable, we understand that great caution is required in the interpretation of the findings because of various biological factors, for example, vitamin C amounts in the diet and the kind of participants used in the trials.

Both Pitt 1979 and Kimbarowski 1967 examined soldiers who had substantially dissimilar living conditions compared with ordinary adults. Furthermore, Kimbarowski's soldiers were hospitalised because of influenza A, making them a very special group of people. Glazebrook 1942 studied teenage boys in a UK boarding school during World War II. The age range of Hunt 1994 patients was from 66 to 94 years, obviously restricting any generalisations towards young people. Mochalkin 1970 included a wide age range of participants, but their social and nutritional backgrounds were not described in the paper.

An important feature related to the patient selection in the prevention trials was the very high incidence of pneumonia. Glazebrook 1942 and Pitt 1979 recorded 60 and 120 cases of pneumonia per 1000 person-years in their control arms, respectively, and Kimbarowski 1967 reported that 10% of their control arm became sick with pneumonia within one week after hospitalisation. In contrast, in the ordinary middle-aged Western population, the incidence of pneumonia is one to three per 1000 person-years (Baik 2000; Hemilä 2004). Thus, the high incidence of pneumonia makes the conditions of the prevention trials very special and limits generalisations of their results.

A further issue of great importance is the level of vitamin C intake, in diet and in supplements. A different outcome between vitamin C and control arms may result from a very low dietary intake in the control arm ('marginal vitamin C deficiency') or from the high-dose supplementation in the vitamin C arm. In the former case, a small dosage of supplement might produce a similar effect, whereas in the latter case the large dose is essential. As reference levels, scurvy may be caused by vitamin C intakes less than 10 mg/day, whereas the mean vitamin C intake in the USA is about 100 mg/day (IOM 2000).

Glazebrook 1942 estimated that their participants got only 10 to 15 mg/day of vitamin C in their diet, so that the baseline intake was close to scurvy levels. Kimbarowski 1967 and Mochalkin 1970 carried out their studies in the former Soviet Union and it seems highly unlikely that their diet was rich in vitamin C. Hunt 1994 reported overall low plasma levels of vitamin C, and the benefit of vitamin C was restricted to patients who had particularly low vitamin C levels (Table 2). Thus, in these trials the benefit of vitamin C supplementation may be explained by treating 'marginal vitamin C deficiency'. A similar proposal, emphasising the low dietary intake levels, was also made to explain the reduction in common cold incidence in a set of trials with UK males by vitamin C (Hemilä 1997b).

However, the explanation based on 'marginal deficiency' is not

applicable to the Pitt 1979 trial, which reported high baseline vitamin C levels. In the Pitt trial, the baseline plasma vitamin C level was 56 μmol/L, which corresponds to a dietary intake of 100 mg/day or more (Levine 1996). In contrast, in the more ill patients of Hunt 1994 the baseline vitamin C level was only 19.9 μmol/L, and in the Mochalkin 1970 trial plasma vitamin C level dropped to 23 μmol/L in the control group. Thus, it seems that low dietary vitamin C intake may not explain the findings in the Pitt 1979 trial. This trial used the highest vitamin C dose: 2 g/day. Participants of the Pitt 1979 trial were marine recruits in a training camp, that is under particularly stressful conditions. It is also worth noting that vitamin E, a lipid-soluble antioxidant which interacts with vitamin C, reduced the incidence of pneumonia by half in male smokers who carried out leisurely exercise (Hemilä 2006b) and vitamin C reduced the risk of common cold in six trials with participants under heavy acute physical stress (Hemilä 1996; Hemilä 2010). Thus, it is possible that the particularly hard training of the military recruits of the Pitt 1979 trial is the reason why the high-dose vitamin C supplementation was beneficial for some of their participants.

