Zinc for the common cold (Review)

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TABLE OF CONTENTS

[Intervention Review]

Zinc for the common cold

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Editorial group: Cochrane Acute Respiratory Infections Group.
Publication status and date: New search for studies and content updated (conclusions changed), published in Issue 2, 2011.
Review content assessed as up-to-date: 31 May 2010.

Citation: Singh M, Das RR. Zinc for the common cold. *Cochrane Database of Systematic Reviews* 2011, Issue 2. Art. No.: CD001364. DOI: 10.1002/14651858.CD001364.pub3.

ABSTRACT

Background

The common cold is one of the most widespread illnesses and is a leading cause of visits to the doctor and absenteeism from school and work. Trials conducted since 1984 investigating the role of zinc for the common cold symptoms have had mixed results. Inadequate treatment masking and reduced bioavailability of zinc from some formulations have been cited as influencing results.

Objectives

To assess the effect of zinc on common cold symptoms.

Search strategy

We searched CENTRAL (2010, Issue 2) which contains the Acute Respiratory Infections Group's Specialised Register, MEDLINE (1966 to May week 3, 2010) and EMBASE (1974 to June 2010).

Selection criteria

Randomised, double-blind, placebo-controlled trials using zinc for at least five consecutive days to treat, or for at least five months to prevent the common cold.

Data collection and analysis

Two review authors independently extracted data and assessed trial quality.

Main results

We included 13 therapeutic trials (966 participants) and two preventive trials (394 participants). Intake of zinc is associated with a significant reduction in the duration (standardized mean difference (SMD) -0.97; 95% confidence interval (CI) -1.56 to -0.38) (P = 0.001), and severity of common cold symptoms (SMD -0.39; 95% CI -0.77 to -0.02) (P = 0.04). There was a significant difference between the zinc and control group for the proportion of participants symptomatic after seven days of treatment (OR 0.45; 95% CI 0.2 to 1.00) (P = 0.05). The incidence rate ratio (IRR) of developing a cold (IRR 0.64; 95% CI 0.47 to 0.88) (P = 0.006), school absence (P = 0.0003) and prescription of antibiotics (P < 0.00001) was lower in the zinc group. Overall adverse events (OR 1.59; 95% CI 0.97 to 2.58) (P = 0.06), bad taste (OR 2.64; 95% CI 1.91 to 3.64) (P < 0.00001) and nausea (OR 2.15; 95% CI 1.44 to 3.23) (P = 0.002) were higher in the zinc group.

Authors' conclusions

Zinc administered within 24 hours of onset of symptoms reduces the duration and severity of the common cold in healthy people. When supplemented for at least five months, it reduces cold incidence, school absenteeism and prescription of antibiotics in children. There is potential for zinc lozenges to produce side effects. In view of this and the differences in study populations, dosages, formulations and duration of treatment, it is difficult to make firm recommendations about the dose, formulation and duration that should be used.

PLAIN LANGUAGE SUMMARY

Zinc for the common cold

The common cold is often caused by the rhinovirus. It is one of the most widespread illnesses and is a leading cause of visits to the doctor and absenteeism from school and work. Complications of the common cold include otitis media (middle ear infection), sinusitis and exacerbations of reactive airway diseases. There is no proven treatment for the common cold. However, a medication that is even partially effective in the treatment and prevention of the common cold could markedly reduce morbidity and economic losses due to this illness.

Zinc inhibits rhinoviral replication and has been tested in trials for treatment of the common cold. This review identified 15 randomized controlled trials, enrolling 1360 participants of all age groups, comparing zinc with placebo (no zinc). We found that zinc (lozenges or syrup) is beneficial in reducing the duration and severity of the common cold in healthy people, when taken within 24 hours of onset of symptoms. People taking zinc are also less likely to have persistence of their cold symptoms beyond seven days of treatment. Zinc supplementation for at least five months reduces incidence, school absenteeism and prescription of antibiotics for children with the common cold. People taking zinc lozenges (not syrup or tablet form) are more likely to experience adverse events, including bad taste and nausea. As there are no studies in participants in whom common cold symptoms might be troublesome (for example, those with underlying chronic illness, immunodeficiency, asthma, etc.), the use of zinc currently cannot be recommended for them. Given the variability in the populations studied (no studies from low- or middle-income countries), dose, formulation and duration of zinc used in the included studies, more research is needed to address these variabilities and determine the optimal duration of treatment as well as the dosage and formulations of zinc that will produce clinical benefits without increasing adverse effects, before making a general recommendation for zinc in treatment of the common cold.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Zinc compared with placebo for the common cold

Patient or population: patients with common cold
Settings: outpatient
Intervention: zinc lozenges or syrup
Comparison: usual care

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Zinc				
Duration of cold symptoms (days)	The mean duration of cold symptoms ranged across control groups from 5.1 to 8.5 days	The mean duration of cold symptoms in the intervention groups was 0.97 lower (1.56 to 0.38 lower)		762 (6 studies[1])	+++O moderate[2,3,4]	
Severity of symptom score	The mean severity of symptom score ranged across control groups from 0.4 to 5.61	The mean severity of symptom score in the intervention groups was 0.39 lower (0.77 to 0.02 lower)		513 (5 studies[5])	+++O moderate[3,6,7]	
Incidence of common cold	618 per 1000	382 per 1000 (354 to 431)	RR 0.64 (0.47 to 0.88)	1522 (2 studies[8])	++OO low[3,9,10,11]	
Number of participants symptomatic after 7 days of treatment	563 per 1000	373 per 1000 (143 to 508)	RR 0.45 (0.2 to 1.0)	476 (5 studies[12])	++OO low[13,14,15]	

School absenteeism (number of days)	The mean days of school absenteeism ranged across control groups from 1.3 to 1.35 days	The mean days of school absenteeism in the intervention groups was 0.37 lower (0.7 to 0.04 lower)		394 (2 studies[8])	+00 very low[9,16,17]
Antibiotic use	330 per 1000	127 per 1000 (52 to 200)	RR 0.27 (0.16 to 0.46)	394 (2 studies[8])	++00 low[9,18,19]
Any adverse event	481 per 1000	562 per 1000 (252 to 898)	RR 1.59 (0.97 to 2.58)	796 (5 studies)	+++0 moderate[20,21,22]

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
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. No serious study limitations: all the studies had adequately concealed allocation and blinded both participants and study staff to be considered at low risk of bias. Free of other bias was unclear in Macknin 1998 and Petrus 1998. Petrus 1998 did not adequately describe the sequence generation.

2. Serious inconsistency: there was high statistical heterogeneity. I^2 statistic = 93%. The heterogeneity may be due to differences in the nature of the different interventions (zinc gluconate or acetate lozenges, zinc sulphate syrup) and dose range (30 to 160 mg/day) as well as mean duration of symptoms prior to administration of zinc (varying from 24 to 48 hours, as well as the characteristics of the study population (children versus adults). However, subgroup analysis was not possible as there were not enough studies for each variable.

3. No serious indirectness: studies both from low-income and high-income regions have assessed this comparison. Therefore, the result can be confidently generalised to all situations.

