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Vitamin C for preventing and treating pneumonia.
Cochrane Database of Systematic Reviews 2017, Issue 2. Art. No.: CD005532.
DOI: 10.1002/14651858.CD005532.pub4.

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[Intervention Review]

Vitamin C for preventing and treating pneumonia

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Editorial group: Cochrane Acute Respiratory Infections Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 2, 2017.
Review content assessed as up-to-date: 29 September 2015.

Citation: Hemilä H, Louhiala P. Vitamin C for preventing and treating pneumonia. *Cochrane Database of Systematic Reviews* 2017, Issue 2. Art. No.: CD005532. DOI: 10.1002/14651858.CD005532.pub4.

ABSTRACT

Background

Pneumonia is one of the most common serious infections, causing two million deaths annually among young children in low-income countries. Pneumonia in high-income countries, by contrast, is predominantly a problem of the elderly. This review assesses the preventive and treatment effects of vitamin C on pneumonia. This latest 2016 updated Cochrane review was first published in 2007, and then updated in 2013.

Objectives

To assess the prevention and treatment effects of vitamin C on children and adults with pneumonia.

Search methods

We searched CENTRAL 2015, Issue 9; MEDLINE (1950 to September 2015); EMBASE (1974 to September 2015); Web of Science (1955 to September 2015); ClinicalTrials.gov; and the World Health Organization (WHO) ICTRP Search Portal.

Selection criteria

We selected controlled trials that used or did not use a placebo in the control group to assess prevention effects. We selected placebo-controlled trials to assess the treatment effects of vitamin C.

Data collection and analysis

The two review authors independently read the trial reports and extracted data.

Main results

We identified three prevention trials, which recorded 37 cases of community-acquired pneumonia in 2335 people. Only one trial was satisfactorily randomised, double-blinded and placebo-controlled. One trial studied US marine recruits, another studied soldiers with an influenza A infection in the former Soviet Union, and the third studied boys from "lower wage-earning classes" who were attending a boarding school in the UK during World War II. Each of the three trials found a statistically significant, 80% or greater, reduction in pneumonia incidence in the vitamin C group (high quality evidence).

We identified two treatment trials involving 197 community-acquired pneumonia patients. Only one was satisfactorily randomised, double-blinded and placebo-controlled. That trial studied elderly patients in the UK and found a reduction in pneumonia severity and a lower mortality in the vitamin C group (moderate quality evidence); however, the effect was restricted to the pneumonia patients

who were most severely ill at admission. There were six deaths and only one of them occurred in the vitamin C group (OR 0.24; 95% CI 0.04 to 1.29; moderate quality evidence). The other treatment trial studied adults with a wide age range in the former Soviet Union and reported 4.0 days (21%) shorter hospital stay in pneumonia patients administered a high dose of vitamin C compared with a low dose (high quality evidence).

We identified one prevention trial that reported 13 cases of hospital-acquired pneumonia in 37 patients with severe burns. One-day administration of vitamin C had no effect on the incidence of pneumonia during the hospital stay (moderate quality evidence). We did not identify trials reporting on the treatment of hospital-acquired pneumonia.

The identified studies are clinically heterogeneous, which limits their comparability and generalisability. The included studies did not find adverse effects of vitamin C.

Authors' conclusions

The prophylactic use of vitamin C to prevent pneumonia should be further investigated in populations that have a high incidence of pneumonia, especially when the dietary vitamin C intake is low. The treatment effects of vitamin C should be studied particularly in patients with low plasma vitamin C levels. The current evidence does not justify the prophylactic use of vitamin C to prevent pneumonia in the general population. Vitamin C supplementation as a treatment may be reasonable for patients with pneumonia with low vitamin C plasma levels.

PLAIN LANGUAGE SUMMARY

Vitamin C for preventing and treating pneumonia

Review question

We investigated vitamin C to prevent and treat pneumonia.

Background

Pneumonia is a lung infection usually caused by bacteria and viruses. Community-acquired pneumonia is picked up outside hospitals; hospital-acquired pneumonia is contracted in hospital.

Severe vitamin C deficiency is associated with high occurrence of pneumonia. Studies in animals indicate that vitamin C may prevent and alleviate infections like pneumonia.

Search date

We searched evidence up to September 2015.

Study characteristics

We included six studies involving 2499 people; three investigated preventing community-acquired pneumonia in 674 US Marines; 226 former Soviet Union soldiers; and 1435 boys in a UK boarding school.

Two studies investigated treating community-acquired pneumonia. One involved 57 older people in the UK admitted to hospital with pneumonia or acute bronchitis; the other did not describe the background of the 70 study participants in the former Soviet Union.

One study examined pneumonia prevention in 37 people in Japan treated for burns.

We did not identify any studies that reported treatment for people with hospital-acquired pneumonia.

Study funding sources

Funding sources were not reported.

Key results

Vitamin C for preventing pneumonia

Three studies on community-acquired pneumonia prevention reported 80% or more reduction in pneumonia incidence among people who received vitamin C supplements.

Vitamin C for treating pneumonia

A UK study reported significant decrease in illness severity among older people who were very unwell at admission, but vitamin C had no effect on those who were less ill at admission. There was one death in the vitamin C group, but five deaths in people who received dummy treatment. The study in the former Soviet Union reported 4.0 (21%) fewer days in hospital among people with pneumonia who received high dose vitamin C.

A study on hospital-acquired pneumonia in Japan found no effect of vitamin C on the incidence of pneumonia.

Community-acquired pneumonia studies were conducted in extraordinary conditions and results cannot be applied to most people with pneumonia. Results suggest a biological effect of vitamin C against community-acquired pneumonia under some conditions, which cannot be determined from the studies.

Adverse effects

No significant adverse effects of vitamin C were reported even at high doses.

Quality of the evidence

The overall quality of the evidence for vitamin C in preventing community-acquired pneumonia was high, but the studies were conducted in extraordinary conditions and therefore the results cannot be directly applied to other contexts. The overall quality of the evidence for vitamin C in treating community-acquired pneumonia was moderate, but the studies were conducted in extraordinary conditions and therefore the results cannot be directly applied to other contexts. The overall quality of the evidence for vitamin C in preventing hospital-acquired pneumonia was moderate, but the study was very small and therefore the results cannot be directly applied to other contexts.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation

Vitamin C compared with no vitamin C for preventing community-acquired pneumonia

Patient or population: see below
Settings: see below
Intervention: vitamin C
Comparison: no vitamin C (placebo or no treatment)

Outcomes	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Incidence of pneumonia in military recruits	**OR 0.16** (0.01 to 0.95)	674 (1)	⊕⊕⊕⊕ **high**[1]	The estimate of the double-blind RCT is based on just 8 cases which explains the inaccuracy
Incidence of pneumonia in boarding school boys with a very low dietary intake of vitamin C	**OR 0.0** (0.0 to 0.80)	1435 (1)	⊕⊕⊕⊕ **high**[2]	The single study was not randomised and the estimate is inaccurate
Incidence of pneumonia in soldiers with influenza A infection	**OR 0.19** (0.03 to 0.77)	226 (1)	⊕⊕⊕⊕ **high**[3]	The single study was not randomised and the estimate is inaccurate
Adverse effects				Urticaria developed in one military recruit in the vitamin C arm, which subsided when the pills were withheld. Otherwise the three trials did not report any adverse effects

CI: Confidence interval; **OR:** Odds Ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]We downgraded the quality of evidence by 1 point for imprecision, but we upgraded the quality of evidence by 2 points for the very large effect (OR < 0.2)
[2]We downgraded the quality of evidence by 1 point because potential limitations are likely to lower confidence in the estimate of effect, but we upgraded the quality of evidence by 2 points for the very large effect (OR < 0.2)

[3]We downgraded the quality of evidence by 1 point for imprecision and 1 point because potential limitations are likely to lower confidence in the estimate of effect, but we upgraded the quality of evidence by 2 points for the very large effect (OR < 0.2)

BACKGROUND

Description of the condition

Pneumonia is an infection of the lungs and can be caused by bacteria, viruses, Rickettsia, fungi or parasites (Ellison 2015; Musher 2014; Prina 2015; Ruuskanen 2011). Although the pathological definition of pneumonia is clear, the clinical diagnosis is sometimes ambiguous (Appendix 1).

The incidence of pneumonia in the average middle-aged Western population is one to three cases per 1000 person-years (Baik 2000; Hemilä 2004b). In low-income countries the incidence of pneumonia in children has been as high as 400 cases per 1000 person-years (Paynter 2010). Pneumonia causes two million deaths annually among children under five years of age in low-income countries (Mizgerd 2006; Paynter 2010; Walker 2013). In marine and naval recruits the incidence of pneumonia has been 60 cases per 1000 person-years (Pazzaglia 1983); heavy physical activity and crowded accommodation may explain the high incidence. The risk of pneumonia is increased in the elderly. In the USA, pneumonia is the sixth most common cause of death and the most common cause of infection-related death (Ellison 2015).

Pneumonias are often classified by where they were acquired. *Community-acquired pneumonia* refers to cases that occur outside of hospitals, and *hospital-acquired (nosocomial) pneumonia* to cases that develop at least 48 hours after hospital admission. On average these two classes of pneumonia differ to such a degree that their treatments are different

Description of the intervention

Vitamin C was identified in the 1930s as the consequence of the search for a substance, the deficiency of which causes scurvy (Carpenter 1986). This led to the assumption that the sole physiological function of vitamin C is to prevent and treat scurvy. Therefore, it is often assumed that higher doses of vitamin C cannot be beneficial, if a person does not suffer from scurvy. This history has therefore put constraints on assessing the role of vitamin C on diseases and conditions other than scurvy in such a way that is not just an empirical question, it is also a conceptual issue.

Physiology and clinical effects of vitamin C

The effects of vitamin C are not limited to the connective tissue. Vitamin C is a specific electron donor for enzymes in the synthesis of carnitine, norepinephrine and peptide hormones (Levine 1999; Rice 2000). Vitamin C also plays a role in the vascular endothelium (May 2013). The antioxidant role of vitamin C may enable a wide range of influences at the biochemical and physiological levels. Effects on the immune system are briefly described in the following section, How the intervention might work.

According to systematic reviews, over two dozen controlled trials have shown that vitamin C shortens the duration of colds (Hemilä 1992; Hemilä 2013a). Five trials found that vitamin C halved the incidence of colds in participants who endured heavy acute physical stress (Hemilä 1996; Hemilä 2013a). Three trials found that vitamin C halved the exercise-induced decline in the forced expiratory volume in one second (FEV_1) in participants who suffered from asthma (Hemilä 2014) and three trials found benefit of vitamin C against common cold-induced asthma (Hemilä 2013b). One trial reported a significant decrease in the tetanus case-fatality rate (Hemilä 2013c). Meta-analyses have also indicated that vitamin C may reduce blood pressure (Juraschek 2012), and it may improve endothelial function of the blood vessels (Ashor 2014).

Two trials found that vitamin C improved the mood of acutely ill hospitalised patients (Wang 2013; Zhang 2011). The effects of vitamin C on mood might lead to secondary benefits for hospital patients, since the discharge from hospital is not just defined by the somatic condition.

Although the above findings indicate that the effects of vitamin C are not limited to preventing overt scurvy, the practical significance of the findings is not yet clear. Two large trials on US male physicians and female health professionals found no benefits of 0.5 g/day of vitamin C against cardiovascular diseases and cancer (Cook 2007; Sesso 2008). A meta-analysis found that $\geq$ 1 g/day of vitamin C had no effect on the incidence of the common cold in the general population (Hemilä 2013a). Nevertheless, these negative findings are not discordant with the possibility that vitamin C administration might influence the susceptibility of patients to contracting pneumonia in special conditions or the severity of pneumonia.

Pharmacokinetics and levels of vitamin C in populations

The relationship between vitamin C dose and its plasma concentration is a relevant issue when considering the potential treatment effects of vitamin C administration. When vitamin C dosage is less than 0.1 g/day, there is a steep relationship between plasma vitamin C levels and the dosage. For example, when the vitamin C dose increases from 0.06 to 0.2 g/day, the level of vitamin C in the plasma approximately triples (Levine 1999). The plasma vitamin C level of healthy people reaches saturation at doses of about 1 g/day (Levine 1999). However, there is no basis to assume that the relationship between the dose and the plasma concentration is the same for patients with infections as for healthy people.

There is evidence that vitamin C metabolism is affected by various infections, including pneumonia, as indicated by decreased levels of vitamin C in plasma, leucocytes and urine (Bakaev 2004; Bhoite 2011; Cemek 2006; Chakrabarti 1955; Hemilä 2006; Hunt 1994; Mochalkin 1970). Thus, it is possible that the relationship between vitamin C dose and its plasma concentration differs between patients with infections from those of healthy people. The changes in metabolism indicate that vitamin C might have a treatment effect on pneumonia patients, irrespective of their dietary intake. When plasma vitamin C levels fall below 11 μmol/L there is risk of frank vitamin C deficiency - scurvy. Vitamin C deficiency is not just of historical relevance. Cases of scurvy in hospitals have been described in several recent case reports such as Holley 2011 and Smith 2011, and a survey estimated that about 10% of hospitalised elderly patients had scurvy (Raynaud-Simon 2010). As much as 25% of men and 16% of women from low-income populations in the UK had vitamin C deficiency "(< 11μmol/L) (Mosdøl 2008), whereas 7% of healthy middle-class participants of a study in the USA had vitamin C deficiency (Schleicher 2009). Thus, if pneumonia risk is increased by low dietary intake of vitamin C, this issue may be important in certain population groups of high-income countries. Low vitamin C levels are even more common in developing countries (Hemilä 2007a).

Possible heterogeneity in the effects of vitamin C

The effect of vitamin C on the common cold has been studied extensively and a major finding from the trials is the heterogeneity of its effects. The largest trials found no effect of vitamin C on the incidence of the common cold. However, vitamin C significantly reduced the incidence of colds in trials with participants under heavy acute physical stress and among British males; the latter could be explained by the low dietary vitamin C intake in the UK when the studies were carried out (Hemilä 1996; Hemilä 1997b; Hemilä 2006; Hemilä 2013a). The effects of vitamin C on pneumonia might be modified by similar factors.