The explanation of 'marginal deficiency' is also not applicable to the comparison of the two vitamin C arms of the Mochalkin 1970 trial. Although the Hunt 1994 trial found a benefit of vitamin C supplementation only in the most ill patients who concurrently had low plasma vitamin C levels (Table 2), the Mochalkin 1970 trial found dose-dependency, indicating that the therapeutic effect of vitamin C supplementation was not limited to treating 'marginal deficiency' (Table 1). An indication of dose-dependency up to 6 g/day of vitamin C was also found in a common cold trial by Karlowski 1975 (see also Hemilä 1996; Hemilä 2006a).

Hunt 1994 combined the cases of acute bronchitis and pneumonia together. In young people, acute bronchitis usually has a viral aetiology, whereas the majority of pneumonia cases are caused by bacteria. However, Hunt 1994 patients were all over 60 years of age and their acute bronchitis was "often acute exacerbation of chronic bronchitis", implying bacterial aetiology. The clinical definition of pneumonia is soft and chest X-ray (CXR) has a substantial proportion of false negatives. For such reasons the combined outcome used in the Hunt 1994 trial was appropriate in the current review.

Quality of the evidence

We identified three trials that reported on the preventive effect of vitamin C against pneumonia, and two trials that reported on the therapeutic effect of vitamin C on patients with pneumonia. Each of these trials found a statistically significant benefit of vitamin C supplementation on at least one clinically relevant outcome. Two of the trials were placebo-controlled, randomised trials, whereas the other three trials were technically deficient to varying degrees. Here we considered whether potential biases could explain the differences between the vitamin C and control groups.

The concept of publication bias is based on an assumption that researchers tend to report a study if the result is 'positive' and tend to leave it unreported if the result is 'negative'. With this reasoning, it might be possible that the five trials analysed in this review were published just because of the significant benefit of vitamin C, whereas there might be several trials unpublished because of their negative results. However, the three papers reporting on the prophylactic effect of vitamin C were published separate to the effect of vitamin C on pneumonia; the benefit on pneumonia not being the motive for publication. Glazebrook 1942 was mainly interested in the common cold and tonsillitis and the effect on pneumonia was mentioned as a secondary issue, indicating that this finding was not the reason for publication. Kimbarowski 1967 considered pneumonia as a nuisance in their trial as they focused on a chemical test. They did not pay any attention to the substantial difference in the occurrence of pneumonia in the trial arms and, for example, in their summary the pneumonia cases in both trial arms were combined. Pitt 1979 focused on the common cold, and pneumonia was a secondary outcome which was reported in the text but not in the abstract. Thus these three reports are inconsistent with publication bias as an explanation for the set of positive reports. This explanation with regard to the background of the investigators is also relevant when considering detection bias (see below).

In the case of the therapeutic trials by Hunt and Mochalkin, there were biological consistencies which are not easily explained by pure chance. Hunt 1994 found that the benefit was limited to the patients with the lowest vitamin C levels, which is biologically reasonable (Table 2). Mochalkin 1970 found a linear dose-response relation in the two vitamin C arms compared with the control group (Table 1). Neither Hunt nor Mochalkin paid proper attention to these findings and thus they were not likely to be the basis for publication. Furthermore, speculation on a large number of unpublished trials to explain positive reported findings is not science in the Popperian sense as such a hypothesis cannot be refuted. Thus, we do not consider publication bias as a reasonable explanation for the reported positive findings in the published prophylactic and therapeutic trials.

Selection bias means that there are systematic differences in the compared groups at baseline. In therapeutic trials, the severity of disease is a factor of obvious importance. The Hunt 1994 trial was randomised and allocation was concealed. The distribution of 'acute bronchitis' and 'bronchopneumonia' and the proportion of 'most severely ill' were closely similar in the treatment arms. Mochalkin 1970 did not describe the distribution of pneumonia severity, but antibiotic treatments were distributed evenly in the three arms, so that if the selection of antibiotics depended on the clinical symptoms they were also divided evenly.