4. No serious imprecision: though the 95% CI around the pooled effect is narrow, the lower limit does not suggest a clinically important reduction in the duration of cold (a decrease in duration of $\leq$1 day is not shown to be important to patients).

5. No serious study limitation: all the studies had adequately concealed allocation and blinded both participants and study staff to be considered at low risk of bias. Whether free of other bias was unclear and adequate sequence was not generated in one study (Petrus 1998).

[6.] No serious imprecision: though the 95% CI around the pooled effect is narrow, the lower limit does not suggests a clinically important reduction in the severity of symptom score (a change of less than 1 point score is not shown to be important to patients).
[7.] Serious inconsistency: there was high statistical heterogeneity. I^2 statistic = 75%. The heterogeneity may be due to differences in the nature of the different interventions (zinc gluconate or acetate lozenges, zinc sulphate syrup) and dose range (30 to 160 mg/day) as well as mean duration of symptoms prior to administration of zinc (varying from 24 to 48 hours), as well as the characteristics of the study population (children versus adults). However, subgroup analysis was not possible as there were not enough studies for each variable.
[8.] Kurugol 2006b is a community-based intervention including 200 healthy school children and studying the effect of daily administration of 15 mg zinc sulphate syrup over a period of 7 months. Vakili 2009 is also a community-based intervention including 200 healthy school children and studying the effect of daily administration of 10 mg zinc sulfate tablets over a period of 7 months.
[9.] Serious study limitation: though the study by Kurugol 2006b was of high quality, that by Vakili 2009 was of poor methodological quality.
[10.] Serious inconsistency: there is substantial heterogeneity between the two trials: I^2 statistic for heterogeneity = 88%. Both trials showed a benefit with zinc, however the size of this effect was much larger in Vakili 2009. The heterogeneity was due to differences in the trial methodology and the nature of the interventions.
[11.] No serious imprecision: the 95% CI around the pooled effect is narrow. Even the lower limit suggests a clinically important reduction in the incidence rate ratio of cold which is shown to be important to patients.
[12.] No serious study limitations: allocation concealment was unclear in two studies, i.e. Smith 1989 and Weismann 1990, though both the studies blinded both participants and study staff.
[13.] Serious inconsistency: there was high statistical heterogeneity. I^2 statistic = 75%. The heterogeneity may be due to differences in the nature of the different interventions (zinc gluconate or acetate lozenges) and dose range (30 to 160 mg/day) as well as mean duration of symptoms prior to administration of zinc (varying from 24 to 48 hours, as well as the characteristics of the study population (children versus adults). However, subgroup analysis was not possible as there were not enough studies for each variable.
[14.] Serious indirectness: only studies from high-income regions have assessed this comparison. Therefore, the result can not be generalised to all situations.
[15.] No serious imprecision: both limits of the 95% CI suggest a clinically important reduction in proportion of participants given the intervention symptomatic after seven days of treatment.
[16.] Serious inconsistency: there is substantial heterogeneity between the two trials: I^2 statistic test for heterogeneity = 64%. Both trials showed reduced days of school absenteeism with intervention, however, the size of this effect was much larger in Kurugol 2006b. The heterogeneity was due to differences in the trial methodology and the nature of the interventions.
[17.] No serious imprecision: though the 95% CI around the pooled effect is narrow, the lower limit does not suggests a clinically important reduction in the duration of school absenteeism (a decrease in duration of $\leq$1 day is not shown to be important to patients).
[18.] No serious inconsistency: there was no statistical heterogeneity. I^2 statistic = 0%.
[19.] No serious imprecision: both limits of the 95% CI suggest a clinically important reduction in the rate of antibiotic use with intervention.
[20.] No serious study limitations: all the studies had adequately concealed allocation (except Weismann 1990, in which allocation concealment is unclear) and blinded both participants and study staff to be considered at low risk of bias. Whether free of other bias was unclear in Macknin 1998 and Weismann 1990. Weismann 1990 did not adequately describe the sequence generation.
[21.] No serious inconsistency: there was moderate statistical heterogeneity. I^2 statistic = 51%.
[22.] Serious imprecision: the 95% CI around the pooled effect is wide. Though the resulting adverse events from use of zinc is higher, this is not significant.

BACKGROUND

Description of the condition

The common cold is one of the most widespread illnesses, with adults having two to four episodes annually (Garibaldi 1985). Children may have six to 10 colds a year (and up to 12 colds a year for school children) (Simasek 2007). In the United States, the common cold leads to 75 to 100 million physician visits annually at a conservative cost estimate of US $7.7 billion per year. Americans spend $2.9 billion on over-the-counter drugs and another $400 million on prescription medicines for symptomatic relief (Garibaldi 1985; Simasek 2007). More than one-third of patients who saw a doctor received an antibiotic prescription, which has implications for antibiotic resistance from overuse of such drugs (Fendrick 2003). An estimated 22 to 189 million school days are missed annually due to a cold. As a result, parents missed 126 million workdays to stay home to care for their children. When added to the 150 million work days missed by employees suffering from a cold, the total economic impact of cold-related work loss exceeds $20 billion per year (Fendrick 2003; Garibaldi 1985). This accounts for 40% of time lost from work (Kirkpatrick 1996). The complications of the common cold include otitis media, sinusitis and exacerbations of reactive airway diseases (Couch 1984; Gwaltney 1966; Turner 2001). Rhinoviruses are the most frequent cause and may account for nearly 80% of common colds during autumn (Turner 2001). There is no proven treatment for the common cold. However, even a medication that is only partially effective in the treatment and prevention of the common cold could markedly reduce morbidity and economic losses due to this illness.

Description of the intervention

The effect of zinc lozenges on the incidence, duration or severity of common cold symptoms has been examined in different studies since 1984. In 1984, Eby et al (Eby 1984) reported for the first time on the efficacy of zinc gluconate lozenges for treatment of the common cold. However, later trials have given variable results. It has been hypothesized that there is a direct correlation between reductions in the duration of common cold symptoms and the daily dosage of all positively charged zinc species released from lozenges at physiologic pH (Eby 1995). The re-analysis of 10 double-blind, placebo-controlled zinc trials by solution chemistry methods showed a significant correlation between total daily dosages of positively charged zinc species and a reduction in the mean duration of common colds (Eby 2004). Zinc gluconate and zinc acetate have very low chemical stability and mainly release positively charged zinc ions in aqueous solutions at physiologic pH, but stronger complexes do not (Eby 2004). Adding a strong zinc binding ligand, such as glycine or citric acid, to a solution containing a zinc complex that is weakly bonded results in the sequestration of zinc to the stronger ligand, reducing or eliminating the benefits of zinc lozenges (Eby 2004). In the review by Marshall it was concluded that zinc gluconate lozenges were effective in reducing the symptoms and duration of the common cold but the side effects and particularly bad taste might limit patient compliance (Marshall 1998). However, results from three trials (Kurugol 2006a; Kurugol 2006b; Kurugol 2007) using zinc sulfate syrup and one trial using zinc sulfate tablet (Vakili 2009) suggested that both the syrup and tablet form are well tolerated and an easy to administer therapy. Adverse effects were mild and had no significant association with the use of zinc sulfate syrup or tablet. The increased incidence of adverse effects noted in the zinc group in various trials may have been related to the use of different ligands (gluconate, acetate) rather than to zinc itself.