Two large common cold 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); and vitamin C decreased the incidence of 'throat colds' (-21%) but not of 'nose colds' (-2%) (Anderson 1973; Hemilä 1997b). These two trials suggest that vitamin C might have a greater effect on infections that affect the lower respiratory tract.

In a close parallel to vitamin C, the lipid-soluble vitamin E is interesting as these two antioxidants may interact. Vitamin C reduces oxidised vitamin E back into the reduced form (Bruno 2006; Hemilä 2006; Hemilä 2009a; Packer 1979). A large-scale trial on vitamin E and pneumonia found heterogeneity in vitamin E effects between different population groups (Hemilä 2016). Although findings from a vitamin E trial cannot be directly extrapolated to vitamin C, the concept that various factors may modify the effects of antioxidants is important. Broad generalisations made on the basis of individual trials, irrespective of whether the finding is positive or negative, and whether or not the trial is large and carefully conducted, are questionable when there is heterogeneity in the effects.

Safety of vitamin C

Approximately 10 mg/day of vitamin C prevents scurvy but the safe dose range extends to grams per day (Hathcock 2005; Hemilä 2006; Levine 1999; IOM 2000). In the USA's nutritional recommendations, the 'tolerable upper intake level' is stated to be 2 g/day for adults. However, the basis for this upper limit is the appearance of diarrhoea (IOM 2000), which is a minor adverse effect that disappears quickly with a reduction in vitamin C intake. Participants of a pharmacokinetic study were administered up to 100 grams of vitamin C intravenously within a period of a few hours without any reported adverse effects, which indicated the safety of such a very large dose in healthy people (Padayatty 2004). Two large-scale trials conducted on 8171 female health professionals and 14,641 male physicians found no adverse effects of 0.5 g/day of vitamin C when administered for eight to nine years, which indicates long-term safety of such a dosage level (Cook 2007; Sesso 2008).

Vitamin C and pneumonia

Alfred Hess carried out extensive studies of scurvy in the early 1900s 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 also commented 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; Hochwald 1937; Slotkin 1944). 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). In the USA, 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). Large oral doses of vitamin C were also claimed to be beneficial for patients with viral pneumonia (Cathcart 1981; Luberoff 1978).

How the intervention might work

Vitamin C is an antioxidant and its effects may be most pronounced under conditions when oxidative stress is increased. Infections and exercise lead to increased oxidative stress.

Viral and bacterial infections lead to the activation of leukocytes, which generate reactive oxygen and nitrogen species that oxidise extracellular vitamin C (Akaike 2001; Galley 1996; Hemilä 1984). This mechanism explains the decrease in vitamin C levels in pneumonia patients and in other patients with infections. The oxidised form of vitamin C (dehydroascorbate) is imported into the leukocytes where it is reduced back to vitamin C and, subsequently, the concentration of vitamin C in the leukocytes can become very high (Nualart 2003; Wang 1997). A recent metabolomic analysis found extremely active vitamin C metabolism in pneumonia patients who developed critical illness (Self 2015).

Exercise causes oxidative stress because of increased oxygen consumption (Ashton 1999; Powers 2008). Therefore the beneficial effects of vitamin C may be pronounced during exercise.

A major role of vitamin C in the immune system seems to be as a physiological antioxidant that protects the host cells against oxidative stress caused by infections. Vitamin C has affected random migration and chemotaxis of phagocytes (Goetzl 1974), the transformation of influenza virus-infected lymphocytes (Manzella 1979), the production of interferon (Siegel 1975), the replication of viruses (Bissell 1980) and the gene expression of monocyte adhesion molecules (Rayment 2003); see reviews by Beisel 1982, Hemilä 1997a, Manning 2013; Thomas 1978 and Webb 2007.

Vitamin C increased resistance against diverse viral and bacterial infections, and against purified bacterial toxins in a large number of animal studies (Hemilä 2006). An early laboratory study found that vitamin C deficiency increased the incidence of pneumonia in rhesus monkeys (Sabin 1939). Influenza infection in mice decreased vitamin C concentration in bronchoalveolar lavage fluid and increased the level of dehydroascorbate (Buffinton 1992). Vitamin C deficiency increased lung pathology caused by influenza infection in mice (Li 2006), and vitamin C administration prevented pneumonia in restraint-stressed mice (Cai 2015).

The effects of vitamin C on the immune system may be apparent only under certain conditions. For example, it is possible that the variation in vitamin C intake does not influence the immune system in the ordinary Western population because of their relatively high dietary intake levels. Nevertheless, vitamin C might be a limiting factor in the immune system in populations with low dietary intakes (Hemilä 2007a). As an extreme example, the reported prevalence of frank vitamin C deficiency, scurvy, has been up to 44% in refugee camps in the Horn of Africa (WHO 1999a). Our review is largely based on the concept that vitamin C affects the immune system, which explains the protection from infections in animals (Hemilä 2006). However, vitamin C also has non-immune effects that may be relevant in treatment trials.

Vitamin C participates in the synthesis of norepinephrine and a series of neuropeptides (Levine 1999; 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 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". One of the earliest symptoms of vitamin C deficiency is fatigue, which is a highly non-specific symptom (Levine 1999). Therefore, it is possible that in a treatment setting the influence of vitamin C is not limited to the immune system.

The decrease in vitamin C levels that is caused by infections might cause psychological symptoms, and vitamin C administration might be beneficial in alleviating such symptoms. Some of the early case reports of pneumonia patients described particularly rapid benefits of vitamin C treatment (Bohnholtzer 1937; Dalton 1962; Hochwald 1937; Klenner 1948), and such rapid effects might be caused by non-immunological effects of vitamin C, rather than by immunological mechanisms. Two recent studies reported that vitamin C administration improved the mood of acutely hospitalised patients, indicating that vitamin C may influence the general well being of hospital patients (Wang 2013; Zhang 2011).

Why it is important to do this review

Pneumonia is a severe and fairly common infection and vitamin C is a safe and inexpensive essential nutrient. The possibility that vitamin C might affect the 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. A previous meta-analysis assessed the preventive effects of vitamin C on pneumonia (Hemilä 1997c), but the treatment effect on pneumonia was not assessed systematically before this current review.

Links to the publications cited in this section can be found at http://www.mv.helsinki.fi/home/hemila/CP.

OBJECTIVES

To assess the prevention and treatment effects of vitamin C on children and adults with pneumonia.

METHODS

Criteria for considering studies for this review

Types of studies

We included controlled trials to assess the preventive effects of vitamin C administration. The use of placebo was not required as it seems unlikely that being aware of, or not, taking vitamin C would affect the occurrence of a severe infection. A recent meta-analysis of trials comparing placebo groups with no treatment groups found no evidence of a placebo effect on binary outcomes (Hrobjartsson 2010), thus there is no empirical evidence that suggests the placebo effect might affect the occurrence of pneumonia.

We used placebo-controlled trials to assess treatment effects of vitamin C on the severity and duration of pneumonia since the outcome (for example, severity) may be affected by the awareness of the treatment by the patients. The recent meta-analysis of trials that compared placebo groups with no treatment groups found evidence of a placebo effect in trials focusing on pain (Hrobjartsson 2010). A placebo control may, therefore, be more useful for the validity of treatment observations.

Types of participants

There was no age restriction in the participants for prevention trials.

We restricted treatment trials to participants with pneumonia, both community-acquired and hospital-acquired (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 considered. We excluded trials in which vitamin C was administered along with other substances, such as other vitamins. We included studies in which vitamin C had a co-intervention if the control group only had the co-intervention, thus the only difference was vitamin C administration.

Types of outcome measures

Primary outcomes

Community-acquired pneumonia and hospital-acquired (nosocomial) pneumonia are different types of medical conditions and we analysed them separately.

Community-acquired pneumonia

The preventive effect of vitamin C:

1. incidence of pneumonia;
2. adverse effects.

The treatment effect of vitamin C:

1. duration of hospital treatment for pneumonia (days);
2. severity of pneumonia;
3. mortality due to pneumonia;
4. adverse effects.

Hospital-acquired (nosocomial) pneumonia

The preventive effect of vitamin C:

1. incidence of pneumonia;
2. adverse effects.

The treatment effect of vitamin C:

1. duration and severity of pneumonic episodes;
2. death caused by pneumonia;
3. adverse effect

In 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-ray (CXR) and we also accepted a clinical diagnosis of pneumonia (see Appendix 1 for detailed comments on this issue).

Secondary outcomes

1. Laboratory findings, such as C-reactive protein or erythrocyte sedimentation rate.
2. CXR changes and body temperature changes during treatment.

Search methods for identification of studies

Electronic searches

For this 2015 update, we searched the Cochrane Central Register of Controlled Trials (CENTRAL; the Cochrane Library 2015; Issue 9), which contains the Acute Respiratory Infections Group's Specialised Register; MEDLINE (1950 to Sept 2015); EMBASE (1974 to Sept 2015) and Web of Science (1945 to Sept 2015). We restricted the search to the time range after our 2013 update and we did not use a filter to identify randomised trials as there were few results (see Appendix 2 for the CENTRAL and MEDLINE search strategy). Details of the earlier searches are shown in Appendix 3. We adapted the search for EMBASE (Appendix 4) and Web of Science (Appendix 5).

We conducted a search of ClinicalTrials.gov (www.ClinicalTrials.gov) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) Search Portal (http://apps.who.int/trialsearch/). We used the search phrase ["vitamin C" AND pneumonia] and carried out the search in October 2015.

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. We did not impose any 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. Both review authors (HH, PL) independently screened titles and abstracts for inclusion of all the potential studies we identified as a result of the search. We retrieved the full-text study reports/publication and both review authors (HH, PL) independently screened the full-text and identified studies for inclusion. We resolved any disagreements through discussion. The reasons for excluding studies are shown in the Characteristics of excluded studies tables. 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. We did not use a data collection form. HH entered the collected data into Review Manager (RevMan 2014), and both authors (HH, PL) checked that data were entered correctly by comparing the data in the RevMan programme with the study reports. When we differed in the interpretation of study findings we sought a consensus. Hunt 1994 published the respiratory symptom scores for all participants and for the most severely ill patients in their report; for this review we calculated the scores for the less ill patients. Hunt was contacted for the details of the trial.

Assessment of risk of bias in included studies

We recorded the following quality features of the trials: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, proportion of drop-outs and other relevant features that may limit the validity of the trial. We considered the possibility of selective outcome reporting, see Discussion section. We graded each potential source of bias as 'high', 'low' or 'unclear' and when possible we provide a quote from the study report in the 'Risk of bias' table. When considering treatment effects, we took into account the risk of bias for the studies that contribute to that outcome.

In 2015 we added "baseline balance" as a new item to the Risk of Bias table, as encouraged by Corbett 2013. If randomisation methods are unclear, then the baseline data may demonstrate that all important prognostic factors were balanced across arms. Therefore we added descriptions of the available information on baseline balances of the included studies.

Measures of treatment effect

We planned to calculate risk ratios (RRs) for dichotomous outcome variables. However, in the three identified prevention 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 sect 16.9.5). Nevertheless, the approximate calculation methods, including the Peto OR method, lead to misleading 95% confidence intervals (CIs) for very small numbers of pneumonia cases (Higgins 2011 sect 16.9.5). Therefore, we also used the "or.midp" procedure of the R 2015 (epitools package) to calculate the mid-P 95% CI (Greenland 1998) for the OR for the Kimbarowski 1967 and Pitt 1979 trials. Because of null cases in the vitamin C group, the "or.midp" procedure could not calculate the CI to the Glazebrook 1942 trial and we used the "fisher.exact" program of the R 2015 (exact2x2 package). With only a few cases observed in the vitamin C groups, the mid-P value is the most appropriate method to calculate the P values for the differences between the treatment groups (Agresti 2001; Greenland 1998; Hemilä 2006; Lydersen 2009) and was used when comparing groups and calculation of the confidence limits. For the 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 was the group of schoolchildren in the administrative division. Glazebrook stated 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 ignoring the divisions. However, we also analysed the data by administrative units as a sensitivity analysis (see Results). We calculated the Fisher-Pitman permutation test with the "oneway_test" procedure of the R 2015 (coin package).

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 comparisons by using the I^2 statistic (Higgins 2003). This examines the percentage of total variation across studies that is due to heterogeneity rather than being caused by pure chance. A value of the 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 useful when considering whether there is publication bias or not (Ioannidis 2007; Lau 2006; Sterne 2011; Terrin 2005). We consider the possibility of publication bias in our Discussion section.

Data synthesis

We planned that if a number of trials were available with sufficient uniformity in settings and outcome definitions, we would pool their 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 were clinically so divergent that pooling was inappropriate.

We created a 'Summary of findings' table using the following outcomes: the incidence of community-acquired pneumonia in military recruits, the incidence of community-acquired pneumonia in schoolboys with particularly low dietary vitamin C intake, the incidence of community-acquired pneumonia in young males with influenza A infection, change in the severity of pulmonary symptoms in elderly patients hospitalised for pneumonia, the duration of hospital treatment of pneumonia patients, the incidence of hospital-acquired pneumonia in patients with burns. We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of a body of evidence as it relates to the studies which contribute data to the specified outcomes. We used methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We justified all decisions to down- or up-grade the quality of studies with footnotes, and we made comments to aid the reader's understanding of the review where necessary. We removed and added points according to the instructions in sections 12.2.2 and 12.2.3 of Higgins 2011.

Subgroup analysis and investigation of heterogeneity

We did not require that pneumonia definition was based on chest x-ray (CXR) (Appendix 1), but we planned to carry out subgroup analyses based on the rigor of outcome definition (CXR or not) and on the level of blinding of outcome assessments. Given the set of 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. We set the limit of subgroup analysis to 100 mg/day in the preventive trials, since it is close to the dosage leading to maximum vitamin C plasma levels in healthy people. We set the limit of subgroup analysis to 1000 mg/day in the treatment trials, since there is evidence of changes in vitamin C metabolism in infections and larger doses might be needed for significant treatment effects. We did not find suitable variation in the doses for a between-study subgroup analysis but there was within-study variation in the Mochalkin 1970 trial (Table 1).

In our protocol (Hemilä 2005) we did not plan subgroup analysis by the severity of pneumonia. Nevertheless, as we found that the severity of pneumonia at admission significantly modified the effect of vitamin C on the change of severity during hospital stay in the Hunt 1994 study, we divided that study into two subgroups in an additional table already in the 2007 version, but in the 2013 update we introduced the division to the Analysis forest plot, since such a presentation is more informative than keeping the less severe and more severe patients combined in the forest plot.