In prophylactic trials, there is a lower possibility of bias caused by baseline differences between the treatment arms. Maldistribution of a strong risk factor, such as smoking in a study of lung cancer, may however lead to erroneous conclusions. Cohort studies have

not identified strong risk factors for community-acquired pneumonia, with the age of the person being most important (Baik 2000; Hemilä 2004). Thus, to explain an 80% or greater reduction in the incidence of pneumonia in the vitamin C arms (Analysis 1.1) would require that there is a strong risk factor that is spectacularly maldistributed. Furthermore, the Pitt 1979 trial was randomised and double-blind, and Glazebrook 1942 used pre-formed divisions and explicitly considered that the groups of schoolboys were similar. In the Kimbarowski 1967 trial, the severity of influenza probably was the most important risk factor for the occurrence of pneumonia, but it was distributed evenly in the trial arms. Thus, it seems unlikely that systematic baseline differences between the trial arms would explain the benefits observed in the vitamin C arms.

Performance bias means systematic differences in the care provided, apart from the intervention being evaluated. The Hunt 1994 and Pitt 1979 trials were double-blinded. According to the Glazebrook 1942 description, the boys in different divisions were treated equally. Kimbarowski 1967 stated that the participants received the same diet, but otherwise the similarity of other treatments was not mentioned. Mochalkin 1970 stated that all patients were tested under equal conditions of placement, care and nutrition and the use of antibiotics was similar in the treatment arms. Although Mochalkin did not use a placebo in the control group, the placebo effect does not explain the difference between the two vitamin C arms (Analysis 2.2 and Table 1). Furthermore, with the significant difference in the duration of pneumonia in the two vitamin C groups, it is not reasonable to assume that the difference between the control group and the low-dose vitamin C group might be caused by the placebo effect alone. Such an explanation would presuppose that there is a threshold dose so that vitamin C has no effects at lower doses; only at higher doses. Such a dose-response model would be opposite to the findings of many studies indicating that the benefits are more pronounced in the low-dose region (see below comments on 'marginal vitamin C deficiency'). Thus, in two trials there was good evidence that participants were treated equally, except for the vitamin C supplementation, and in the other trials there was no explicit reason to assume that the other treatments would substantially differ between the trial arms.

Attrition bias means high or divergent drop-out proportions and does not seem to be a substantial concern in these five trials. The three trials examining the preventive effect of vitamin C were carried out within military organisations or in a boarding school. The background and descriptions in the papers did not suggest a considerable drop-out problem. Pitt 1979 stated that 22% of the initial population were removed from their platoons or did not continue to take their pills, and were not included in the final analysis, but the drop-outs were distributed evenly in the treatment arms. Hunt 1994 followed up the patients for four weeks and did not report any drop-outs. Mochalkin 1970 did not comment on drop-outs, but the distribution of antibiotic usage was even in the trial arms, which would seem to exclude any drop-outs.

Detection bias means systematic differences in outcome assessment. The Hunt 1994 and Pitt 1979 trials were double-blinded and, therefore, bias caused by the knowledge of participants or investigators was unlikely to have affected the outcome assessment. As noted above, in the Glazebrook 1942, Kimbarowski 1967 and Pitt 1979 trials, pneumonia was a secondary issue and it is unlikely that under such conditions the investigators would have any tendency to diagnose pneumonia differently in the trial arms. The Mochalkin 1970 report did not allow any direct or indirect conclusions on the possibility of detection bias.

Thus, two of the pneumonia trials were placebo-controlled, double-blind randomised controlled trials. Even though the three other trials were methodologically less satisfactory in comparison with modern trial standards, the positive findings of these latter three trials are not easily explained by biases.

Potential biases in the review process

Our search of databases for trials meeting the criteria for our review was exhaustive but we also read reference lists of several reviews, such as Briggs 1984, which contained 413 references to papers related to vitamin C and infections. Although there might be some unpublished trials or trials published in very difficult to reach journals or books, it seems unlikely that we could have missed major controlled trials.

Agreements and disagreements with other studies or reviews

Although the proponents of evidence-based medicine argue that "if you find that the study was not randomised, we'd suggest that you stop reading it and go on to the next article" (Sackett 1997) we consider that cohort studies can give an important perspective to the possible prophylactic effects of higher vitamin C intake.