How the intervention might work

Interest in the use of zinc for the common cold grew following the results of a randomized controlled trial (RCT) conducted by Eby 1984. Results suggested that if treatment of a cold commenced within three days of the development of cold symptoms and consisted of one 23 mg zinc lozenge dissolved in the mouth every second waking hour, the average duration of cold symptoms was reduced by about seven days. This result was consistent with the earlier observation by Eby (Eby 1984) that a three-year old girl diagnosed with acute lymphocytic leukaemia who had been treated with a 50 mg zinc tablet to improve her zinc status and to stimulate T-cell lymphocyte responsiveness recovered from a cold within several hours of receiving treatment. In addition, this effect was claimed to be reproducible in other children and adults. Later trials gave inconclusive results (Turner 2001). Results of trials in which no effect of zinc was demonstrated were criticised for having inadequate sample sizes or formulations that reduced the release of zinc ions from the lozenge (Eby 1995).

In-vitro assays indicate that zinc possesses antiviral properties (concentrations of 0.1 mM zinc inhibited growth of eight of nine strains of rhinoviruses) and although such activity suggests Eby's results are biologically plausible, only a handful of RCTs have been able to duplicate his findings. Of the 18 trials conducted since 1984, 11 trials have shown zinc may be useful in the treatment of the common cold and seven have shown no benefit. Most trials showing beneficial effects have been criticised for failing to mask treatment adequately due to the occurrence of side effects, while trials showing no benefit have been criticised for using formulations that reduced the bioavailability of zinc.

Although several possibilities have been suggested, the mechanisms of the efficacy of zinc on the common cold are still unexplained. One possibility is that the interaction of zinc with host immune function may have a beneficial effect on common cold symptoms (Macknin 1999). Human rhinoviruses, attaching to the nasal epithelium via the intracellular adhesion molecule-1 (ICAM-1) receptor, cause most colds. The zinc ion, based on its electrical charge, has an affinity for ICAM-1 receptor sites and may exert

an antiviral effect by attaching to the ICAM-1 receptors in the rhinovirus structure and nasal epithelial cells (Novick 1996). In addition, zinc inhibits viral replication by preventing the formation of viral capsid proteins (Geist 1987; Korant 1976). It has also been suggested that zinc stabilises cell membranes (Pasternak 1987), prevents histamine release (Harisch 1987) and inhibits prostaglandin metabolism (Kelly 1983).

Why it is important to do this review

There is no proven method of prevention or treatment for the common cold. However, any medication that is only partially effective in the treatment and prevention of the common cold could markedly reduce morbidity and economic losses due to this illness. There have been many clinical trials describing the effect of zinc (lozenges and syrup) on common cold symptoms; therefore it is important to know the effect of zinc on the common cold. The last review of all available RCTs of zinc for the common cold was published in 1999. Since then, several new studies (Kurugol 2006a; Kurugol 2006b; Kurugol 2007; Macknin 1998; McElroy 2003; Petrus 1998; Prasad 2000; Prasad 2008; Turner 2000; Vakili 2009; Veverka 2009) have been published. It is therefore important to update the information by including all the new clinical trials. We therefore undertook the review to assess the overall effectiveness of zinc (lozenges or syrup) in treating the common cold and to provide some guidance with respect to future research.

OBJECTIVES

The objective of the review was to investigate whether zinc (irrespective of the zinc salt or formulation used) is efficacious in reducing the incidence, severity and duration of common cold symptoms. In addition, we aimed to identify potential sources of heterogeneity in results obtained and to assess their clinical significance.

METHODS

Criteria for considering studies for this review

Types of studies

Double-blind, placebo-controlled randomized controlled trials (RCTs).

Types of participants

Trial participants were of either gender and of any age.

Types of interventions

Therapeutic trials: interventions commenced within three days of participants developing common cold symptoms and consisted of 1.5 to 2-hourly treatments with a zinc or placebo lozenge during waking hours, for more than six hours a day for a period of five or more consecutive days.
Prophylactic trials: intervention commenced and continued throughout the cold season for at least five months.
We considered all formulations of zinc (irrespective of the type of salt, formulation and concentration of zinc).

Types of outcome measures

Outcome measures frequently used to determine the clinical efficacy of any common cold treatment are the incidence, severity and duration of cold symptoms. Accordingly, for inclusion in this review, the incidence and severity of at least throat and nasal symptoms and cough needed to be assessed.

Primary outcomes

1. Duration of symptoms.
2. Severity of symptoms.
3. Incidence of the common cold.

Secondary outcomes

1. Proportion of participants symptomatic after three, five or seven days of treatment.
2. Time to resolution of individual symptoms: cough, nasal congestion, nasal drainage and sore throat.
3. Change in individual severity symptom scores: cough, nasal score.
4. School absence (days).
5. Antibiotic use.
6. Adverse events.

We defined duration as the number of days to cold resolution from start of treatment. We considered cold resolution to be the resolution of all cold symptoms or resolution of all but one cold symptom, or the participant believed they had recovered from the cold. Severity of cold symptoms needed to be graded: 0 - no symptoms, 1 - mild symptoms, 2 - moderate symptoms and 3 - severe symptoms. We defined incidence as number of colds per study participant during the study period. Adverse events included any or individual adverse events during or after taking the medications.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2010, Issue 2) which contains the Acute Respiratory Infections Group's Specialised Register, MEDLINE (1966 to May week 3, 2010) and EMBASE (1974 to June 2010). We combined the MEDLINE search with the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximising version (2009 revision); Ovid format (Lefebvre 2009). See Appendix 1 for the EMBASE search strategy.

MEDLINE (OVID)

1 Common Cold/
2 common cold*.tw.
3 Rhinovirus/
4 rhinovir*.tw.
5 Rhinitis/
6 rhinit*.tw.
7 coryza.tw.
8 (respiratory infection* adj3 upper).tw.
9 (infection* adj3 upper respiratory).tw.
10 (urti or uri).tw.
11 or/1-10
12 Zinc/
13 (zinc or zn).tw.
14 Micronutrients/
15 micronutrient*.tw.
16 Trace Elements/
17 (trace adj (mineral* or element*)).tw.
18 or/12-17
19 11 and 18

Searching other resources

We searched bibliographies of published papers for unpublished trials. Two review authors (RRD, MS) assessed the studies to ensure appropriate trials were included in the review and to minimise the potential for selection bias.

Data collection and analysis

More information on the statistical methods used in this review can be found in the relevant section of the Cochrane Acute Respiratory Infections Review Group Module. Comparisons were zinc (lozenges or syrup or tablet) with placebo. We compared outcome measures before and after treatment, as well as after day three, five or seven to accommodate trials of different lengths.

Selection of studies

Two review authors (RRD, MS) independently reviewed the results for inclusion in the analysis. We resolved differences regarding study quality through discussion.

Data extraction and management

We recorded data on a pre-structured data extraction form. The lead review author (MS) entered data directly into Review Manager (RevMan) (RevMan 2008). An independent coder verified accuracy of data entry. We made no attempt to contact investigators. Most trials were conducted over 10 years ago and in view of the information required to be provided by the investigators, we thought that they would be unable to comply.