Sensitivity analysis

Two of the identified trials were double-blind, placebo-controlled, randomised controlled trials (Hunt 1994; Pitt 1979), whereas three studies were methodologically less rigorous (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 division in a boarding school. In our primary analysis, we assumed a similar risk for each participant in each administrative unit in the primary analysis. As a sensitivity analysis we also analysed their data by the administrative divisions.

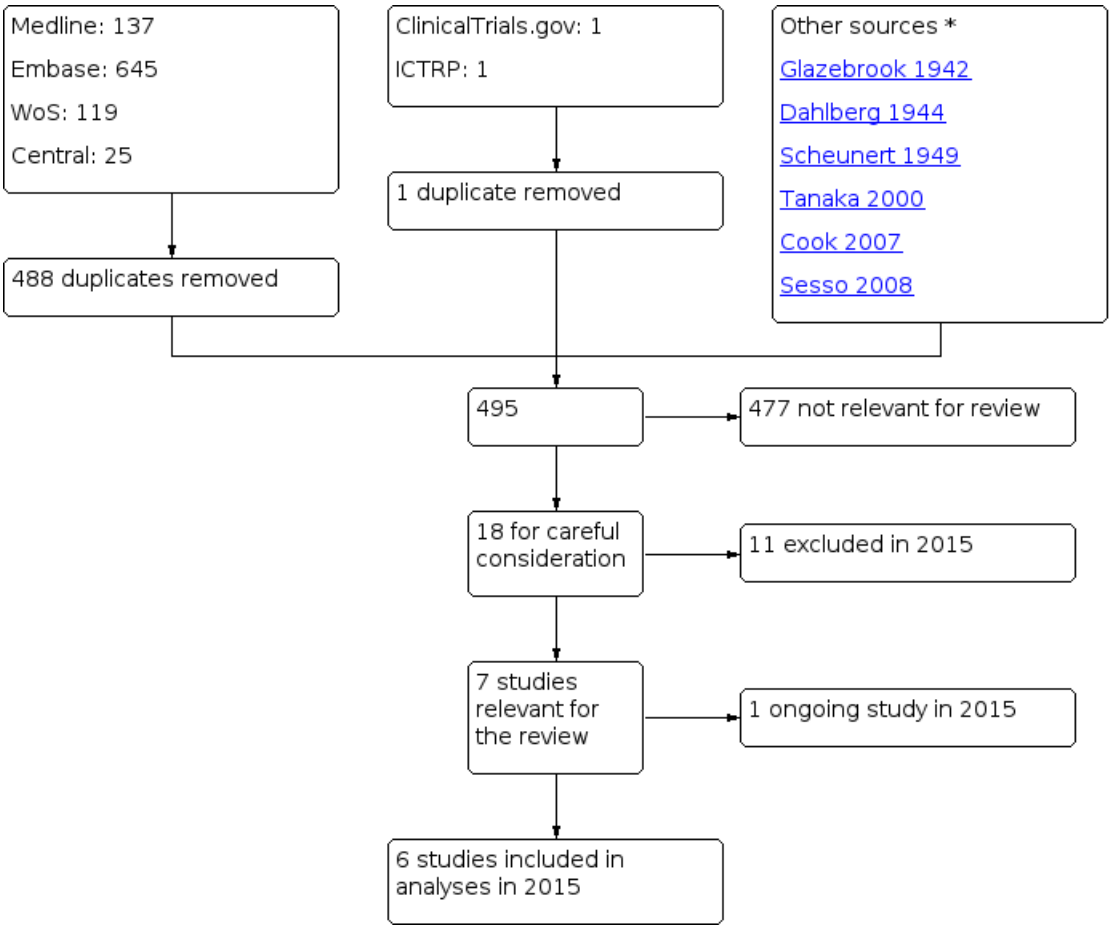
RESULTS

Description of studies

Results of the search

We identified no new trials for inclusion in the 2015 update searches (out of 178 records recovered). The MEDLINE search for the 2015 update retrieved 22 publications, the EMBASE search retrieved 132, the Web of Science search 14 and the CENTRAL search 10 publications. From these search results we found no new trials in addition to the earlier identified trials. We added one study to our excluded studies list (Pico Sirvent 2013). The ClinicalTrials.gov search identified one record of a study that is ongoing, and the ICTRP search identified the same record (Lafargue 2015). Earlier searches are described in Appendix 3. Figure 1 shows a flow diagram of the searches.

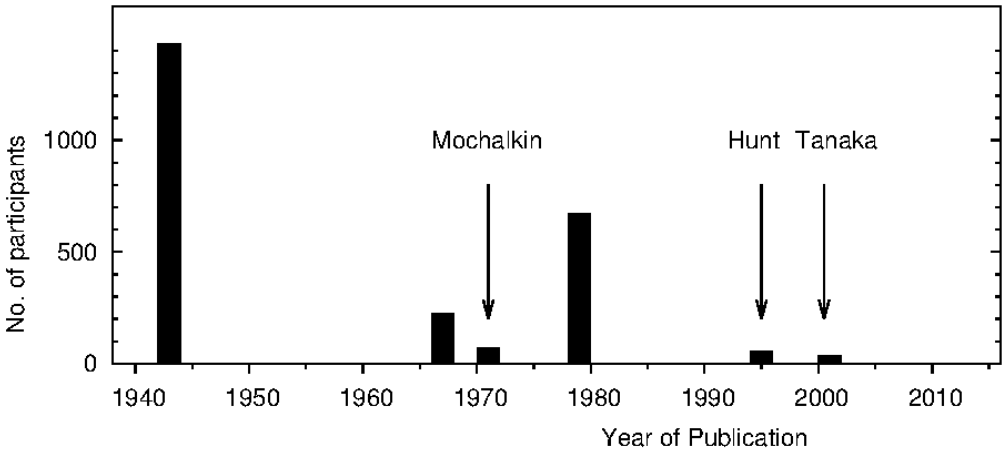
Figure 1. Flow diagram.*Other sources indicates literature searches other than those carried out for this particular review, reading reference lists of various journal articles and books, and reading the publications themselves. The Cook 2007 and Sesso 2008 trials are listed as potentially relevant, because they were particularly large and long studies on vitamin C, the authors were contacted to ask whether any data on pneumonia might be available.



Included studies

Six controlled trials are included in our review. Figure 2 shows the year of publication and the number of participants in the trials.

Figure 2. The year of publication and the number of participants in the vitamin C and pneumonia trials. The three tallest bars are the preventive trials by Glazebrook 1942, Kimbarowski 1967 and Pitt 1979. The two therapeutic trials by Mochalkin 1970 and Hunt 1984, and the preventive hospital-acquired pneumonia trial by Tanaka 2000 are indicated by names.



Three studies investigated the effect of vitamin C in the prevention of community-acquired pneumonia. They were published in the time range from 1942 to 1979. The number of participants ranged from 226 to 1435. All participants of the three prevention trials were males (Glazebrook 1942; Kimbarowski 1967; Pitt 1979).

Two studies investigated the treatment of community-acquired pneumonia. They were published in 1970 and 1994. The number of patients in the vitamin C-placebo comparisons were 70 and 57 (Mochalkin 1970; Hunt 1984).

One study examined the prevention effect of vitamin C against hospital-acquired pneumonia, but the number of participants was only 37 (Tanaka 2000).

The main features of the included trials are briefly summarised in the Characteristics of included studies tables. The methods of the six trials are described in more detail in this section, largely using direct excerpts from the original papers, as the excerpts show the strengths and weaknesses of the trials in the words of the original trial authors. The methodological strengths and weaknesses are crucial when considering the validity of their findings and the possibility of extrapolating their findings. Links to the trial reports and translations can be found at http://www.mv.helsinki.fi/home/hemila/CP.

Prevention of community-acquired pneumonia

Pitt 1979

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 randomised 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 1999). 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).

Kimbarowski 1967

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 hospital-acquired 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 probable 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 but this was not explicitly stated in the paper.

Glazebrook 1942

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.

Treatment of community-acquired pneumonia

Hunt 1994

Hunt 1994 stated 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 in this study 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 mentioned in the Background and Types of outcome measures sections and the high false negative proportion in CXR versus high-resolution computed tomography (HRCT) comparison (Appendix 1), 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 hospitalisation“ (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 randomised ’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% of 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).

Mochalkin 1970

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. This is a three-arm trial with one control arm and two vitamin C arms with different doses. 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 pa-

tients 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 and 35 μmol/L (-15%) in the low-dose vitamin C group but only 23 μmol/L (-44%) in the control group.

Prevention of hospital-acquired pneumonia

Tanaka 2000

Tanaka 2000 was primarily interested in resuscitation fluid volume requirements and oedema generation in severely burnt patients. The study is reported as a "randomised study" but the methods section states that "randomisation was performed according to the month of admission" suggesting that randomisation may have been used as a synonym for allocation. There is no description of the level of blinding. Incidence of pneumonia is reported as a secondary outcome but the criteria for diagnosis are not described. Vitamin C was administered for only 24 hours after hospitalisation with a dose of 66 mg/kg/h (corresponding to 110 grams per 70 kg per 24 h). Compared with the control group, the plasma vitamin C level remained much higher in the vitamin C groups for three days, and thereafter the plasma vitamin C levels were similar.

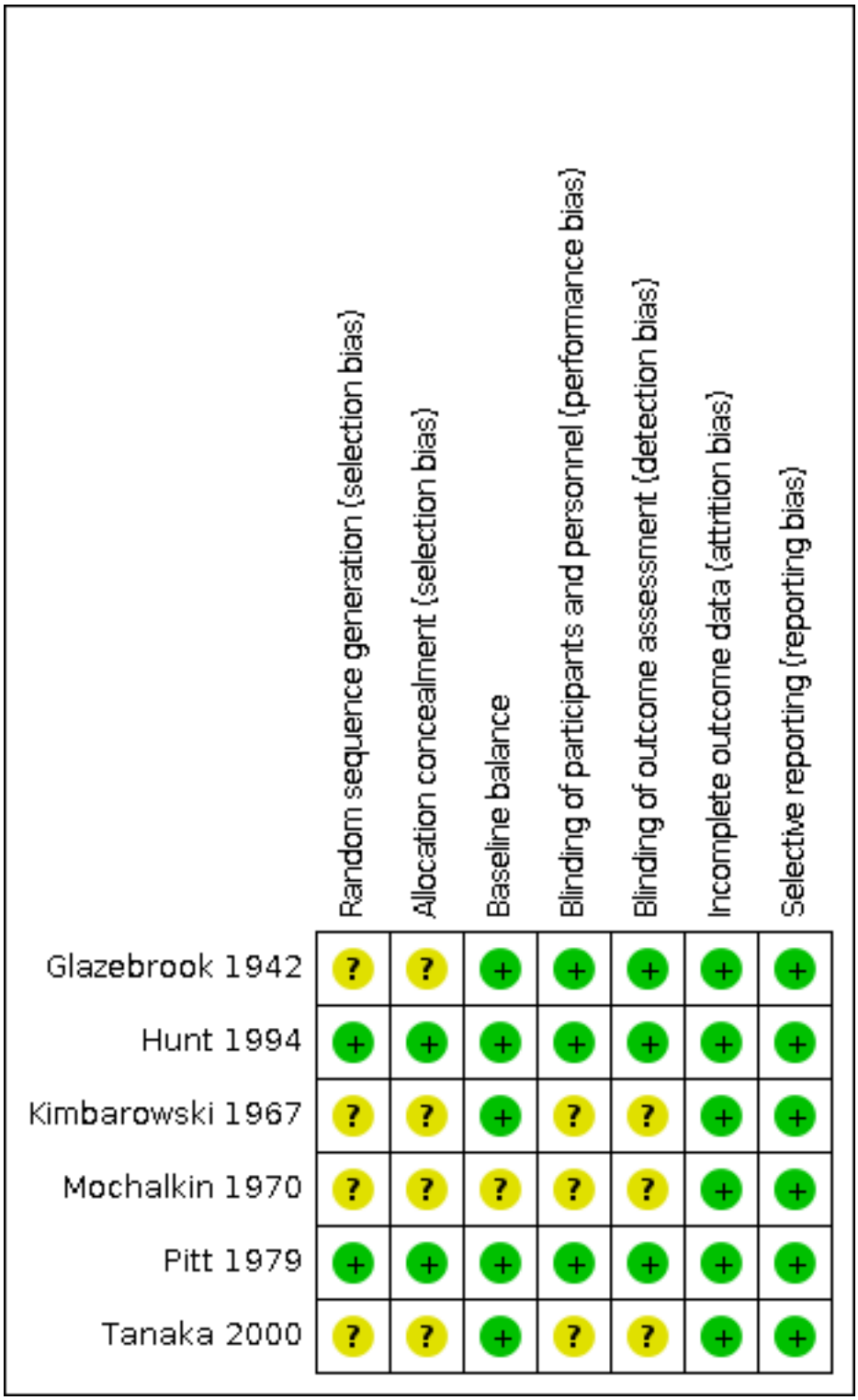
Excluded studies

Eleven studies were excluded in the 2015 version. Three studies reported on respiratory infections which included pneumonia, but there were no specific data about pneumonia (Dahlberg 1944; Scheunert 1949; Hunt 1984). Three studies examined the combination of vitamin C with quite a high dose of vitamin E (Nathens 2002; Mahalanabis 2006a; Mahalanabis 2006b). One study examined vitamin C together with beta-glucan (Pico Sirvent 2013). One study used term controlled trial in its abstract, but the study was observational (Kahn 2011). The reporting of one study was very poor and the data were inconsistent with expected random variations for example in drop-out rates (Wahed 2008). We contacted authors of two large-scale studies on vitamin C, but the studies did not collect data on pneumonia (Cook 2007; Sesso 2008). For more details on the excluded studies, see the Characteristics of excluded studies table. Links to the trial reports and translations can be found at http://www.mv.helsinki.fi/home/hemila/CP.

Risk of bias in included studies

Two of the trials were double-blinded, placebo-controlled randomised trials without serious methodological defects (Hunt 1994; Pitt 1979). Four other trials had methodological shortcomings of varying degrees, as described in the previous section (Glazebrook 1942; Kimbarowski 1967; Mochalkin 1970; Tanaka 2000), 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 3.