A recent cohort study found no association between vitamin C intake and community-acquired pneumonia in middle-aged men in the USA (Merchant 2004). There are, however, substantial differences between this cohort study and the three prophylactic trials of the Analysis 1.1. Merchant 2004 investigated male US health professionals of 40 to 75 years of age, the selection of which meant a population with a much greater than average interest in factors that affect health and whose working conditions are quite sedentary. In Merchant's cohort, the median vitamin C intake of the lowest quintile was 95 mg/day (overall median 218 mg/day), whereas the overall median of the ordinary US population is about 100 mg/day (IOM 2000). Thus the range of vitamin C intake in Merchant's cohort was substantially higher than in the three prophylactic trials analysed in this review, and the living conditions were very different compared with the three trials. Furthermore, Merchant 2004 recorded three pneumonia cases per 1000 person-years. Thus, even though the Merchant cohort study indicated

that the level of vitamin C intake did not affect the risk of pneumonia in sedentary, health-conscious, middle-aged populations when the intake range started from 100 mg/day, their findings cannot be extrapolated to substantially different population groups such as those in the trials analysed in the current review. Nevertheless, the Merchant cohort study gives certain explicit limits to putative generalisations of the analysed trials. Thus, we consider that biological differences, rather than methodological differences, are the most appropriate explanations for the divergence in the role of vitamin C in the Merchant cohort study and the intervention trials in Analysis 1.1.

Also, some further trials are relevant to the current topic. Dahlberg 1944 reported respiratory infections more severe than the common cold in military recruits (five in the vitamin C, 10 in the control group of the same size; RR 0.5; 95% CI 0.2 to 1.5), but their outcome included otitis and sinusitis and not just lower respiratory infections. Nathens 2002 reported that in critically ill surgical patients vitamin C and E combination had no effect on pneumonia risk (RR 0.79; 95% CI 0.53 to 1.20); however, patients in the vitamin C and E group required 0.9 days (95% CI 0.6 to 1.2 days) less mechanical ventilatory support and had a 1.2 day (95% CI 0.81 to 1.5 days) reduction in their intensive care unit (ICU) length of stay, indicating benefits of antioxidant supplementation. However, the role of vitamin C per se is ambiguous and the benefit was for an outcome not directly linked to infection, even though a longer ICU stay is associated with a greater risk of pneumonia. Mahalanabis 2006 reported that 400 mg vitamin E and 200 mg vitamin C per day had no therapeutic effect on 2 to 35-month old children with severe acute lower respiratory infection; however, the vitamin E dose was very high for children of this age and the study did not allow any specific conclusions on the possible role of vitamin C.

Safety of vitamin C

Pitt 1979 administered 2 g/day of vitamin C to 331 participants for two months. None of the reported symptoms that participants thought to be caused by the pills were statistically more frequent in the vitamin C than in the placebo arm. Urticaria developed in one recruit in the vitamin C arm which subsided when the pills were withheld and recurred when he resumed taking his pills. He was instructed to stop taking pills and was excluded from the final analysis. The other trials used lower vitamin C doses and were much less informative on the safety of high doses.

In general, vitamin C is considered safe in doses up to several grams per day and although there have been speculations of potential harms of large doses they have been shown to be unfounded (Hathcock 2005; 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). Cathcart 1981 reported that he had administered orally over 100 g per day of vitamin C to pneumonia patients, which indicated safety of such high doses for pneumonia patients, although such an uncontrolled observation does not provide evidence of benefit. There are few reports of severe harm caused by high-dose vitamin C administration and 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 (G-6-PD) deficiency (Campbell 1975).

Mechanism of effect

Our review is largely based on the concept that vitamin C affects the immune system and thereby protects against infections in animals (Hemilä 2006a). Such effects on the immune system are plausible explanations for the benefits observed in the prophylactic trials (Analysis 1.1). However, vitamin C also has non-immune effects that might be relevant in therapeutic trials.