Assessment of risk of bias in included studies

We assessed risk of bias in all included studies using the Cochrane Collaboration's 'Risk of bias' tool (Higgins 2009).

1. Sequence generation: assessed as yes, no or unclear
Yes: when the study described the method used to generate the allocation sequence in sufficient detail.
No: sequence not generated.
Unclear: when it was not described or incompletely described.

2. Allocation concealment: assessed as yes, no or unclear
Yes: when the study described the method used to conceal the allocation sequence in sufficient detail.
No: described details where allocation concealment was not done.
Unclear: when it was not described or incompletely described.

3. Blinding of participants, personnel and outcome assessors: assessed as yes, no or unclear
Yes: when it was a double-blind study.
No: when it was an unblinded study.
Unclear: not clearly described.

4. Incomplete outcome data: assessed as yes, unclear
Yes: describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis.
Unclear: either not described or incompletely described.

5. Free of selective outcome reporting: assessed as yes, no or unclear
Yes: results of study free of selective reporting. Details of all the patients enrolled in the study are included in the paper.
No: details of all the enrolled patients not given in the paper.
Unclear: details of all the enrolled patients incompletely described.

6. Other sources of bias
Among the other sources of potential bias considered was funding agencies and their role in the study. We recorded funding agencies as government agencies, universities and research organisations or pharmaceutical companies. We considered studies supported by pharmaceutical companies to be unclear unless the study defined the role of the pharmaceutical companies. We also considered studies not mentioning the source of funding as unclear under this heading.

Trials were assessed with respect to the extent to which investigators minimised the potential for bias to occur and addressed other issues in relation to methodological quality. Two review authors (RRD, MS) assessed the quality of each trial. When the methodological description was unambiguous, one review author entered the methodological description to the 'Risk of bias' tables in Characteristics of included studies tables. When the description of methods was ambiguous, the same review author discussed the issue with the co-author to reach a consensus. The methodological descriptions are summarised in Figure 1 and Figure 2.

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

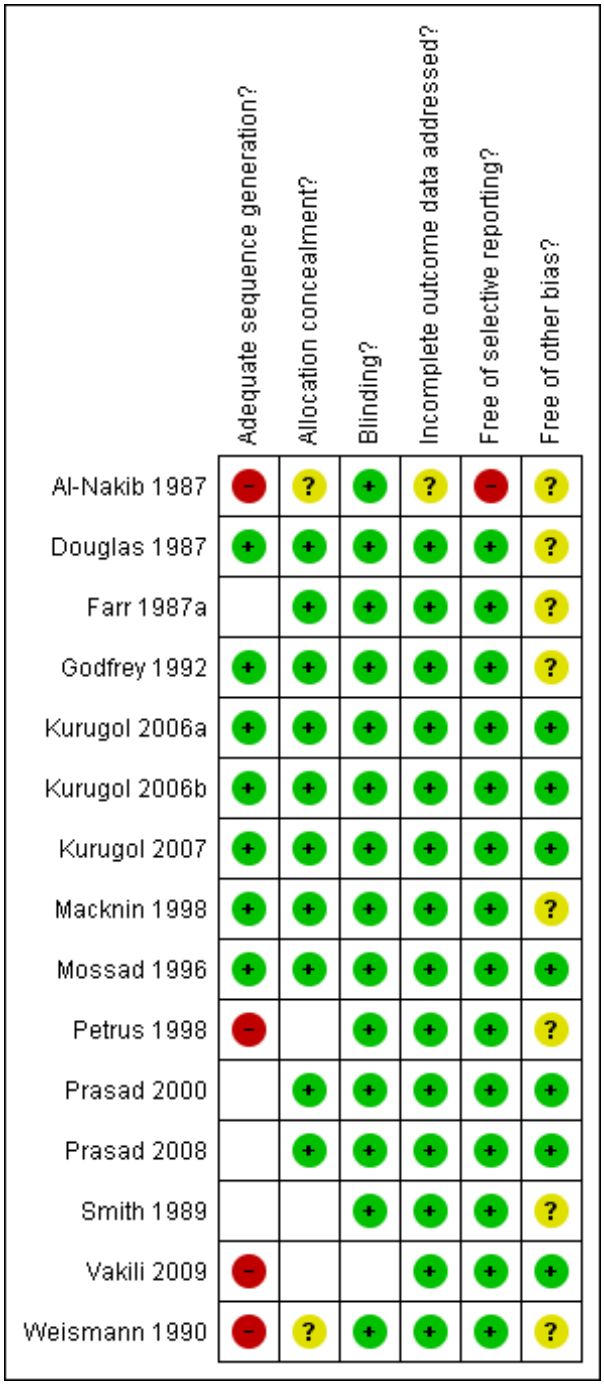
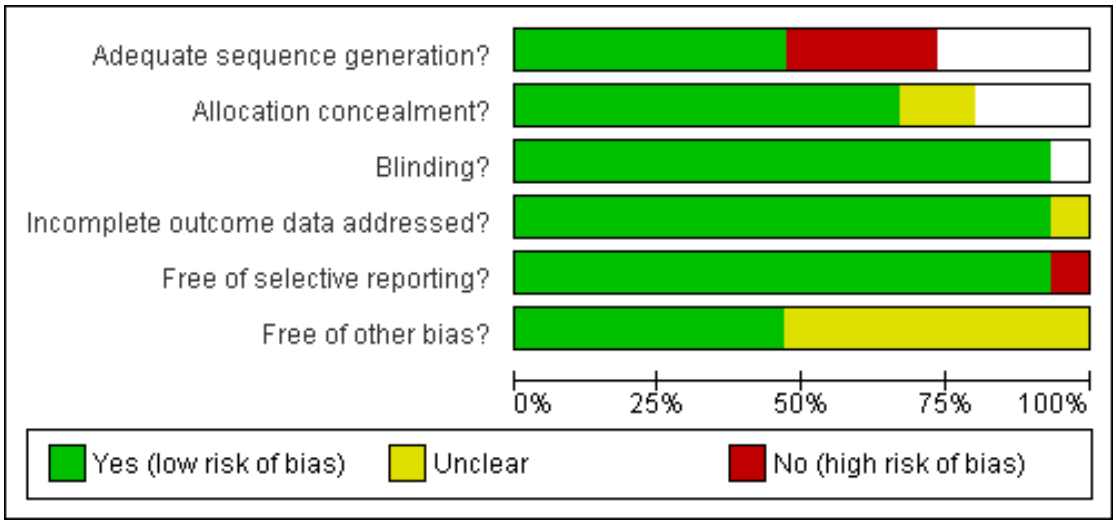


Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.



We assessed the potential for selection (systematic differences in the comparison groups), performance (systematic difference in the care provided apart from the intervention being evaluated), exclusion (systematic differences in withdrawals from the trial) and detection (systematic differences in outcome assessment) bias.
Given that the extent to which trial investigators addressed each criterion could influence the potential for bias to occur, and the extent to which the resulting bias could influence the results is not known, we considered the potential for each criterion to bias the results of a trial equal to the other criterion used.