Figure 3. '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 also concealed. Hunt 1994 states 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 also 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. Tanaka 2000 does not describe the method of allocation. Even though they use the term "randomised", it seems that the groups were formed by the treatment month: "randomisation was performed according to the month of admission" (p.327).

Baseline balance (selection bias)

The Pitt 1979 trial had large groups and the reported relevant baseline variables were closely balanced. Hunt 1994 reported that age, total respiratory clinical score and plasma vitamin C levels were closely balanced. Glazebrook 1942 described that they had kept careful records about the incidence of all infections for one and a half years before the study and a preceding epidemic of tonsillitis had affected all the school divisions uniformly, indicating that risk of pneumonia may also have been uniform. In addition, because of the type of study, sex was identical in both groups and age distribution was closely similar. Kimbarowski 1967 reported that the severity of influenza A was closely similar in both study groups. In addition, because of the type of study, sex was identical in both groups and age distribution was closely similar. The vitamin C and control groups of the Tanaka 2000 study were small and there were rather large differences in age, in the area of burns relative to total body surface area, and in full-thickness burn between the groups, but these differences are unlikely to substantially bias the reported findings. Mochalkin 1970 reported that the distribution of antibiotics was similar in the low and high vitamin C groups, thus, if the selection of antibiotics depended on the clinical symptoms, they were also divided evenly. Nevertheless, the distribution of clinically directly relevant variables was not reported, and therefore we do not classify that the risk of bias on the basis of baseline balance as low.

Blinding

The Pitt 1979 and Hunt 1994 studies were double-blind. Glazebrook 1942 stated 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, Mochalkin 1970 and Tanaka 2000 trials.

Incomplete outcome data

Pitt 1979 stated 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 not take their pills but there was no difference between the study arms. One recruit was removed from the vitamin C group because of an adverse effect. Thus, 22% of participants were not included in the 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 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. 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. However, the distribution of the usage of four different antibiotic treatments is given in the three arms and these groups are identical in size within the arms which suggests that they were planned and that there were no drop-outs. In the Tanaka 2000 trial, there is no indication of drop-outs.

Selective reporting

Tanaka 2000, Pitt 1979, Kimbarowski 1967 and Glazebrook 1942 considered pneumonia either of secondary interest or as a nuisance and therefore the findings for pneumonia were not selectively reported because of the type of findings. Hunt 1994 was specifically

interested in the treatment of pneumonia but there are no indications in the paper that the reported outcomes would have been selected from a larger set of outcomes. Mochalkin 1970 measured temperature, erythrocyte sedimentation rate, leukocyte level, time of wet crackle 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

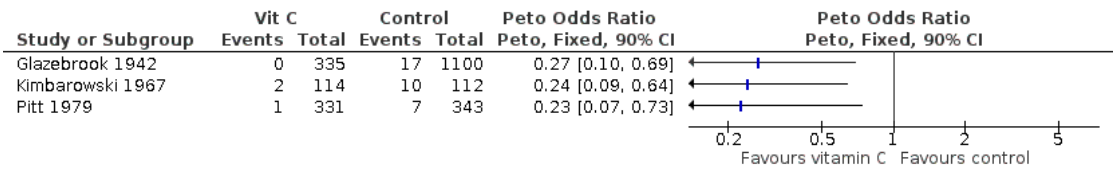
See: **Summary of findings for the main comparison** Summary of findings for vitamin C in preventing community-acquired pneumonia; **Summary of findings 2** Summary of findings for vitamin C in treating community-acquired pneumonia; **Summary of findings 3** Summary of findings for vitamin C in preventing hospital-acquired pneumonia

Preventing community-acquired pneumonia

1. Incidence of pneumonia

Three trials reported the number of pneumonia cases in the vitamin C and control groups. All three trials found an 80% or greater decrease in the incidence of pneumonia in the vitamin C group (Figure 4; Analysis 1.1). Since the number of cases in the vitamin C groups was very low (zero to two cases in all three trials) we used the Peto method for calculating the odds ratio (OR) as an approximation to the risk ratio (RR).

Figure 4. Prophylactic effect of vitamin C against pneumonia in three trials



The confidence intervals (CIs) in the three trials were wide and overlapped substantially and there is no evidence of statistical heterogeneity (I^2 statistic = 0%; Chi^2 [2 df] = 0.03). However, the trials were clinically so heterogeneous that we did not calculate a pooled estimate of the 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 the susceptibility to pneumonia.

With only few cases in the vitamin C groups, approximate methods such as the Peto OR method are inaccurate. In such a case, exact methods are more appropriate for calculating the 95% CI. We used the R-package and calculated the exact 95% CI ranges for the odds ratio (OR) as follows: for Glazebrook 1942, OR = 0.0 (95% CI 0.0 to 0.80; mid-P = 0.011), for Kimbarowski 1967, OR = 0.19 (95% CI 0.03 to 0.77; mid-P = 0.018) and for Pitt 1979, OR = 0.16 (95% CI 0.01 to 0.95; mid-P = 0.044). For each of the three studies the evidence is high on the GRADE scale (Summary of findings for the main comparison). The combined mid-P value for the three trials was 0.00004 (Hemilä 1997c), which indicated that the differences between the vitamin C and the no-vitamin C arms in these three trials were unlikely to be explained by random variation.

Subgroup and sensitivity analyses

We carried out sensitivity analysis in this set of prevention trials by excluding those trials that did not use randomisation and placebo. This left Pitt 1979 as the only trial with highly robust methodological quality. Nevertheless, the findings of the Pitt 1979 trial did not differ from the other two trials. The trials were clinically heterogeneous, therefore we did not expect the same treatment effect in such variable conditions. However, there was no evident trend for the most positive findings to occur in the two methodologically less rigorous trials.

We had planned subgroup analysis by the vitamin C dosage, but the trials were clinically so heterogeneous, and the 95% CIs so wide, that such a subgroup analysis was not feasible.

All three prevention trials mentioned the usage of the chest X-ray (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.

The allocation to treatment groups in the Glazebrook 1942 trial 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 3.40 cases per division, variance 1.30) 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 Glazebrook's publication, but the two vitamin C divisions had on average 167 boys (335/2) and the five control divisions, 220 boys (1100/5), thus the mean size of the vitamin C divisions was 0.76 times the size of the control divisions. Therefore, we adjusted the mean incidence by this ratio, and calculated that 2.6 pneumonia cases were expected per vitamin C division, assuming the same incidence as for the control divisions. We used this Poisson mean to calculate the probability that there were no cases of pneumonia in two separate vitamin C divisions to be P = 0.006. As a second approach to analyse the difference between vitamin C and control divisions, we used Fisher-Pitman permutation test, which gives P = 0.048.

Accordingly, using a 'division' as the unit of observation does not change the conclusions of the Glazebrook 1942 trial.

2. Adverse effects

Pitt 1979 administered 2 g/day of vitamin C to 331 participants for two months. None of the 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 subsequently recurred when he resumed taking his pills. He was instructed to stop taking pills and was excluded from the final analysis.

Glazebrook 1942 and Kimbarowski 1967 did not report about any adverse effects, but they used lower vitamin C doses.

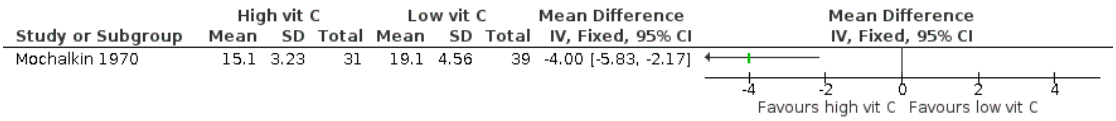
Treating community-acquired pneumonia

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

1. Duration of pneumonia (days)

Mochalkin 1970 had three trial arms: control, low vitamin C and high vitamin C. The control arm was not administered a placebo. Therefore, we restricted our main analysis to the comparison of the two vitamin C arms so that the low vitamin C group served as a placebo group in our comparison (Figure 5, Analysis 2.1). Because of Mochalkin's protocol, the mean vitamin C dose of the high-dose arm was on average double that of the low-dose arm, although the dose ranges for both vitamin C arms overlapped (Characteristics of included studies). There was a statistically highly significant decrease in the duration of hospital stay in the pneumonia patients in the high-dose vitamin C arm compared with the low-dose arm (Figure 5). The evidence is high on the GRADE scale (Summary of findings 2).

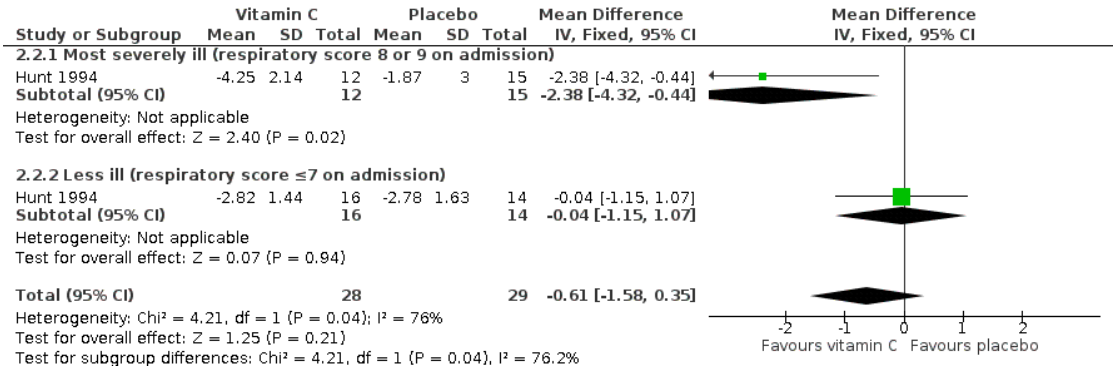
Figure 5. Effect of vitamin C on the duration of hospital stay (days) in Mochalkin 1970



2. Severity of pneumonia

As a measure of pneumonia severity, Hunt 1994 used 'total respiratory score', which had a range from three (least ill) to nine (most ill) and 10 (dead). On this pneumonia severity score, vitamin C caused a marginally non significant benefit at four weeks: P = 0.053, which is based on a decrease in the respiratory score: -2.31 (standard deviation (SD) 2.44) versus -3.43 (SD 1.77) in the placebo and vitamin C groups, respectively. However, the benefit was restricted to patients who were most severely ill when admitted to the hospital (see subgroup analysis below; Figure 6, Analysis 2.2). The evidence is moderate on the GRADE scale (Summary of findings 2).

Figure 6. Effect of vitamin C on the respiratory symptom score (scale 3 to 10) in Hunt 1994



3. Mortality due to pneumonia

Hunt 1994 found an 85% lower mortality rate in the vitamin C group compared with the placebo group, but this comparison was based on six cases only (Analysis 2.3; mid-P = 0.12) (moderate level evidence, Summary of findings 2). All deaths occurred in the patients who were most severely ill when admitted to the hospital and all deaths were caused by the respiratory infection.

Subgroup and sensitivity analyses

Hunt 1994 published the mean 'total respiratory score' values for all participants and for the most severely ill participants (baseline score eight or nine). We calculated the mean scores of the less ill patients (baseline score seven or less). There was significant heterogeneity in the effect of vitamin C on the more ill and the less ill patients with P = 0.04 and I^2 = 76% (Figure 6). The benefit of vitamin C was restricted to patients who were most severely ill when admitted to hospital (P = 0.02). The most severely ill patients had substantially lower vitamin C plasma levels compared with the less ill patients (20 versus 26 μmol/l, respectively). There was no effect of vitamin C in the patients who were less ill when admitted (Figure 6).

We had planned a subgroup analysis of treatment trials by vitamin C dosage using 1 g/day as the cut off limit. Hunt 1994 used 0.2 g/day of vitamin C. One of the Mochalkin 1970 vitamin C arms was administered less than 1 g/day but the other arm had a range of vitamin C dosage from 0.5 to 1.6 g/day and the planned subgroup analysis was not feasible.

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

Both treatment 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 CXR was included as a criterion to define pneumonia.

4. Adverse effects

Mochalkin 1970 and Hunt 1994 did not report about any adverse effects by vitamin C.

Secondary outcomes

1. Laboratory findings

C-reactive protein (CRP) levels were not reported in the treatment studies. Mochalkin 1970 reported that the number of participants who had normalisation of erythrocyte sedimentation rate within 16 days was higher, but non significantly so, in the high-dose vitamin C group (Table 1).

2. CXR changes and body temperature changes during treatment

Mochalkin 1970 reported the number of participants with normalisation of the CXR within 10 days and the number of participants with no fever after seven days. Both were non significantly higher in the high-dose vitamin C group (Table 1).

Secondary analysis

We present a secondary analysis of the three arms of the Mochalkin 1970 trial in Table 1. The control arm did not receive a placebo. The duration of hospital stay in the pneumonia patients was 23.7 days in the control group. The decrease in the duration of hospital stay was 4.6 days (19%) in the low-dose vitamin C arm and 8.6 days (36%) in the high-dose vitamin C arm. The mean vitamin C

dose in the high-dose arm was on average twice the mean of dose in the low-dose arm and therefore the linearity in dose response is striking (Table 1). Thus, the secondary analysis of the Mochalkin 1970 study indicates dose-dependence.

Mochalkin also reported the number of participants who had normalisation of erythrocyte sedimentation rate, the number of participants who had no fever after seven days and who had normalisation of the CXR within 10 days. Both vitamin C arms fared significantly better than the control arm for each outcome. The number needed to treat to benefit (NNTB) was 2 to 6 for the three outcomes compared to the control group (Table 1).

Preventing hospital-acquired pneumonia

1. Incidence of pneumonia

Tanaka 2000 reported the incidence of pneumonia within two weeks in severely burned patients after a single day of high-dose vitamin C administration. No difference in the occurrence of hospital-acquired pneumonia between the groups was seen (Analysis 3.1). The study was very small with only 37 participants, and the confidence interval is wide (RR = 1.1; 95% CI 0.5 to 2.7). The evidence is moderate on the GRADE scale (Summary of findings 3).

2. Adverse effects

Tanaka 2000 did not report about any adverse effects by vitamin C although the dosage was particularly high. they administered vitamin C intravenously 66 mg/kg/h during the 24 hours after admission, which corresponds to 110 grams for a 70 kg person per 24 h.