Vitamin C participates in the synthesis of norepinephrine and a series of neuropeptides (Rice 2000) and carnitine which participates in energy metabolism (Hughes 1988; Jones 1982). In a study of experimentally-induced vitamin C deficiency, Kinsman 1971 compared the state with high and low levels of vitamin C in whole blood, 93 μmol/L and 25 μmol/L, and found that "scores in the neurotic triad of the Minnesota Multiphasic Personality Inventory (the hypochondriasis, depression and hysteria scales) became elevated as deficiency of vitamin C progressed". Therefore, it is possible that in a therapeutic setting the effects of vitamin C supplementation are not limited to the immune system. Vitamin C levels in whole blood are higher than plasma levels, and thus Kinsman's levels cannot be directly compared with the low plasma levels reported by Hunt 1994 and Mochalkin 1970. Still, low vitamin C levels might cause psychological symptoms, for which vitamin C supplementation might be beneficial. Some of the early case reports of pneumonia patients described particularly rapid benefits of vitamin C (Bohnholtzer 1937; Dalton 1962; Hochwald 1937; Klenner 1948) and such rapid benefits might be caused by non-immunological effects of vitamin C, rather than by immunological mechanisms. Consistent with the concept that vitamin C might have an influence on general well-being, a recent study reported that vitamin C administration improved the mood of acutely hospitalised patients (Zhang 2011). It is noteworthy that in the Mochalkin 1970 trial the vitamin C level dropped by 44% in 10 days in the control group (Table 1), consistent with other studies that have found reductions in vitamin C levels with infections (Hemilä 2006a). Neither Hunt 1994 nor Mochalkin 1970 measured any index of general well-being or psychological status.

Conclusions

The incidence of pneumonia is low in the middle-aged in the Western countries; one to three per 1000 person-years (Baik 2000; Hemilä 2004) and there is no rationale to study the prophylactic effect of vitamin C in such a population. Even if vitamin C did have an effect, the low baseline incidence would lead to very high number needed to treat (NNT) values. Also, the Merchant 2004 cohort study suggests that vitamin C intake level has no association with pneumonia risk in well-nourished, middle-aged people.

Certain populations have a high risk of pneumonia. In low-income countries the incidence of lower respiratory tract infection in children has, at the upper extreme, been over 1000 cases per 1000 person-years (Selwyn 1990). Also, in many low-income countries prevalence of malnutrition is high, indicating low vitamin C intakes. Another population group with an elevated risk of pneumonia is elderly people, since the incidence increases with age (Baik 2000; Hemilä 2004). A further population group with high risk of pneumonia is military recruits; the average incidence of pneumonia in marine and naval recruits in the 1970s was 60 per 1000 person-years in a US study (Pazzaglia 1983).

The prophylactic effects of vitamin C should be investigated in such populations with a high incidence of pneumonia. Even if the benefit of vitamin C was substantially lower than in the three prophylactic trials analysed in this review, the effect might still be important. For example, with a baseline pneumonia incidence of 60 per 1000 person years, a reduction of risk by half would correspond to a NNT of 33 over one year of such high risk.

In the USA, pneumonia is the sixth most common cause of death and the most common cause of infection-related mortality, reflecting its importance (Donowitz 2005). Various infections lead to decreased vitamin C levels in plasma, leucocytes and urine, suggesting that vitamin C supplementation might have therapeutic effects on patients with infections (Hemilä 2006a). In addition, numerous animal studies found that vitamin C supplementation reduced mortality and morbidity caused by infections (Hemilä 2006a). With this background, the two published therapeutic trials analysed in this review seem particularly important as they indicate that vitamin C supplementation might be beneficial for some groups of pneumonia patients. Furthermore, even if the benefit of vitamin C supplementation was limited to specific groups of patients, such as those with low vitamin C levels, the effect may be of wide interest given the common occurrence of this severe infection.

AUTHORS' CONCLUSIONS

Implications for practice

Vitamin C is relatively cheap and it is safe in doses of grams per day. Nevertheless, with the current evidence there is no basis for the prophylactic use of vitamin C to prevent pneumonia, because it would require continuous supplementation with poorly understood effects.