Measures of treatment effect

We extracted outcome data and entered data into RevMan 5 for statistical analysis. We used the standard methods of the Cochrane Acute Respiratory Infections (ARI) Review Group to synthesise the data. For dichotomous data, we calculated a pooled estimate of the treatment effect for each outcome across trials using the odds ratio (OR). For continuous outcomes, we recorded both mean post-treatment or post-intervention values and standard deviation (SD). If standard errors (SE) had been reported (and if it were possible) we planned to convert these to standard deviations. We calculated a pooled estimate of treatment effect by calculating the standardized mean difference (SMD). For both dichotomous and continuous outcomes, we calculated the 95% confidence interval (95% CI) for individual studies. We used fixed-effect models to obtain summary statistics of all types of outcome measures. When significant heterogeneity was found, we calculated the overall efficacy using random-effects models, which provided more realistic estimates of the CIs under these circumstances (Lau 1997). In this context, a P value < 0.05 indicated significant differences between studies and raised questions as to whether the results could be meaningfully combined. Where it was not possible to perform a meta-analysis, we summarised the data for each trial.

Unit of analysis issues

Only randomized, double-blind, placebo-controlled trials were included in this review. None of the trials were cross-over or cluster-randomised trials.

Dealing with missing data

As many trials were conducted 10 years ago, we thought that the investigators would be unable to compile the missing data, so we did not contact them. For all the outcomes, we considered that incomplete outcome data had been adequately addressed if 85% or more of the participants were included in the analysis, or if less than 85% were included but adequate steps were taken to ensure or demonstrate that this did not bias the results. We performed intention-to-treat (ITT) analysis where the above was not clear.

In trials with missing statistics (such as SDs or correlation coefficients), we calculated the data from the available information.

Assessment of heterogeneity

We assessed the degree of heterogeneity by using the Chi^2 test and the I^2 statistic (Higgins 2003; Higgins 2009). The Chi^2 test is known to be poor at detecting true heterogeneity among studies; while a statistically significant result indicates heterogeneity, a non-significant result is not evidence of no heterogeneity. The I^2 statistic describes the percentage of total variation across studies that is due to heterogeneity rather than chance. The values of the I^2 statistic lie between 0% and 100%. For the current meta-analysis, we used a simplified categorisation of the I^2 statistic as follows: if significant heterogeneity (I^2 statistic > 50%) was found, we used a random-effects model and if low heterogeneity (I^2 statistic < 50%) was found, we used a fixed-effect model.

Assessment of reporting biases

We sought further information from trial authors, although this was not possible for the current meta-analysis as many of the studies were very old. We looked hard for evidence of collection by study investigators of a small number of key outcomes that are routinely measured in the area in question, and reported which studies reported data on these and which do not. We also constructed a matrix indicating which outcomes were recorded in which studies (for example, with rows as studies and columns as outcomes). Complete and incomplete reporting was also indicated. This matrix showed us which studies did not report outcomes reported by most other studies. We assessed risk of bias due to selective reporting of outcomes for the study as a whole, rather than for each outcome. We also assessed the likelihood of small study effects, such as publication bias, by examining the funnel plot for asymmetry (Egger 1997).

Data synthesis

We analysed data using a fixed-effect model in cases of low heterogeneity (I^2 statistic value of < 50%) and a random-effects model in cases of moderate to high heterogeneity between studies (I^2 statistic value of > 50%).

Subgroup analysis and investigation of heterogeneity

The factors considered as possible explanations for the heterogeneity observed across the results of these studies were: dosage and formulations of zinc used, age of participants (children and adults) and the mean duration of symptoms prior to administration of zinc. We plan to investigate these with subgroup analyses when there are sufficient studies included in the review.

Sensitivity analysis

We had planned to perform sensitivity analyses based on methodological quality of the trials with and without quasi-randomised trials, but this was not possible.

RESULTS

Description of studies

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

Results of the search

Two review authors (RRD, MS) screened the search results. Prior to 1999, 87 search results resulted in seven included trials in the earlier version of this review (Marshall 1999). After 1999, a total of 57 search results were obtained after removing duplicates (MEDLINE = 37, CENTRAL = 19 and EMBASE = 41 search results). Fifteen trials are included in the review (eight trials were included in this updated review), including 996 participants in the therapeutic trials and 394 in the preventive trials. No trials were found through contact with pharmaceutical companies.

Included studies

We identified 15 trials for inclusion.

Location

All 15 trials were conducted in high-income countries. Three trials were conducted in Turkey (Kurugol 2006a; Kurugol 2006b; Kurugol 2007); one trial each in Iran (Vakili 2009), Denmark (Weismann 1990), UK (Al-Nakib 1987) and Australia (Douglas 1987); and eight trials in the USA (Farr 1987a; Godfrey 1992; Macknin 1998; Mossad 1996; Petrus 1998; Prasad 2000; Prasad 2008; Smith 1989).

Participants

All the trial participants included in the analysis were both adults and children with age range varying from one to 65 years at the start of the trials. Five trials included children only and among these, three trials included children aged one to 10 years (Kurugol 2006a; Kurugol 2006b; Kurugol 2007); one included children and adolescents aged six to 16 years (Macknin 1998); and another included children aged 6.5 to 10 years (Vakili 2009). Two trials recruited participants from volunteers experimentally inoculated with human rhinovirus (Al-Nakib 1987; Farr 1987a). Given that not all participants had cold symptoms at the beginning of the

intervention in one trial (Farr 1987a), this trial would be excluded from the statistical overview. In one trial neither the health status of the participants nor the exclusion criteria were stated, while in other trials only healthy subjects from the general population were included. In one trial, participants with cold durations of more than 24 hours (Macknin 1998) and in another trial participants with cold durations of more than 48 hours (Kurugol 2007) were excluded. The trials varied widely in size; two trials had fewer than 50 participants (Prasad 2000; Prasad 2008), four had more than 50 but fewer than 100 participants (Douglas 1987; Farr 1987a; Godfrey 1992; Mossad 1996), eight had more than 100 but fewer than 200 participants (Al-Nakib 1987; Kurugol 2006a; Kurugol 2006b; Kurugol 2007; Petrus 1998; Smith 1989; Weismann 1990; Vakili 2009) and the largest trial had 247 participants (Macknin 1998).

Interventions

Zinc supplements were provided in the form of either syrup, lozenges or tablets. One trial used zinc sulfate tablet (Vakili 2009) and three trials used zinc sulphate syrup (Kurugol 2006a; Kurugol 2006b; Kurugol 2007). Among the trials using lozenge preparations, two different salts were used: zinc gluconate (Al-Nakib 1987; Farr 1987a; Godfrey 1992; Macknin 1998; Mossad 1996; Smith 1989; Weismann 1990) and zinc acetate (Douglas 1987; Petrus 1998; Prasad 2000; Prasad 2008). The supplements were given for different periods of time in all the trials. In the therapeutic trials the duration of supplement was five days (Farr 1987a), six days (Al-Nakib 1987; Douglas 1987), seven days (Farr 1987a; Godfrey 1992; Smith 1989), 10 days (Kurugol 2006a; Kurugol 2007; Weismann 1990), 14 days (Petrus 1998) and no duration mentioned (i.e. participants were given zinc as long as they were symptomatic) (Macknin 1998; Mossad 1996; Prasad 2000; Prasad 2008). In the three trials also studying the prophylactic role of zinc, the duration of supplement was 4.5 days (Al-Nakib 1987), five months (Vakili 2009) and seven months (Kurugol 2006b).