Treating hospital-acquired pneumonia

We did not identify any trials on vitamin C for treating hospital-acquired pneumonia.

GRADE and 'Summary of findings' tables

We constructed 'Summary of findings' tables (Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3). The six included trials are clinically highly heterogeneous and given the small number of included studies such tables may not be quite informative for summarising their results. We used the GRADE assessment in the tables. Although the evidence for benefit of vitamin C in preventing community-acquired pneumonia (Analysis 1.1) and in treating community-acquired pneumonia (Analysis 2.1 and Analysis 2.2) is strong, the conditions of the studies are quite different from each other, and far from the conditions of the current general population. We do not consider that the calculated estimates can be extrapolated to the general population or to average pneumonia patients.

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Vitamin C compared with no vitamin C for treating community-acquired pneumonia

Patient or population: Patients hospitalised for pneumonia
Settings: hospital
Intervention: vitamin C
Comparison: no vitamin C (placebo or no treatment)

Outcomes	Effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Duration of hospital treatment for pneumonia (days)	**mean -4.0 d** (-5.8 to -2.2)	70 (1)	⊕⊕⊕⊕ **high**[1]	The single study was not randomised and reporting was poor
Change in the severity of pulmonary symptoms (scale 3 (least severe) to 10([death]) in elderly pneumonia patients admitted to a hospital with respiratory score 8 or 9 at admission	**mean -2.4** (-4.3 to -0.44)	27 (1)	⊕⊕⊕◯ **moderate**[2]	This is a subgroup of a double-blind RCT; vitamin C had no effect on the less ill participants with score 7 or less on admission
Mortality due to pneumonia	**OR 0.24** (0.04 to 1.29)	57 (1)	⊕⊕⊕◯ **moderate**[3]	
Adverse effects				No adverse effects were reported in the two trials, but the studies were small and vitamin C doses were low

CI: Confidence interval; **OR:** Odds Ratio; **RR:** Risk Ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]We downgraded the quality of evidence by 1 point because potential limitations are likely to lower confidence in the estimate of effect, but we upgraded the quality of evidence by 1 point for the dose-response gradient
[2]We downgraded the quality of evidence by 1 point because potential limitations are likely to lower confidence in the estimate of effect

[3] We downgraded the quality of evidence by 1 point because of imprecision and 1 point because potential limitations are likely to lower confidence in the estimate of effect, but we upgraded the quality of evidence by 1 point because of the large effect (OR < 0.5)

Vitamin C versus no vitamin C for preventing hospital-acquired pneumonia

Patient or population: hospital patients with severe burns
Settings: hospital
Intervention: vitamin C
Comparison: no vitamin C (placebo or no treatment)

Outcomes	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Incidence of pneumonia	**RR 1.1** (0.4 to 2.7)	37 (1)	⊕⊕⊕◯ **moderate**[1]	Vitamin C was administered one day only in the small study
Adverse effects				None reported although the dosage was very high: intravenously 110 grams for a 70 kg person per 24 h

CI: Confidence interval; **RR:** Risk Ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low quality: We are very uncertain about the estimate

[1]We downgraded the quality of evidence by 1 point because potential limitations are likely to lower confidence in the estimate of effect

DISCUSSION

Summary of main results

We identified three prevention trials, which recorded 37 cases of community-acquired pneumonia in 2335 people and two treatment trials that involved 197 community-acquired pneumonia patients. We also identified one prevention trial, which recorded 13 cases of hospital-acquired pneumonia in 37 patients. The five trials on community-acquired pneumonia found a benefit of vitamin C against pneumonia, whereas the trial on hospital-acquired pneumonia did not. We did not identify trials reporting on the treatment of hospital-acquired pneumonia.

One prevention and one treatment trial on community-acquired pneumonia were satisfactorily randomised, double-blind and placebo-controlled. The benefits of vitamin C were not restricted to the trials that were methodologically less rigorous, instead the two methodologically satisfactory trials also found an effect of vitamin C. However, the five community-acquired pneumonia tri-

als with positive findings were all carried out on people who were living under conditions that are far from the ordinary way of life compared to the normal populations of high-income countries.
To allow conclusions specific to vitamin C, we did not include studies that investigated the effect of vitamin C together with other substances against a control group.

Overall completeness and applicability of evidence

We consider that the positive findings of the five analysed community-acquired pneumonia trials (Glazebrook 1942; Hunt 1994; Kimbarowski 1967; Mochalkin 1970; Pitt 1979) are reliable and the studies indicate a biological effect of vitamin C under the conditions of the trials. However, we urge great caution when extrapolating the findings to the general population because of limitations caused by various biological factors. The main limitations are the kind of participants in the trials and the level of vitamin C intake in their diet.

Participants in the trials and the incidence of pneumonia

Both Pitt 1979 and Kimbarowski 1967 examined soldiers: a population that lives under substantially dissimilar conditions compared to those of ordinary adults. Furthermore, Kimbarowski's soldiers were hospitalised because of influenza A. Glazebrook 1942 studied teenage boys in a UK boarding school during World War II. The age range of the Hunt 1994 patients was from 66 to 94 years, and the findings for their more ill participants cannot be directly generalised to pneumonia patients in other settings. Mochalkin 1970 included a wide age range of participants but their social and nutritional background was not described in the paper.
An important feature in the three 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 being hospitalised for influenza A.
The incidence of pneumonia in the ordinary middle-aged Western population is 1 to 3 cases per 1000 person-years (Baik 2000; Hemilä 2004b). In contrast, much higher rates of pneumonia have been reported in 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), which is of the same magnitude as the pneumonia rates in the Glazebrook 1942 and Pitt 1979 trials. Thus, the high incidence of pneumonia makes the conditions of all the three prevention trials very special and thus restrains generalisations of their results to the general population. Nevertheless, the consistency in positive findings indicates that vitamin C may influence the pneumonia risk in some groups of people.

Vitamin C dose in diet and supplements

Another issue of great importance in the interpretation of vitamin C supplementation trials is the level of vitamin C intake in the control group and the level of administration to the vitamin C group. A different outcome between the vitamin C group and the control group may result from a very low baseline dietary intake in the control group ('marginal vitamin C deficiency') or from a high-dose supplementation in the vitamin C group.
In the case of marginal deficiency, a small dosage of vitamin C supplement may be sufficient. Previously, a low dietary vitamin C intake level was proposed to explain the reduction in common cold incidence by vitamin C in a set of trials with British males (Hemilä 1997b; Hemilä 2006). On the other hand, under some conditions high-dose vitamin C might be beneficial even if the level of dietary intake is not low. In the latter case, high doses of vitamin C are needed. As reference levels, scurvy may be caused by vitamin C intakes of 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 obtained only 10 to 15 mg/day of vitamin C from their diet, so that the baseline intake was close to the levels that may cause frank scurvy. The dose of vitamin C administered to the treatment group was 50 to 300 mg/day and such vitamin C doses in the control and the vitamin C groups indicate that the benefit is explained by alleviating marginal deficiency.
Kimbarowski 1967 and Mochalkin 1970 carried out their studies in the former Soviet Union and it seems unlikely that the diet of their participants was rich in vitamin C. Kimbarovski administered 300 mg/day of vitamin C which is not a high dose.
Hunt 1994 reported low plasma levels of vitamin C and the benefit of vitamin C was restricted to the most ill patients who had particularly low plasma vitamin C levels at baseline, only 20 μmol/L (Figure 6). The Mochalkin 1970 trial reported that the mean plasma vitamin C level of the control group dropped to 23 μmol/L during the hospital stay, whereas the mean plasma vitamin C level remained at 43 μmol/L for the high vitamin C dose group. Thus, the control group participants of these two trials may have been suffering from 'marginal vitamin C deficiency'.
Low vitamin C levels are not rare in Western hospital patients nor in the Western community populations (Mosdøl 2008; Raynaud-Simon 2010; Schleicher 2009). Thus, if pneumonia risk is increased by low intakes of vitamin C, then this issue may be important in certain population groups of high-income countries and not just in low-income countries.
The explanation of 'marginal deficiency' is not applicable for the Pitt 1979 trial with US marine recruits, which reported high baseline vitamin C levels. The plasma vitamin C level in the Pitt trial was 56 μmol/L, which corresponds to a dietary intake of 100 mg/

day or more (Levine 1999). Furthermore, the Pitt trial used the highest vitamin C dose of the five trials, 2000 mg/day. It seems probable that the benefit in that trial is explained by the particularly high dose of vitamin C.

The explanation of correcting a 'marginal deficiency' is also not applicable to the comparison between the two vitamin C arms of the Mochalkin 1970 trial (Table 1). The dose-dependency over the three arms of the Mochalkin trial indicates that the treatment effect of vitamin C supplementation was not limited to treating 'marginal deficiency' in the control group. If vitamin C administration simply had alleviated the marginal deficiency, then we would not see any difference between the two vitamin C arms both of which had a rather high vitamin C dose. Evidence of linear dose-dependency up to 6000 mg/day of vitamin C was also found in a common cold trial carried out by Karlowski 1975 (see Hemilä 1996a; Hemilä 1999; Hemilä 2006).

Physical activity

Participants of the Pitt 1979 trial were marine recruits in a training camp setting, which entails heavy physical activity. There is much evidence that heavy exertion increases oxidative stress (Powers 2008). The administration of vitamin C prevented exercise-induced oxidative stress in a study that used electron spin resonance measurements (Ashton 1999). Thus an increased intake of vitamin C might be beneficial for physically stressed people.

In support of this conjecture, vitamin C was found to halve the risk of the common cold in five trials that studied participants under heavy acute physical stress (Hemilä 1996; Hemilä 2013a), and also halved the exercise-induced FEV_1 decline in three trials on participants who suffered from asthma (Hemilä 2014). It is also worth noting that vitamin E, a lipid-soluble antioxidant that interacts with vitamin C, significantly reduced the incidence of pneumonia in middle-aged males who participated in leisure time exercise but had no effect on sedentary men (Hemilä 2016). This difference in response also indicates that physical activity may modify the effects of antioxidants.

Thus, it is probable that the strenuous physical training of the US marine recruits of the Pitt 1979 trial is the reason why the high-dose 2000 mg/day vitamin C supplementation was beneficial for the participants of that trial, but its findings should not be extrapolated to a sedentary population. Several trials with military personnel have found benefits of vitamin C against respiratory infections, which may be explained by heavy exertion and by accommodation in crowded barracks (Hemilä 2004a).

Diagnosis of pneumonia

Hunt 1994 combined the cases of acute bronchitis and pneumonia together. In young people, acute bronchitis usually has a viral aetiology, whereas pneumonia is usually caused by bacteria. However, the patients in the Hunt 1994 trial were all over 60 years of age and their acute bronchitis was "often acute exacerbation of chronic bronchitis", which implies bacterial aetiologies. The clinical definition of pneumonia is ambiguous and CXR has a substantial proportion of false negatives. This evidently limits the applicability of any studies on pneumonia (see Appendix 1). The combined outcome used in the Hunt 1994 trial seems justified in the current review.

Hospital-acquired pneumonia

Tanaka 2000 administered vitamin C for one day only but recorded pneumonia cases for two weeks. Thus, the follow-up was substantially longer than the vitamin C administration period. Furthermore, the confidence interval for the effect of vitamin C is very wide (Analysis 3.1). Therefore we consider that this trial is not informative about the potential effects of vitamin C on hospital-acquired pneumonia, it does not refute or support benefits.

Quality of the evidence

We primarily focus in this section on the five trials on community-acquired pneumonia with positive findings. We briefly comment on the Tanaka 2000 trial at the end of this section.

Two of the five positive trials were placebo-controlled, randomised trials, whereas the methodology of the other three community-acquired pneumonia trials were technically limited to varying degrees. Here we consider 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 when the result is "positive" and tend to leave it unreported when the result is "negative". With this reasoning, it is possible that the five community-acquired pneumonia trials analysed in this review were published just because of the significant benefit of vitamin C they observed, whereas there might be several unpublished trials that showed negative results. However, the three papers that observed the prevention effect of vitamin C were not published because of their positive findings on vitamin C and pneumonia.

Glazebrook 1942 was mainly interested in the common cold and tonsillitis and the effect on pneumonia was mentioned as a secondary issue, which indicates that this finding was not the primary reason for publication. Kimbarowski 1967 considered pneumonia as a nuisance in their trial as they focused on a diagnostic test. They did not pay any attention to the significant difference in the occurrence of pneumonia in the trial arms, for example, in their summary the pneumonia cases in both trial arms were combined. Pitt 1979 focused on the common cold, and for them pneumonia was a secondary outcome, which was reported in the text but not in the abstract. Thus these three trials were not published because of their findings on pneumonia. Low interest of the authors in

pneumonia is also relevant when considering detection bias (see below).

Hunt 1994 found a significant modification of the vitamin C effect by the baseline disease severity. Mochalkin 1970 found a linear dose-response association between the duration of pneumonia and the dose of vitamin C over the three trial arms (Table 1). Neither Hunt nor Mochalkin put proper emphasis on these findings and thus these findings were not the reason for the publication.

Selection bias occurs when there are systematic differences between the compared groups at baseline. In prevention trials, there is a low risk of bias by baseline differences between the treatment arms. Maldistribution of a strong risk factor, such as smoking in a study on lung cancer, would lead to erroneous conclusions on less important risk factors. However, cohort studies have not identified strong risk factors for community-acquired pneumonia, though the age of the person is the most important factor(Baik 2000; Hemilä 2004b). Thus, to explain the 80% or greater reduction in the incidence of pneumonia in the vitamin C arms by baseline imbalance would require that there is spectacular maldistribution in a strong risk factor for pneumonia to explain such a difference (Figure 4). Furthermore, the Pitt 1979 trial was randomised and double-blind and Glazebrook 1942 used pre-formed divisions and explicitly ascertained that the groups were similar to each other. The severity of influenza in the Kimbarowski 1967 trial was probably the most important risk factor for the occurrence of pneumonia but it was distributed evenly between the trial arms.

The baseline severity of disease in treatment trials 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 close and similar for both treatment arms. Mochalkin 1970 did not describe the distribution of pneumonia severity but antibiotic treatments were distributed evenly amongst the three arms. Therefore, if the selection of antibiotics in the Mochalkin 1970 trial depended on the clinical symptoms, they were also divided evenly. Thus, it seems unlikely that there might have been systematic baseline differences in the treatment trials that could explain the reported findings.