While waiting for new trials, therapeutic vitamin C supplementation may be reasonable for patients with pneumonia who have low vitamin C plasma levels, since therapeutic administration is limited in time. With the low price of vitamin C, the cost-benefit ratio may be reasonable even if the benefit might be substantially lower than that observed in the therapeutic trials analysed in this review.

Implications for research

The prophylactic use of vitamin C to prevent pneumonia should be investigated in populations who have a high incidence of pneumonia, in particular if the dietary vitamin C intake is low. This means, for example, children in low-income countries, military recruits and elderly people. In ordinary middle-aged Western populations, there is no rationale to study the prophylactic effects of vitamin C.

The study of the therapeutic effects of vitamin C on pneumonia patients is well-justified, in particular in patients with low vitamin C plasma levels but possibly also in participants with ordinary plasma vitamin C levels. The outcomes of therapeutic trials should include soft outcomes measuring well-being because vitamin C may also have non-immune effects, especially in participants with very low plasma vitamin C levels and pneumonia leads to a substantial reduction in vitamin C levels.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Glazebrook 1942

Methods	Allocation in groups Quasi-placebo control, see text Carried out in winter, duration 6 months
Participants	1435 schoolboys in a boarding school in the UK 335 boys in vitamin C divisions (n = 2) and 1100 in control divisions (n = 5) Age range 15 to 20, mean 16 years
Interventions	Vitamin C 0.05 to 0.3 g/day added to the food in the kitchen
Outcomes	Incidence of pneumonia
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Treatment groups were based on administrative divisions of boarding school, no allocation on individual level
Allocation concealment (selection bias)	High risk	Concluding from the report, allocation was not concealed from the researchers, but may have been from the school boys, although this is not explicitly stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Concluding from the report, the participants were blinded to vitamin C administration (see Included studies for details)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Concluding from the report, the diagnosis of pneumonia was made in the Sick Quarter by physicians who were not involved in the study so that they probably were blinded to the treatment group (see Included studies for details)

Hunt 1994

Methods	Randomised, placebo-controlled, double-blind trial Carried out in October to December
Participants	57 elderly patients: 27 males, 30 females, age range 66 to 94, mean 81 years (28 vitamin C; 29 placebo) Hospitalised for acute bronchitis (n = 40) or pneumonia (n = 17)
Interventions	Vitamin C 0.2 g/day Treatment for up to 4 weeks after hospitalisation
Outcomes	Mortality Change in a score of clinical symptoms in 4 weeks (scale 3 to 10 (3 = no symptoms, 10 = death))
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Reported as randomised, but no details of randomisation are described
Allocation concealment (selection bias)	Low risk	Study was double-blind so that neither participants nor researchers knew to which group the participant had been allocated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind trial
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind trial

Kimbarowski 1967

Methods	Allocation method not described, but study arms were of similar size (112 and 114 initially) Placebo not used Blinding of outcome assessment not described, see text Groups were balanced on the basis of disease severity at baseline, see text
Participants	226 soldiers hospitalised for influenza A (114 vitamin C; 112 control)
Interventions	Vitamin C 0.3 g/day
Outcomes	Incidence of bronchopneumonia after hospitalisation

Kimbarowski 1967 (*Continued*)

Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Concluding from the report, probably not randomised, but possibly groups were formed by alternative allocation (114 versus 112) though this is not explicitly stated
Allocation concealment (selection bias)	High risk	Concluding from the report, there is no reason to assume that allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Concluding from the report, there is no reason to assume that researchers were blinded to the intervention
Blinding of outcome assessment (detection bias) All outcomes	High risk	Concluding from the report, there is no reason to assume that researchers were blinded when assessing pneumonia

Mochalkin 1970

Methods	Allocation method not described Quasi-placebo control, see text Antibiotic treatments were balanced in study groups
Participants	70 in control group, 39 in low vitamin C group and 31 in high vitamin C group
Interventions	High vitamin C: vitamin C 2 mg per 2000 antibiotic units (vitamin C range: 0.5 to 1.6 g/day) Low vitamin C (used as placebo group in the primary comparison): vitamin C 1 mg per 2000 antibiotic units (vitamin C range: 0.25 to 0.8 g/day)
Outcomes	Period of recovery Duration of fever Duration of chest X-ray normalisation
Notes	Control group was not administered placebo and thus the primary analysis focuses on the high and low vitamin C groups