Outcomes

Primary

Ten trials (Godfrey 1992; Kurugol 2006a; Kurugol 2007; Macknin 1998; Mossad 1996; Petrus 1998; Prasad 2000; Prasad 2008; Smith 1989; Weismann 1990) reported the duration of symptoms, and the results could be pooled from all the trials except four (Godfrey 1992; Mossad 1996; Smith 1989; Weismann 1990), due to different formats of reporting results. Ten trials measured the total severity score of cold symptoms (Al-Nakib 1987; Douglas 1987; Godfrey 1992; Kurugol 2006a; Kurugol 2007; Petrus 1998; Prasad 2000; Prasad 2008; Smith 1989; Weismann 1990) but results from only five trials (Kurugol 2006a; Kurugol 2007; Petrus 1998; Prasad 2000; Prasad 2008) could be pooled, as in five trials (Al-Nakib 1987; Douglas 1987; Godfrey 1992; Smith 1989; Weismann 1990) the results were not reported in a standard format. The incidence of cold symptoms was measured in two trials (Kurugol 2006b; Vakili 2009).

Secondary

The proportion of participants asymptomatic by day three or day five was reported in three trials (Mossad 1996; Smith 1989; Weismann 1990), whereas the proportion of participants asymptomatic by day seven was reported in five trials (Douglas 1987; Godfrey 1992; Mossad 1996; Smith 1989; Weismann 1990). In all these trials, ITT analysis was conducted. Time to resolution of individual cold symptoms was reported as follows: time to resolution of cough in four trials (Kurugol 2006a; Macknin 1998; Prasad 2000; Prasad 2008), time to resolution of nasal congestion in five trials (Kurugol 2006a; Macknin 1998; Petrus 1998; Prasad 2000; Prasad 2008), time to resolution of nasal drainage in five trials (Kurugol 2006a; Macknin 1998; Petrus 1998; Prasad 2000; Prasad 2008) and time to resolution of sore throat in four trials (Kurugol 2006a; Macknin 1998; Prasad 2000; Prasad 2008). Change in individual severity symptom score was reported as follows: change in cough symptom score in two trials (Douglas 1987; Petrus 1998), change in nasal symptom score in four trials (Douglas 1987; Kurugol 2006a; Kurugol 2007; Petrus 1998), change in throat symptom score in two trials (Douglas 1987; Petrus 1998). Standard error of mean (SEM) was not provided in one trial (Douglas 1987). Effect on school absence and antibiotic use were provided in two trials (Kurugol 2006b; Vakili 2009).

Adverse events

Eleven trials (Douglas 1987; Kurugol 2006a; Kurugol 2006b; Kurugol 2007; Macknin 1998; Mossad 1996; Prasad 2000; Prasad 2008; Smith 1989; Weismann 1990; Vakili 2009) reported adverse events. Common adverse events included bad taste, nausea, constipation, diarrhoea, abdominal pain, dry mouth and oral irritation.

Other

Two trials using experimentally-induced colds with rhinovirus also studied the number of participants shedding the virus, duration of viral shedding, number of virus-positive days, as well as rise in antibody titre. These were not included in the outcome measures as we thought that it would not be of help in drawing conclusions. Three trials reported the effect of zinc supplementation on school absenteeism. Among these, two (Kurugol 2006b; Vakili 2009) reported this outcome during a prophylactic trial, though another (Macknin 1998) was a therapeutic trial.

Excluded studies

We excluded four trials.

1. Inclusion criteria not defined, disproportionate number of drop outs from the zinc group (Eby 1984).
2. Two studies were not RCTs (McElroy 2003; Turner 2000).
3. Measured upper respiratory tract infection as a whole (including common cold, seasonal influenza) (Veverka 2009).

Risk of bias in included studies

Allocation

Allocation concealment was adequate in 10 studies (Douglas 1987; Farr 1987a; Godfrey 1992; Kurugol 2006a; Kurugol 2006b; Kurugol 2007; Macknin 1998; Mossad 1996; Prasad 2000; Prasad 2008). It was unclear in four studies (Al-Nakib 1987; Petrus 1998; Smith 1989; Weismann 1990) and not described in one (Vakili 2009).

Adequate sequence generation was described in seven studies (Douglas 1987; Godfrey 1992; Kurugol 2006a; Kurugol 2006b; Kurugol 2007; Macknin 1998; Mossad 1996). However, it was not clear in four studies (Farr 1987a; Prasad 2000; Prasad 2008; Smith 1989) and not generated in four studies (Al-Nakib 1987; Petrus 1998; Vakili 2009; Weismann 1990).

Blinding

All 15 studies were blinded but placebo blinding was adequately described in ten trials (Douglas 1987; Smith 1989; Godfrey 1992; Macknin 1998; Mossad 1996; Prasad 2000; Kurugol 2006a; Kurugol 2006b; Kurugol 2007; Prasad 2008). Zinc-treated participants also experienced higher incidences of side effects and/or complaints, and in nine trials, zinc-treated participants complained of altered, bad or unpalatable taste which suggests that the zinc lozenges were distinct from the placebo lozenges and, in this respect, blinding may have been compromised.

Incomplete outcome data

Data were fully detailed in 14 studies and in the remaining one study (Al-Nakib 1987) details of attrition and exclusions from the analysis were unavailable.

Selective reporting

Except two studies (Al-Nakib 1987; Weismann 1990), 13 studies scored 'yes' for being free from selective reporting.

Other potential sources of bias

Eleven studies were funded by pharmaceutical companies (Al-Nakib 1987; Douglas 1987; Godfrey 1992; Farr 1987a; Kurugol 2006a; Kurugol 2006b; Kurugol 2007; Macknin 1998; Petrus 1998; Smith 1989; Weismann 1990). Five studies were supported Medical Research Foundation (Godfrey 1992; Mossad 1996; Prasad 2000; Prasad 2008; Vakili 2009) and in addition by National Institute of Health (NIH) (Prasad 2008). Information on clearance by Ethics Committees or Institutional Review Boards was available for all except one study (Smith 1989).