Performance bias describes the 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, which is an essential issue in a vitamin C study 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, as noted above, the use of antibiotics was similar for the three treatment arms. Although Mochalkin did not use a placebo in the control group, performance bias does not reasonably explain the difference between the two vitamin C arms (Figure 5; Table 1). Furthermore, given the great difference between the two vitamin C supplementation groups, it seems reasonable to assume that the difference between the control group and the low-dose vitamin C group is also caused by a difference in vitamin C intake, instead of other factors.

Thus, in two trials there was good evidence to indicate that participants were treated equally except for the vitamin C administration. In the other three trials there was no explicit reason to assume that the other treatments would substantially differ between the trial arms.

Attrition bias refers to high or divergent drop-out proportions but it does not seem to be a substantial concern in these five trials. The three trials that examined the preventive effect of vitamin C were carried out within two military organisations (Kimbarowski 1967; Pitt 1979) and a boarding school (Glazebrook 1942). Such a background and the descriptions given in the respective publications do 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 between 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 reported distribution of antibiotic usage was similar in the trial arms, which suggests that there were no drop-outs.

Detection bias refers to a systematic differences in an outcome assessment. The Hunt 1994 and Pitt 1979 trials were double-blinded and bias caused by the knowledge of participants or investigators was unlikely affect the outcome assessment. Pneumonia was a secondary issue in the Glazebrook 1942, Kimbarowski 1967 and Pitt 1979 trials as noted above and it is unlikely that under such conditions the investigators would have a 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.

Even though three of the trials with positive results were methodologically less rigorous in comparison with modern trial standards, the positive findings of these three trials are not easily explained by biases.

We used the GRADE approach to assess the quality level of the body of evidence of the five trials on community-acquired pneumonia. GRADE approach involves consideration of five items: within-study risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias (Higgins 2011, sect 12.2). We do not consider that the five included community-acquired pneumonia trials have serious limitations in these items. However, the conditions of the five trials on community-acquired pneumonia are very special. We do not consider it reasonable to express an opinion about whether further research is likely or unlikely to change our confidence in the calculated estimates of effects. All the five trials imply that vitamin C has a true physiological effect against pneumonia under some conditions, but the estimates of effect of those five studies

should not be extrapolated to current population groups.
The Tanaka 2000 trial was poorly described and the allocation method and the level of blinding are not clear from the study report. Nevertheless, we did not ignore the trial on the basis of these methodological shortcomings. Vitamin C was administered for one day only but the pneumonia cases were recorded for two weeks. The confidence interval obtained was wide. We consider that these issues make the study uninformative about the role of vitamin C on hospital-acquired pneumonia.

Potential biases in the review process

Our searches of databases for trials meeting the criteria for our review were exhaustive and we also read reference lists of several reviews, such as Briggs 1984, which contains 413 references to papers related to vitamin C and infections. Although there might be unpublished trials, or trials published in difficult to access journals or books, it seems unlikely that we could have missed large controlled trials.
We conducted this review according to the published protocol (Hemilä 2005), and reported any deviations from the protocol in the 'Differences between protocol and review' section of this review.

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 association between vitamin C intake and pneumonia risk. A cohort study found no association between vitamin C intake and community-acquired pneumonia in middle-aged men in the USA (Merchant 2004). However, there are substantial differences between that cohort study and the three prevention trials shown in Figure 4. Merchant 2004 investigated male US health professionals of 40 to 75 years of age, the selection of whom entailed 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 and the overall median was 218 mg/day, whereas the overall median of the ordinary US population is about 100 mg/day (IOM 2000). Thus, vitamin C intake in Merchant's cohort was substantially higher than those of the three prevention trials analysed in this review and the living conditions were also very different compared with the participants of the three trials analysed in this review. Furthermore, the incidence of pneumonia was 3.0 cases per 1000 person-years, which is much lower than the 60– 120 cases per 1000 person-years in the control arms of Glazebrook 1942 and Pitt 1979.

Thus, the Merchant cohort study indicates that the level of vitamin C intake does not affect low pneumonia risk in sedentary, health-conscious, middle-aged, upper-class populations when their baseline dietary vitamin C intake is over 100 mg/day. Their findings cannot be extrapolated to substantially different population groups such as those in the three prevention trials analysed in the current review. Nevertheless, the Merchant cohort study does set certain limits on the 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 Merchant 2004 and in the intervention trials shown in Figure 4.
Some other studies are also relevant to the current topic. Dahlberg 1944 reported the number of respiratory infections that were more severe than the common cold in military recruits: five in the vitamin C group, 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 tract infections.
Although Tanaka 2000 found no effect of vitamin C on the incidence of hospital-acquired pneumonia, they found a 43% (P = 0.03) reduction in the duration of mechanical ventilation and a significant decrease in infusion fluid volumes from a single-day, high-dose intravenous vitamin C administration, which indicated other benefits of vitamin C administration for hospital patients. Similarly, Nathens 2002 reported that vitamin C and E combination had no effect on pneumonia risk (RR 0.79, 95% CI 0.53 to 1.20) in critically ill ICU patients, but 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 reduction of 1.2 days (95% CI 0.81 to 1.5 days) in their ICU length of stay. The significant effect on the duration of mechanical ventilation, which was found in the two trials mentioned above, was also found in a few vitamin C studies on cardiac surgery patients (Bjordahl 2012; Dehghani 2014; Sadeghpour 2015).
Mochalkin 1970 found a significant reduction in the duration of hospital stay of their pneumonia patients. Significant reduction in hospital stay has also been found in a few vitamin C studies with cardiac surgery patients (Dehghani 2014; Papoulidis 2011; Sadeghpour 2015; Sarzaeem 2014).

Safety of vitamin C

None of the included studies reported concerns about adverse effects caused by vitamin C. Pitt 1979 reported about a single participant to whom vitamin C caused urticaria, but that disappeared after stopping the dosage of 2 g/day of vitamin C.
In general, vitamin C is considered safe in doses of up to several grams per day. Although there have been speculation about the potential harms of large doses, these have been shown to be unfounded (Hathcock 2005; Hemilä 2006; IOM 2000; Levine 1999; Rivers 1987).
Cathcart 1981 reported that he had administered orally over 100

g per day of vitamin C to pneumonia patients, which indicates the safety of such high doses for pneumonia patients, although such an uncontrolled observation does not provide evidence of benefit. Large doses of vitamin C have also been administered intravenously to tens of thousands of patients without serious adverse effects (Padayatty 2010).

Low interest in the possible effects of vitamin C against pneumonia

Early scientific literature recognised the association between the deficiency of vitamin C and the frequent occurrence of pneumonia (Hess 1920; Robertson 1934). In addition, dozens of animal studies with several species of animals have found that vitamin C is effective against diverse bacterial and viral infections (Hemilä 2006). Given such a background, the positive findings in the five studies on community-acquired pneumonia are not surprising. However, the absence of further studies on community-acquired pneumonia after the 1990s is striking (Figure 2). The lack of interest in vitamin C and pneumonia after the 1990s cannot be explained by negative findings in large randomised trials. There must be other reasons for the lack of interest in the possibility that vitamin C might decrease the risk of pneumonia by 80% in some population groups that have a very high incidence of pneumonia.

The dominant theory of vitamins in mainstream medicine is that the function of vitamins in the body is to prevent deficiency diseases, and therefore, other uses of vitamins belong to the domain of alternative medicine (Louhiala 2014). Thus, it seems possible that the low level of interest in the reported effects of vitamin C on pneumonia is caused by general prejudices against vitamins as medicines. Goodwin 1998 gave several examples that illustrated the prejudices of the mainstream medicine towards vitamins. Prejudices have also been documented on the topic of vitamin C and the common cold (Hemilä 1996a; Hemilä 1996b; Hemilä 2006). Although the five studies on community-acquired pneumonia published by the 1990s do not give definitive answers on the role of vitamin C in preventing and treating pneumonia, they call for further research in pneumonia patients and in population groups with high incidence of pneumonia.

AUTHORS' CONCLUSIONS

Implications for practice

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

While waiting for new trials to be conducted, treatment vitamin C supplementation may be reasonable for patients with pneumonia who have low vitamin C plasma levels, since such administration is limited in time. The low price of vitamin C indicates that it might be a reasonable intervention even if the benefit might be substantially lower than that observed in the treatment trials analysed in this review.

Implications for research

The incidence of pneumonia in the middle-aged population in high-income countries is low (1 to 3 cases per 1000 person-years) and there is no rationale for studying the prevention effects of vitamin C in such a population. Even if vitamin C had a true biological effect, the low baseline incidence would lead to very high values of numbers needed to treat to benefit (NNTB).

Certain populations have a high risk of pneumonia. In low-income countries the incidence of pneumonia in children has been as high as 400 cases per 1000 person-years (Paynter 2010). In many low-income countries the prevalence of malnutrition is high, and low vitamin C intake is common (Hemilä 2007a). Elderly people also have an elevated risk of pneumonia, since the incidence increases with age (Baik 2000; Hemilä 2004b). Another population group with a particularly high risk of pneumonia is military recruits (Pazzaglia 1983).

Even if the benefit of vitamin C was substantially lower than indicated in the three prevention trials analysed in this review, the effect may still be important in populations with a high incidence of pneumonia. For example, given a baseline pneumonia incidence of 60 per 1000 person-years (Pazzaglia 1983), a reduction of risk by half would correspond to a NNTB of 33 over one year.

Pneumonia is the sixth most common cause of death in the USA and the most common cause of infection-related mortality, which reflects its importance (Ellison 2015). Treatment trials on vitamin C in pneumonia patients should be carried out; particularly in patients with low vitamin C plasma levels, but also in pneumonia patients with ordinary plasma vitamin C levels. The outcomes of treatment trials should include soft outcomes that measure the quality of life because vitamin C also has non-immune effects, especially in participants with very low plasma vitamin C levels and pneumonia *per se* leads to a substantial reduction in vitamin C levels.

ACKNOWLEDGEMENTS

English translation of the Gander 1936 paper was kindly arranged by Eva Wintergerst from Bayer Consumer Care AG, Basel, Switzerland. English translations of the Bohnholtzer 1937 and Hochwald 1937 papers were kindly arranged by Angelique Boyer from Proctor and Gamble Co, Cincinnati, OH.

We are grateful to Sharon Gudu, Anwar Merchant, Vladimir Bakaev, Andrey Duntau, Bahi Takkouche, Lize van der Merwe and Paul Glasziou for commenting on the draft protocol, which helped us to rewrite the Methods section.

Finally, the authors would like to thank the following people who commented on the draft review: Ann Fonfa, Vladimir Bakaev, Andrey Duntau, Anwar Merchant, Rob Ware and Chris Del Mar.

The authors would like to thank the following people who commented on the draft of this 2016 updated review: Janet Wale, Ann Fonfa, Allen Cheng, Teresa Neeman, and Mieke van Driel.

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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)	Unclear risk	Treatment groups were based on administrative divisions of boarding school, no allocation on the individual level (see Included studies and Quality of the evidence sections for details)
Allocation concealment (selection bias)	Unclear risk	Concluding from the report, allocation was not concealed from the researchers but may have been from the schoolboys, although this is not explicitly stated (see Included studies and Quality of the evidence sections for details)
Baseline balance	Low risk	The authors describe the baseline comparability of the study groups as follows "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" (p. 12). Evidently, because of the type of selection, the sex distribution was identical and age distributions in the groups were closely similar

Glazebrook 1942 (*Continued*)

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 and Quality of the evidence sections 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 and Quality of the evidence sections for details)
Incomplete outcome data (attrition bias) All outcomes	Low risk	The study was carried out in a boarding school. Such a background and the descriptions given in the report does not suggest a considerable drop-out problem
Selective reporting (reporting bias)	Low risk	The authors were mainly interested in the common cold and tonsillitis and the effect on pneumonia was mentioned as a secondary issue, which indicates that this finding was not the primary reason for publication. Thus, pneumonia cases were not selected for reporting on the basis that there was a significant difference between the treatment groups

Hunt 1994

Methods	Randomised, placebo-controlled, double-blind trial Carried out in October to December
Participants	57 elderly patients in the UK: 27 males, 30 females, age range 66 to 94, mean 81 yr (28 vit 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	Change in a score of clinical symptoms in 4 weeks (scale 3 to 10: 3 = no symptoms, 10 = death) Mortality
Notes	
Risk of bias	

Hunt 1994 (*Continued*)

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
Baseline balance	Low risk	The mean age (81.4 versus 80.4 yr in males; 82.0 versus 78.9 yr in females), mean baseline total respiratory clinical score (7.18 versus 7.45), and mean baseline plasma vitamin C level (23.2 versus 23.9 μmol/L) were closely similar in vitamin C and placebo groups, respectively
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
Incomplete outcome data (attrition bias) All outcomes	Low risk	The authors followed up the patients for four weeks and did not report any drop-outs
Selective reporting (reporting bias)	Low risk	Based on the study report, change in the clinical score was the primary outcome and there is no indication that it was selected out of several outcomes

Kimbarowski 1967

Methods	Allocation method not described but study arms were of similar size (112 and 114 initially); apparently all males 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 vit C; 112 control); apparently all males Carried out in the former Soviet Union
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)	Unclear risk	Concluding from the report, probably alternative allocation because the groups were nearly identical in size (114 versus 112) though this is not explicitly stated (see Included studies and Quality of the evidence sections for details)
Allocation concealment (selection bias)	Unclear risk	Concluding from the report, there is no reason to assume that allocation was concealed (see Included studies and Quality of the evidence sections for details)
Baseline balance	Low risk	One of the most essential baseline factors in this study is the severity of influenza. The number of severe cases was 64 versus 65, moderate cases 26 versus 32 and mild cases 12 versus 14 in vitamin C and no-treatment arms, (page 2414). The type of selection of the patients causes that the sex distribution is identical (all males), the cause of hospitalisation is identical (influenza A), and the age distribution is probably closely similar in the 2 study arms
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Concluding from the report, there is no reason to assume that researchers were blinded to the intervention (see Included studies and Quality of the evidence sections for details)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Concluding from the report, there is no reason to assume that researchers were blinded when assessing pneumonia (see Included studies and Quality of the evidence sections for details)
Incomplete outcome data (attrition bias) All outcomes	Low risk	The study was carried out with hospitalised military recruits. Such a background and the descriptions given in the report does not suggest a considerable drop-out problem