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Mochalkin 1970 (*Continued*)

Random sequence generation (selection bias)	High risk	Randomisation not described and groups are of such different sizes that it is unlikely they originate from randomisation
Allocation concealment (selection bias)	High risk	Concluding from the report, there is no reason to assume that allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Concluding from the report, there is no reason to assume that researchers were blinded to the intervention
Blinding of outcome assessment (detection bias) All outcomes	High risk	Concluding from the report, there is no reason to assume that researchers were blinded when assessing pneumonia

Pitt 1979

Methods	Randomised, placebo-controlled, double-blind trial Carried out in October to December, 8-week trial
Participants	674 marine recruits in a training camp in the USA (331 vitamin C; 343 placebo)
Interventions	Vitamin C 2 g/day
Outcomes	Incidence of pneumonia
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Participants were assigned randomly to the groups from a list of consecutive numbers randomised in pairs
Allocation concealment (selection bias)	Low risk	Study was double-blind so that neither participants nor researchers knew to which group the participant had been allocated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind

n = number

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

Study	Reason for exclusion
Dahlberg 1944	Military recruits in Sweden. 50 mg/day of vitamin C. The outcome is a mixture of tonsillitis, otitis, sinusitis, bronchitis and pneumonia making the trial potentially relevant. However, the cases of pneumonia or lower respiratory tract infection cannot be inferred from the outcome containing also upper respiratory infections
Hunt 1984	One group of diagnoses in the hospitalised patients was "respiratory infections" but it was not separated into lower and upper respiratory infections
Kahn 2011	The study recorded the frequency of pneumonia in burn patients. The abstract suggests that it was a controlled trial: "patients were divided into two groups", one of which was administered i.v. vitamin C. However, the text indicates that the study was not a trial, but an analysis of a cohort of patients admitted to burn care unit
Mahalanabis 2006a	Combination of vitamins C (200 mg/d) and E (200 mg/d) was used for 6 d. Children aged 1 to 10 y with measles and associated pneumonia; all were clinically diagnosed to have pneumonia. No difference in recovery rate between treatment (n = 36) and placebo groups (n = 35)
Mahalanabis 2006b	Combination of vitamins C (200 mg/d) and E (400 mg/d) was used for 5 d. Children aged 2 to 35 months with severe acute lower respiratory tract infection. No difference in recovery rate between treatment (n = 89) and placebo groups (n = 85)
Mochalkin 1975	No placebo in the control group. Benefit was reported in the vitamin C versus no treatment comparison
Nathens 2002	Combination of vitamins C (1000 mg/d) i.v. and vitamin E (1000 IU/d) per naso-orogastric tube for up to 28 d. No difference in the incidence of pneumonia, but significant decrease in the duration of mechanical ventilation and ICU length of stay
Scheunert 1949	Different doses of vitamin C were administered to several study groups (range 20 to 300 mg/day) so that the lowest dose arm might be used as the control group. "Lung disease" was used as one of the outcomes making the trial potentially relevant The data are, however, presented so ambiguously that no data could be extracted to this review
Wahed 2008	The description of methods of the 7-arm trial is minimal. The dose of vitamin C is not described. It is not clear whether a placebo was used. The authors describe that "initially data was collected from 1150 children and after exclusions only 800 children were selected for analysis." However, the original number of children in each of the 7 groups is not reported. When the reasons for exclusion seem to be random (complications of pneumonia etc) it does not seem possible that random dropping out would lead to 5 groups which each had exactly 40 children and a placebo group which had exactly 400 children. The duration of hospital stay because of pneumonia in the control group (400 children) was 7.75 days and in the vitamin C group (40 children) was 7.00 days. However, the SD is not given for the estimates. Due to these and many further problems we excluded the trial

d = days
ICU = intensive care unit
i.v. = intravenous
n = number
SD = standard deviation
y = years