Effects of interventions

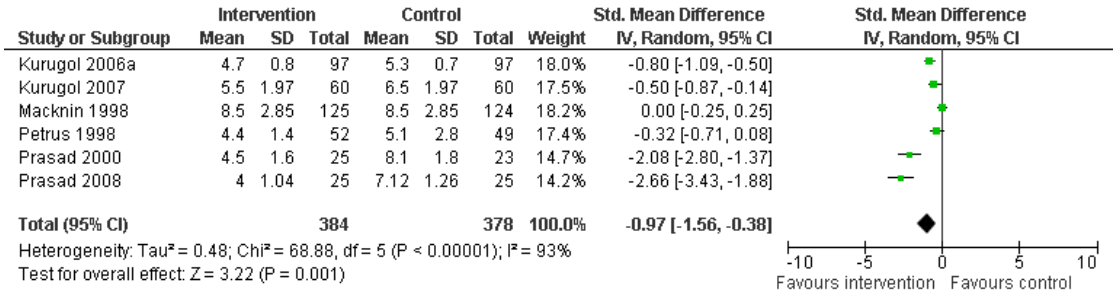
See: **Summary of findings for the main comparison**

1. Primary outcomes

Duration of cold symptoms

Ten studies (Godfrey 1992; Kurugol 2006a; Kurugol 2007; Macknin 1998; Mossad 1996; Petrus 1998; Prasad 2000; Prasad 2008; Smith 1989; Weismann 1990) reported this outcome. Results could be pooled from all except four studies (Godfrey 1992; Mossad 1996; Smith 1989; Weismann 1990) and there were 762 participants including children and adults (Analysis 1.1; Figure 3). The studies were heterogenous in terms of variable formulations (zinc gluconate or acetate lozenges, zinc sulphate syrup) and dose range (30 to 160 mg/day) as well as mean duration of symptoms prior to administration of zinc (varying from 24 to 48 hours). However, subgroup analysis was not possible as there were not enough studies for each variable. Intake of zinc lozenges or syrup was associated with a significant reduction in the duration of common cold symptoms (SMD -0.97; 95% CI -1.56 to -0.38) (P = 0.001), when it was administered within 24 hours of the onset of symptoms. In one study (Godfrey 1992) the authors found a significant decrease in the duration of symptoms when treatment was administered within 24 hours, compared to treatment administration within 48 hours.

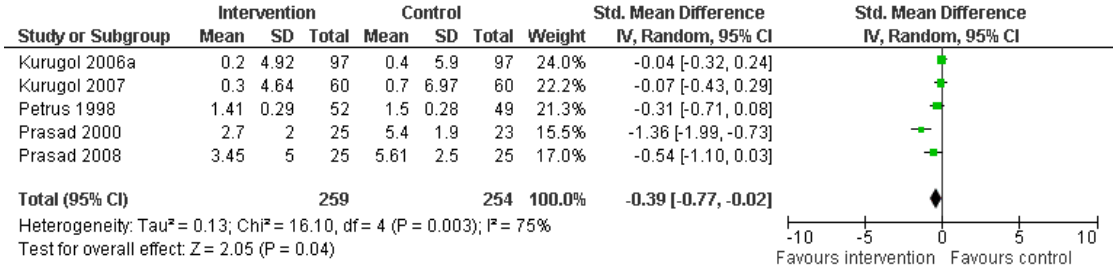
Figure 3. Forest plot of comparison: 1 Primary outcomes, outcome: 1.1 Duration of cold symptoms (in days).



Severity of cold symptoms

Ten studies measured the mean severity score of cold symptoms (Al-Nakib 1987; Douglas 1987; Godfrey 1992; Kurugol 2006a; Kurugol 2007; Petrus 1998; Prasad 2000; Prasad 2008; Smith 1989; Weismann 1990). Results from five studies (Kurugol 2006a; Kurugol 2007; Petrus 1998; Prasad 2000; Prasad 2008) including a total of 513 participants (Analysis 1.2; Figure 4) could be pooled. There was a significant difference between the intervention and control groups for reduction in the severity of cold symptoms (SMD -0.39; 95% CI -0.77 to -0.02) (P = 0.04). In all but two studies, the intervention started within 24 hours of onset of symptoms. In the studies by Douglas 1987 and Kurugol 2007 the intervention started within 24 to 48 hours after the onset of symptoms. In the study by Godfrey 1992 the authors found a significant decrease in the severity of symptoms when treatment was administered within 24 hours, compared to treatment administration within 48 hours. In the trial by Al-Nakib 1987, the zinc group had a significantly lower mean daily clinical score than the placebo group; the difference in scores attaining statistical significance by day four and day five of treatment. However, in the study conducted by Douglas 1987, there were no significant differences between the two groups. Two studies (Smith 1989; Weismann 1990) reported summed severity scores which could not be pooled. One study (Smith 1989) found a reduction in summed severity score in the zinc group, whereas another (Weismann 1990) did not. Again the dosages, formulations and time of administration of zinc differed among the studies, and the studies also included both children and adults.

Figure 4. Forest plot of comparison: 1 Primary outcomes, outcome: 1.2 Severity of symptoms (score).

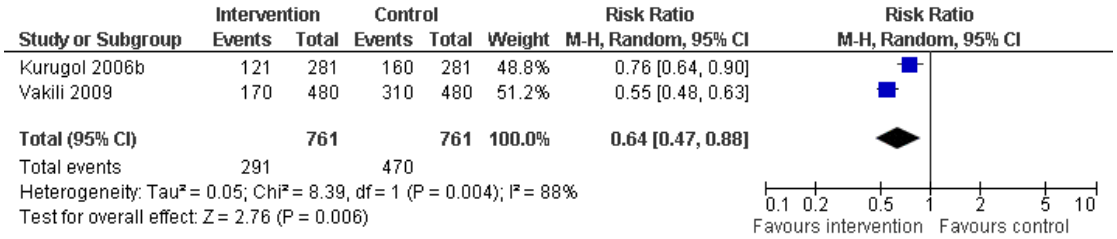


Incidence of common cold

This was reported in two studies (Kurugol 2006b; Vakili 2009). The two studies used variable dose, formulation and duration of zinc use. The follow-up periods of the two studies were different, therefore we based the calculation of the incidence rates on person-years. The person-time incidence rate is an appropriate measure of incidence when follow-up times are unequal (Rothman 1988). Incidence density is defined as the number of incident cases occur-

ring in a susceptible population followed over a given time period; its units are therefore expressed as the number of cases per unit of person-time. The incidence density ratio is defined as the ratio of incidence density of an exposed group to that of an unexposed group. For each study, we calculated the incident rate ratio (IRR) of catching a cold in treatment participants compared to the risk in control participants (Analysis 1.3; Figure 5). The IRR of developing a cold in subjects who received the intervention was 0.64 (95% CI 0.47 to 0.88), compared to participants in the control group (P = 0.006).

Figure 5. Forest plot of comparison: 1 Primary outcomes, outcome: 1.3 Incidence of common cold (IRR).



2. Secondary outcomes

Proportion of participants symptomatic after three, five or seven days of treatment

Proportion of participants symptomatic after three days of treatment

Three studies (Mossad 1996; Smith 1989; Weismann 1990) included a total of 340 participants. There was no significant difference between the intervention and control group for the proportion of participants symptomatic after day three of treatment (OR 0.81; 95% CI 0.27 to 2.42) (P = 0.7) (Analysis 2.1).

Proportion of participants symptomatic after five days of treatment

Three studies (Mossad 1996; Smith 1989; Weismann 1990) included a total of 340 participants. There was no significant difference between the intervention and control group for proportion of participants symptomatic after day five of treatment (OR 0.78; 95% CI 0.32 to 1.95) (P = 0.6) (Analysis 2.2).

Proportion of participants symptomatic after seven days of treatment

Five studies (Douglas 1987; Godfrey 1992; Mossad 1996; Smith 1989; Weismann 1990) included a total of 476 participants. There was a significant difference between the intervention and control group for proportion of participants symptomatic after day seven of treatment (OR 0.45; 95% CI 0.20 to 1.00) (P = 0.05) (Analysis 2.3).