Kimbarowski 1967 (*Continued*)

Selective reporting (reporting bias)	Low risk	The authors considered pneumonia as a nuisance in their trial as they focused on a diagnostic test. They did not pay any attention to the significant difference in the occurrence of pneumonia in the trial arms, for example, in their summary the pneumonia cases in both trial arms were combined. Thus, pneumonia cases were not selected for reporting on the basis that there was a significant difference between the treatment groups

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. Sex distribution not reported Carried out in the former Soviet Union
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 the 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 CXR normalisation
Notes	Control group was not administered placebo and thus the primary analysis focuses on the high and low vitamin C groups, so that we consider the low vitamin C group the placebo group in our comparison We did a secondary analysis in which all 3 arms were included (Table 1) The same data were published by Mochalkin in slightly different versions in 1974 and 1975, see refs

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation not described and groups are of such different sizes that it is unlikely they originate from randomisation

Mochalkin 1970 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Concluding from the report, there is no reason to assume that allocation was concealed
Baseline balance	Unclear risk	Distribution of antibiotics was similar in the low and high vitamin C groups, but this does not directly imply similarity in clinically relevant factors
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Concluding from the report, there is no reason to assume that researchers were blinded to the intervention (see Included studies and Quality of the evidence sections for details)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Concluding from the report, there is no reason to assume that researchers were blinded when assessing pneumonia (see Included studies and Quality of the evidence sections for details)
Incomplete outcome data (attrition bias) All outcomes	Low risk	The study is poorly reported. However, the equal distribution of control (n = 70) and vitamin C (0 = 70 = 31 + 39) (see Table 1) and the equal distribution of antibiotic use within each of the 3 groups (see Mochalkin 1970) indicates that it is unlikely that drop out occurred
Selective reporting (reporting bias)	Low risk	Concluding from the report, pneumonia duration was the primary focus of the trial. There is no indication that it was selected out of several outcomes

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); apparently all males
Interventions	Vitamin C 2 g/day
Outcomes	Incidence of pneumonia
Notes	

Pitt 1979 (*Continued*)

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
Baseline balance	Low risk	Large vitamin C and placebo groups. There were no substantial differences between the two groups with respect to age; race; previous common cold history, including number, duration, or disability from colds; and previous medical history of respiratory-related illness, allergy, smoking, or vitamin intake (Table 1)
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
Incomplete outcome data (attrition bias) All outcomes	Low risk	The study was carried out in US marine recruits. Such a background and the descriptions given in the report does not suggest a considerable drop-out problem. Specifically, the authors described 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 between the treatment arms
Selective reporting (reporting bias)	Low risk	The authors focused on the common cold, and for them pneumonia was a secondary outcome, which was reported in the text but not in the abstract. Thus, pneumonia cases were not selected for reporting on the basis that there was a marginally significant difference between the treatment groups

Tanaka 2000

Methods	Parallel-group controlled trial but possibly not randomised although the term is used. Level of blinding not described
Participants	37 consecutive patients with burns over 30% of their total body surface area who were admitted to the ICU within 2 h after the injury
Interventions	Intravenous vitamin C (66 mg/kg/h) during the 24 hours after admission (i.e. 110 grams for a 70 kg person per 24 h)
Outcomes	Incidence of pneumonia within 2 weeks (Analysis 2.2)
Notes	Primary focus of the study was fluid balance The study reported also on the length of hospital stay and the length of mechanical ventilation. These are not for pneumonia patients and thus we do not include them in our Results section, but include them in our Discussion section

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomization was performed according to the month of admission", which suggests that the authors used 'randomisation' as a synonym for 'allocation'
Allocation concealment (selection bias)	Unclear risk	Not described
Baseline balance	Low risk	Sex (13 versus 12), body weight (57 kg versus 58 kg), number of flame/scald burns (15/4 versus 15/3) and number of inhalation injuries (15 versus 12) were quite evenly distributed among 19 vitamin C and 18 no-vitamin C participants, respectively. However, the differences in age (40 (SD 20) y versus 49 (SD 22) y), in the area of burns relative to total body surface area (63% versus 53%), and in full-thickness burn (51% versus 40%) between the groups was rather large, but unlikely to substantially bias the reported findings
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described, but it seems unlikely that there is placebo effect on ICU patients when they receive one intravenous drug in addition to the other drugs
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described, but bias in the detection of pneumonia does not seem highly likely

Tanaka 2000 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Based on the study report, there were no drop-outs
Selective reporting (reporting bias)	Low risk	Occurrence of pneumonia was a secondary outcome. Given that there was no difference between vitamin C and placebo groups in the occurrence of pneumonia it is not reasonable to assume that pneumonia was selected out of numerous infections on the basis of positive findings

h = hour
ICU = intensive care unit
n = number

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

Study	Reason for exclusion
Cook 2007	No data on pneumonia. This is a large-scale trial in which 0.5 g/d vitamin C was administered to 8171 US female health professionals for 9 y. We asked whether any data on the incidence of pneumonia might have been collected and received a reply: "WACS ... did not ask about occurrence of pneumonia" (email Dr. Cook 23 April 2013). This large-scale trial does give relevant information about adverse effects of vitamin C
Dahlberg 1944	Military recruits in Sweden (n = 2525). 0.05 g/d 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 which also contains upper respiratory infections
Hunt 1984	One group of diagnoses in the hospitalised patients (n = 199) 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 (n = 40). The abstract suggests that it was a controlled trial: "patients were divided into two groups", one of which was administered IV 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 (0.2 g/d) and E (0.4 g/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). The dose of vitamin E is very high for young children, compared e.g. with the dose of 0.05 g/day for middle-aged males in Hemilä 2009a, in which vitamin E supplementation for males with high dietary vitamin C intake increased mortality

(*Continued*)

Mahalanabis 2006b	Combination of vitamins C (0.2 g/d) and E (0.2 g/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). The dose of vitamin E is very high for children, compared e. g. with the dose of 0.05 g/day for middle-aged males in Hemilä 2009a, in which vitamin E supplementation for males with high dietary vitamin C intake increased mortality
Nathens 2002	Critically ill surgical patients (n = 595). Combination of vitamins C (1 g/d) IV and vitamin E (1000 IU/d) per naso-orogastric tube for up to 28 d. No difference in the incidence of pneumonia, but a significant decrease in the duration of mechanical ventilation and ICU length of stay
Pico Sirvent 2013	Vitamin C was administered together with beta-glucan to 166 children from 1 to 10 years old. "Number of respiratory infections ... registered during four visits and compared with the same 6 months period from previous year" which is not an appropriate comparison
Scheunert 1949	Different doses of vitamin C were administered to 4 study groups (0.02, 0.05, 0.1 and 0.3 g/d) (n = 1066) 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 However, the data are presented so ambiguously that no data could be extracted for this review
Sesso 2008	No data on pneumonia. This is a large-scale trial in which 0.5 g/d vitamin C was administered to 14,641 US male physicians for 8 y. We asked whether any data on the incidence of pneumonia might have been collected and received a reply: "data on incident pneumonia has unfortunately not been collected" (email Dr. Sesso 19 April 2013). This large-scale trial does give relevant information about adverse effects
Wahed 2008	The description of the methods of this 7-arm trial is minimal. The dose of vitamin C is not described. It is not clear whether a placebo was used. The authors state 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 plausible 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 (n = 400) was 7.75 d and in the vitamin C group (n = 40) was 7. 00 d. However, the SD is not given for the estimates. Due to these and many further problems we excluded the trial. We made attempts to contact the author to ask for details, but we were not successful

d = days
ICU = intensive care unit
IV = intravenous
n = number
SD = standard deviation
y = years

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

Lafargue 2015

Trial name or title	Interest of ascorbic acid in the management of pneumonia in elderly people hospitalised (PNEUMO-VITA-C)
Methods	Randomised, double-blind, placebo-controlled, single-centre trial
Participants	Hospitalised elderly patients
Interventions	Intravenous injection of 2.5 mL ascorbic acid (0.5 g) twice a day
Outcomes	
Starting date	February 2015
Contact information	Aurelie LAFARGUE, MD; Jessica DURRIEU
Notes	

DATA AND ANALYSES

Comparison 1. Vitamin C for preventing community-acquired pneumonia

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of pneumonia	3		Peto Odds Ratio (Peto, Fixed, 90% CI)	Totals not selected

Comparison 2. Vitamin C for treating community-acquired pneumonia

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duration of hospital treatment for pneumonia (days)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2 Change in the severity of pulmonary symptoms (scale 3 to 10)	1	57	Mean Difference (IV, Fixed, 95% CI)	-0.61 [-1.58, 0.35]
2.1 Most severely ill (respiratory score 8 or 9 on admission)	1	27	Mean Difference (IV, Fixed, 95% CI)	-2.38 [-4.32, -0.44]
2.2 Less ill (respiratory score ≤7 on admission)	1	30	Mean Difference (IV, Fixed, 95% CI)	-0.04 [-1.15, 1.07]
3 Mortality due to pneumonia	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected

Comparison 3. Vitamin C for preventing hospital-acquired pneumonia

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 The number of pneumonia cases during the follow-up	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Vitamin C for preventing community-acquired pneumonia, Outcome 1 Incidence of pneumonia.

Review: Vitamin C for preventing and treating pneumonia

Comparison: 1 Vitamin C for preventing community-acquired pneumonia

Outcome: 1 Incidence of pneumonia

Study or subgroup	Vit C n/N	Control n/N	Peto Odds Ratio Peto,Fixed,90% CI	Peto Odds Ratio Peto,Fixed,90% CI
Glazebrook 1942	0/335	17/1100		0.27 [0.10, 0.69]
Kimbarowski 1967	2/114	10/112		0.24 [0.09, 0.64]
Pitt 1979	1/331	7/343		0.23 [0.07, 0.73]

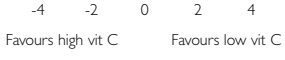
Analysis 2.1. Comparison 2 Vitamin C for treating community-acquired pneumonia, Outcome 1 Duration of hospital treatment for pneumonia (days).

Review: Vitamin C for preventing and treating pneumonia

Comparison: 2 Vitamin C for treating community-acquired pneumonia

Outcome: 1 Duration of hospital treatment for pneumonia (days)

Study or subgroup	High vit C N	Mean(SD)	Low vit C N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Mochalkin 1970	31	15.1 (3.23)	39	19.1 (4.56)		-4.00 [-5.83, -2.17]

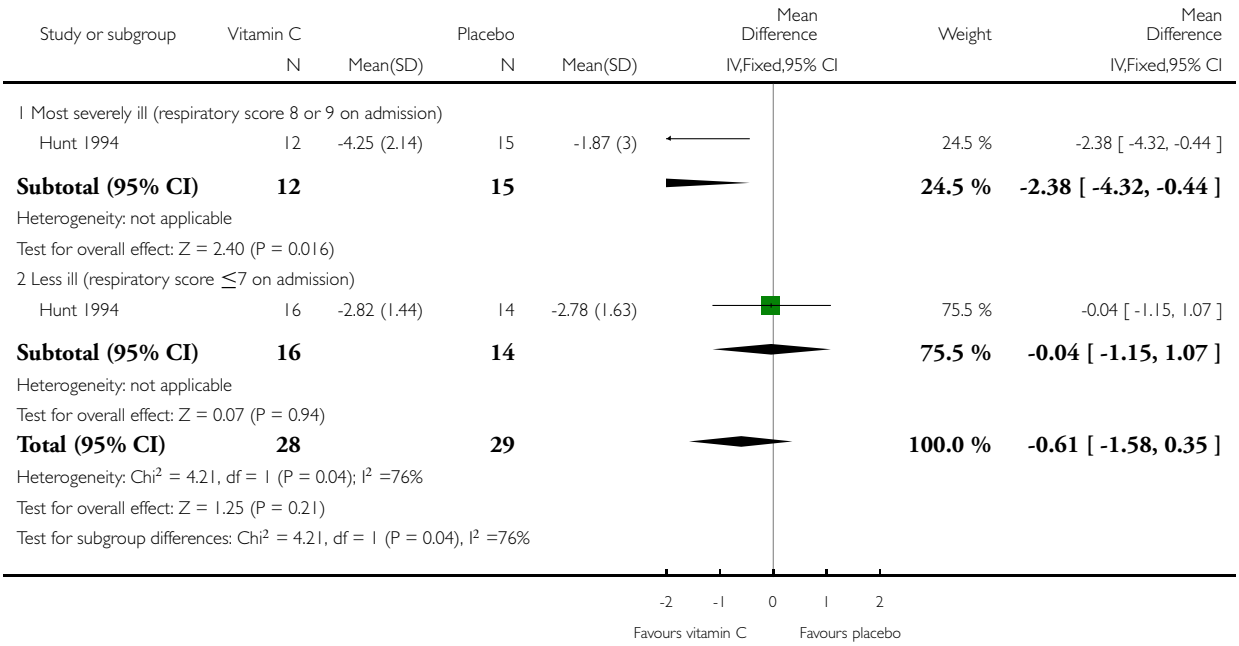


Analysis 2.2. Comparison 2 Vitamin C for treating community-acquired pneumonia, Outcome 2 Change in the severity of pulmonary symptoms (scale 3 to 10).

Review: Vitamin C for preventing and treating pneumonia

Comparison: 2 Vitamin C for treating community-acquired pneumonia

Outcome: 2 Change in the severity of pulmonary symptoms (scale 3 to 10)

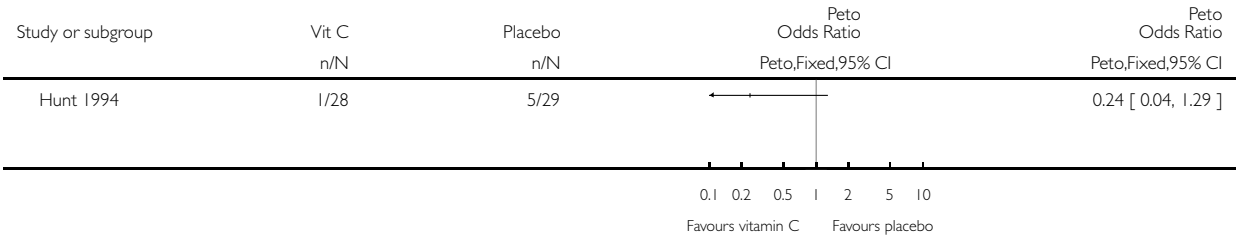


Analysis 2.3. Comparison 2 Vitamin C for treating community-acquired pneumonia, Outcome 3 Mortality due to pneumonia.

Review: Vitamin C for preventing and treating pneumonia

Comparison: 2 Vitamin C for treating community-acquired pneumonia

Outcome: 3 Mortality due to pneumonia

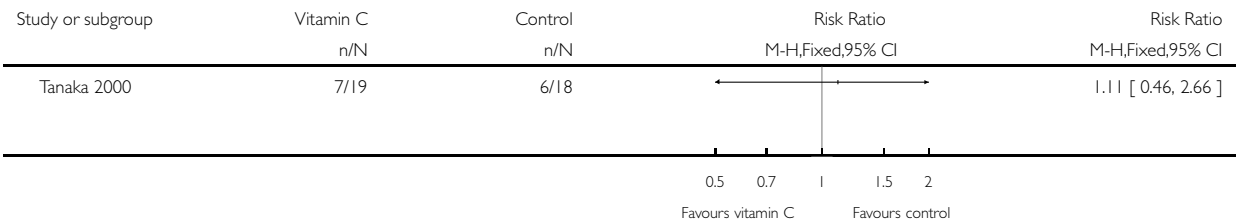


Analysis 3.1. Comparison 3 Vitamin C for preventing hospital-acquired pneumonia, Outcome 1 The number of pneumonia cases during the follow-up.

Review: Vitamin C for preventing and treating pneumonia

Comparison: 3 Vitamin C for preventing hospital-acquired pneumonia

Outcome: 1 The number of pneumonia cases during the follow-up



ADDITIONAL TABLES

Table 1. Mochalkin 1970: All results of all three trial arms

Outcome	Control (no placebo)	Low vit C group	High vit C group	P (high versus control)
Participants in the trial arms (N)	70	39	31	
Vitamin C level in plasma				
Initial level (μmol/L)	41	41	40	
Level at 10 days (μmol/L)	23	35	43	
Outcomes				
Normalisation of erythrocyte sedimentation rate in 16 days (n) (n/N in %)	41 (58%)	36 (92%)	31 (100%)	10^{-5}
NNTB, compared with the control		3.0	2.1	
Temperature normal in 10 days (n) (n/N in %)	54 (77%)	37 (95%)	31 (100%)	0.002
NNTB, compared with the control		5.5	4.4	
Chest radiograph normal in 16 days (n) (n/N in %)	47 (67%)	33 (84%)	29 (93%)	0.003
NNTB, compared with the control		5.9	3.8	
Duration of hospital stay (days) mean (SD)	23.7 (3.2)	19.1 (4.6)	15.1 (3.3)	10^{-20}
Difference from control (days), mean (95% CI)		4.6 (3.1 to 6.1)	8.6 (7.2 to 10.0)	

CI = confidence interval
n = number
NNTB = number needed to treat to benefit; the number of people who need to be treated so that one of them gets benefit.
SD = standard deviation

APPENDICES

Appendix 1. Diagnosis of pneumonia

We did not require that the pneumonia diagnosis was based on chest X-ray (CXR). CXR is objective in the sense that the picture is permanent. However, CXR is not an accurate test for pneumonia.

Syrjälä 1998 reported that of 26 adult pneumonia cases that were diagnosed as pneumonia using computed tomography (CT), only 18 were identified when using CXR; thus 30% of the HRCT-identified pneumonias were false negatives in the CXR. Claessens 2015 reported that CT revealed a parenchymal infiltrate in 40 (33%) of the 172 patients without infiltrate on CXR. On the other hand, CT excluded CAP in 56 (29.8%) of the 188 with parenchymal infiltrate on radiograph. Thus, in 56 (18%) cases out of 308, CT and CXR gave contradictory findings,

Doherty 1991 reported that of six cases of pneumonia in children identified at autopsy, only three were identified by a radiologist using CXR. Evidently the sensitivity of CXR is often low. Also, the interpretation of CXR to conclude that a patient has pneumonia is quite subjective.

Kappa (K) score is a measure for inter-observer variability, with K = 1 indicating perfect agreement and K = 0 indicating agreement explained by pure chance. In both adults and children, interpretation of a set of CXR to decide whether the patient has pneumonia or not yielded low agreement between two observers: K of 0.4 to 0.5 (Albaum 1996; Bloomfield 1999; Hopstaken 2004; Melbye 1992) and inter-observer variability ranged from 20% to 30% (Kiekara 1996; Young 1994). In patients with chronic obstructive pulmonary disease, Hopstaken 2004 found a K of 0.2 for the diagnosis of pneumonia using CXR indicating very poor agreement between two radiologists.

Because of its inconsistency and low sensitivity, CXR is not a 'gold standard' for the diagnosis of pneumonia, even though it is a very popular method. CT is more sensitive but rarely available.

Pneumonia can be diagnosed clinically without CXR. In low-income countries, the World Health Organization (WHO) has proposed the use of respiratory rate and chest in-drawing to decide whether children presenting to outpatient clinics with cough or difficulty in breathing have 'clinical pneumonia' (Pio 2003). A multi-centre study facilitated by the WHO evaluated the efficacy of predicting pneumonia from clinical signs and symptoms and found that a combination of respiratory rate, rectal temperature, weight-for-age and a set of other clinical findings accurately predicted pneumonia (WHO 1999b). This study was motivated by the fact that "in low-income countries laboratory facilities to perform tests such as the blood count and CXR are often unavailable and clinical decisions must be made without them". A Cochrane Review analysed whether clinical symptoms and signs might be used to identify pneumonia caused by *Mycoplasma pneumoniae* but they were not good at identifying mycoplasma pneumonia cases (Wang 2012).

Clinical diagnosis of pneumonia and CXR-based diagnosis of pneumonia have modest disagreement but we do not know how they both compare with CT. It is possible that some of the clinical pneumonia cases that are negative in CXR might be positive in CT. Thus, the divergence between clinical diagnosis and CXR should not be considered categorically as a measure of error in the former.

Furthermore, CXR does not necessarily add useful information to the clinical diagnosis of pneumonia. Swingler found that "interpretation of CXR did not affect clinical outcome in outpatient children with an acute lower respiratory infection. There are no clinically identifiable subgroups of children within the WHO case definition of pneumonia who are likely to benefit from a CXR" (Swingler 1998). Finally, Dirlewanger 2002 in Switzerland found that of 47 children fulfilling the WHO clinical criteria of pneumonia, 46 children had consolidation or diffuse infiltrate in CXR; thus showing that pneumonia can be accurately diagnosed clinically in high-income countries without the use of CXR. For these reasons we have not limited our review to trials using pneumonia diagnosis based on CXR but have also included trials with clinical pneumonia diagnosis.

Appendix 2. CENTRAL and MEDLINE search strategy in 2015

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

Appendix 3. Earlier searches

Search in the 2013 version: We searched the Cochrane Central Register of Controlled Trials (CENTRAL) 2013, Issue 3, part of *The Cochrane Library*, www.thecochranelibrary.com (accessed 8 April 2013) which contains the Acute Respiratory Infections Group's Specialised Register, MEDLINE (1950 to March week 4, 2013), EMBASE (1974 to April 2013) and Web of Science (1945 to April 2013).

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

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

Search in the 2011 version: 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.

[The MEDLINE search strategy in 2011 was the same as in the 2013 version, see above.]

Search in the 2009 version: We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2008, Issue 4), which contains the Acute Respiratory Infections Group's Specialised Register, Ovid MEDLINE (1950 to January Week 1, 2009), EMBASE (1974 to January 2009), Web of Science (1945 to January 2009) and reference lists of reviews and articles.

[The MEDLINE search in 2009 was as in the 2007 version, see below.]

Search in the 2007 version: We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2006, Issue 1), OLD MEDLINE (1950 TO 1965), MEDLINE (1966 to February Week 2, 2006), EMBASE (1974 to March 2006), Web of Science (1945 to February 2006) and reference lists of reviews and articles.

MEDLINE (OVID) (2007 and 2009 searches)

1 vitamin C.mp. or exp Ascorbic Acid/
2 pneumonia.mp. or exp Pneumonia/
3 bronchitis.mp. or exp Bronchitis/
4 2 or 3
5 1 and 4

Appendix 4. Embase.com search strategy in 2015

#13. #6 AND #12
#12. #7 OR #8 OR #9 OR #10 OR #11
#11. 'vit c':ab,ti
#10. 'vitamin c':ab,ti
#9. ascorb*:ab,ti
#8. 'l-ascorbic':ab,ti
#7. 'ascorbic acid'/exp
#6. #1 OR #2 OR #3 OR #4 OR #5
#5. bronchit*:ab,ti
#4. 'bronchitis'/exp
#3. bronchopneumon*:ab,ti
#2. pneumon*:ab,ti
#1. 'pneumonia'/exp

Appendix 5. Web of Science search strategy in 2015

Topic=(pneumon* or bronchopneumon* or bronchit*) AND Topic=("ascorbic acid" or "vitamin c" or "vit c")

WHAT'S NEW

Last assessed as up-to-date: 29 September 2015.

Date	Event	Description
29 September 2015	New citation required but conclusions have not changed	Our conclusions remain unchanged. We revised parts of the text
29 September 2015	New search has been performed	Searches conducted. No new trials were identified for inclusion. We exluded one new trial (Pico Sirvent 2013) and identified one new ongoing study (Lafargue 2015). Mochalkin (1974) and Mochalkin (1975) reports were moved to the Mochalkin 1970 trial, since the 1974 and 1975 reports were found to be duplicate publications of the 1970 report

HISTORY

Protocol first published: Issue 4, 2005

Review first published: Issue 1, 2007

Date	Event	Description
8 April 2013	New citation required but conclusions have not changed	Our conclusions remain unchanged.
8 April 2013	New search has been performed	Searches conducted. No new trials identified from the searches but an older study (Tanaka 2000) was included. We excluded two new trials (Cook 2007; Sesso 2008).
7 February 2011	New search has been performed	Searches conducted. No new trials were included in this update. Three new studies were excluded (Kahn 2011; Mochalkin 1975; Wahed 2008). The conclusions remain unchanged.
30 January 2009	New search has been performed	Searches conducted and minor changes made to the text. Conclusions remain unchanged. No new trials found
26 August 2008	Amended	Converted to new review format.
9 February 2006	New search has been performed	Searches conducted.

CONTRIBUTIONS OF AUTHORS

HH planned the review, carried out the literature searches and RevMan analyses and wrote the draft of the text. HH and PL selected the included trials, extracted the data, interpreted the results and finished the text. HH updated the review and PL commented on the update.

DECLARATIONS OF INTEREST

HH: Within 36 months, one talk paid by a pharmaceutical company about the possible effects of vitamins C and E on respiratory symptoms of physically active people, in Finnish.

PL: none known.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In 2016 we added "adverse effect" as a primary outcome.

In 2016 we added "baseline balance" as a new item to the Risk of Bias table, as encouraged by Corbett 2013. They commented that "if randomisation methods are unclear, then the risk of selection bias in the included studies will be unclear, with consequent reticence to draw firm conclusions from the review. But if baseline data demonstrate that all important prognostic factors were balanced across arms, then that reticence may be misplaced. Alternatively, randomisation methods may appear robust, but important group baseline imbalance not noticed, leading to unwarranted confidence in the findings of the study and hence in the broader findings of the review; selection bias is low as formally defined, but chance differences may need to be considered." (p. 80) ... "Use of suboptimal randomisation methods may be due to clinical practicalities or resource limitations. ... Suboptimal methods do not necessarily imply that the allocations were manipulated. Examination of a study characteristics table may be able to clarify whether such bias is present. In some trials, adequate similarity across baseline will be achieved. The results of such studies could therefore be considered as being at a low risk of bias (p. 83)."

In our protocol (Hemilä 2005) we did not plan subgroup analysis by the severity of pneumonia. Nevertheless, as we found that the severity of pneumonia at admission significantly modified the effect of vitamin C on the change of severity during hospital stay in the Hunt 1994 study, we divided that study to two subgroups in an additional table already in the 2007 version, but in the 2013 update we introduced that subgroup division to the Analysis 2.2 forest plot, since such a presentation is more informative than keeping the patients of that study combined in the forest plot.

In our 2005 protocol we defined primary outcomes for treatment as: "the duration and severity of pneumonic episode, duration of hospital stay and death caused by pneumonia". However, "the duration of hospital stay" is one way of measuring "the duration of pneumonia" and therefore in the 2013 update we simplified the primary treatment outcomes to: "the duration and severity of pneumonic episode and death caused by pneumonia".

In our 2005 protocol, we planned to calculate risk ratios (RRs) for dichotomous outcome variables. However, in the three identified prevention 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 sect 16.9.5). Nevertheless, the approximate calculation methods, including the Peto OR method, lead to misleading 95% confidence intervals (CIs) for very small numbers of pneumonia cases (Higgins 2011 sect 16.9.5). Therefore, we also used the "fisher.exact" program of the R 2015 to calculate the exact 95% CI for the OR. Also, with only a few cases observed in the prevention trial groups, the mid-P value is the most appropriate method to calculate the P values for the differences between the treatment groups (Hemilä 2006; Lydersen 2009) and was used when comparing groups.

Mochalkin 1970 reported differences between study groups for erythrocyte sedimentation rate and CXR. We added these as secondary outcomes to our review. They were not listed in our protocol.

In our 2005 protocol, we described: "Types of outcome measures (1) In assessing the preventive effect of vitamin C, the outcome is occurrence of pneumonia during vitamin C supplementation. (2) In assessing the treatment effect of vitamin C, the outcomes of interest are duration and severity of pneumonia episode, duration of hospital stay, and death caused by pneumonia." We revised this outcome definition later to separately cover community-acquired and hospital-acquired pneumonia. We also deleted the "during vitamin C supplementation" from the preventive effect examination, since in hospital-acquired pneumonia a short vitamin C administration for a day or a few days might lead to longer effects in a time scale of a week or a few weeks. This change allowed us to include the Tanaka 2000 trial to our review.

NOTES

Full text versions of references which are available either free or from the publishers' databases can be accessed via the home page of the contact author, Harri Hemilä: http://www.mv.helsinki.fi/home/hemila/CP .