Time to resolution of individual cold symptoms

This was reported in five studies.

Time to resolution of cough

Four studies (Kurugol 2006a; Macknin 1998; Prasad 2000; Prasad 2008) included a total of 453 participants (intervention = 219, control = 234). The time taken for resolution of cough was significantly shorter in the intervention group (SMD -0.55; 95% CI -1.04 to -0.05) (P = 0.03) (Analysis 2.4).

Time to resolution of nasal congestion

Five studies (Kurugol 2006a; Macknin 1998; Petrus 1998; Prasad 2000; Prasad 2008) included a total of 605 participants (intervention = 302, control = 303). The time taken for resolution of

nasal congestion was significantly shorter in the intervention group (SMD -0.25; 95% CI -0.41 to -0.09) (P = 0.002) (Analysis 2.5).

Time to resolution of nasal drainage

Five studies (Kurugol 2006a; Macknin 1998; Petrus 1998; Prasad 2000; Prasad 2008) included a total of 599 participants (intervention = 298, control = 301). The time taken for resolution of nasal drainage was significantly shorter in the intervention group (SMD -0.32; 95% CI -0.62 to -0.01) (P = 0.04) (Analysis 2.6).

Time to resolution of sore throat

Four studies (Kurugol 2006a; Macknin 1998; Prasad 2000; Prasad 2008) included a total of 430 participants (intervention = 211, control = 219). The time taken for resolution of sore throat was significantly shorter in the intervention group (SMD -0.24; 95% CI -0.44 to -0.03) (P = 0.02) (Analysis 2.7).

Change in individual severity symptom scores

Change in cough symptom score

This was reported in two studies (Douglas 1987; Petrus 1998). In the study by Douglas 1987, a total of 63 treatment courses were evaluated (intervention = 33, control = 30) and the mean cough score (standard error of mean (SEM) not provided) was lower in the control group (6.3) than in the intervention group (10.6), which was statistically insignificant (P = 0.2). In the study by Petrus 1998, a total of 101 participants were included and there was a significant decrease in the mean cough score in the intervention group (SMD -2.84; 95% CI -3.4 to -2.28) (P < 0.00001) (Analysis 2.8).

Change in nasal symptom score

This was reported in four studies (Douglas 1987; Kurugol 2006a; Kurugol 2007; Petrus 1998). In the study by Douglas 1987, a total of 63 treatment courses were evaluated and the mean nasal score (SEM not provided) was lower in the control group (9.8) than in the intervention group (11.7), which was statistically insignificant (P = 0.5). In the study by Petrus 1998, a total of 101 participants were included and there was a decrease in the mean nasal score (not significant) in the intervention group (nasal congestion: placebo 1.43 ± 0.05, zinc 1.54 ± 0.08; nasal drainage: placebo 1.61 ± 0.07, zinc 1.45 ± 0.07). In the Kurugol 2006a and Kurugol 2007 studies a total of 314 participants were included and there was no difference between the two groups for the change in nasal symptom score (SMD -0.06; 95% CI -0.42 to 0.30) (P = 0.73) (Analysis 2.9).

Change in throat symptom score

This was reported in two studies (Douglas 1987; Petrus 1998). In one study (Douglas 1987), a total of 63 treatment courses were evaluated and the mean throat score (SEM not provided) was lower in the intervention group (6.1) than in the control group (6.2), which was statistically insignificant (P = 0.96). In another study (Petrus 1998), a total of 101 participants were included and there was a decrease in the mean throat score (not significant) in the intervention group (sore throat: placebo 1.34 ± 0.11, zinc 1.26 ± 0.06; scratchy throat: placebo 1.53 ± 0.08, zinc 1.38 ± 0.1).

School absenteeism

Three trials reported this outcome. The pooled result from the two preventive trials (Kurugol 2006a; Vakili 2009) showed that zinc supplemented children were absent for fewer days from school (SMD -0.37; 95% CI -0.7 to -0.04) (P = 0.03) (Analysis 2.10). In one of the therapeutic trials (Macknin 1998), children taking zinc were less likely to be absent than children taking placebo (OR 0.60; 95% CI 0.32 to 1.13) (P = 0.12).

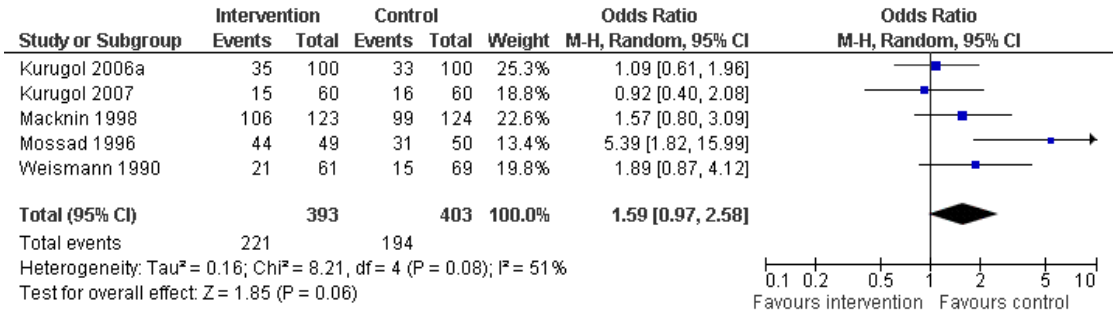
Antibiotics use

Two trials reported this outcome (Kurugol 2006b; Vakili 2009). The antibiotic prescription was more likely in placebo than in zinc supplemented children (OR 0.27; 95% CI 0.16 to 0.46) (P < 0.00001) (Analysis 2.11).

Adverse events

Ten trials (Douglas 1987; Kurugol 2006a; Kurugol 2006b; Kurugol 2007; Macknin 1998; Mossad 1996; Prasad 2000; Prasad 2008; Smith 1989; Weismann 1990) were included for reporting of any or individual adverse events. The incidence of any adverse event was higher in the zinc group (OR 1.59; 95% CI 0.97 to 2.58) (P = 0.06) than in the control group (Analysis 2.12; Figure 6). Among individual events, bad taste (OR 2.64; 95% CI 1.91 to 3.64) (P < 0.00001) (Analysis 2.13) and nausea (OR 2.15; 95% CI 1.44 to 3.23) (P = 0.002) (Analysis 2.14) had a higher incidence in the zinc group. There was no significant difference between the two groups in the incidence of constipation (P = 0.17) (Analysis 2.15), diarrhoea (P = 0.08) (Analysis 2.16), abdominal pain (P = 0.25) (Analysis 2.17), dry mouth (P = 0.09) (Analysis 2.18) and oral irritation (P = 0.50) (Analysis 2.19).

Figure 6. Forest plot of comparison: 2 Secondary outcomes, outcome: 2.12 Any adverse event.



DISCUSSION

The discussion is divided into two parts: the first will discuss important methodological issues that have emerged from research in this area, and the second part will discuss the results obtained and their clinical significance.

Part 1: methodology

Since Eby's trial in 1984 (Eby 1984), 18 studies have investigated whether zinc is efficacious in the treatment or prevention of the common cold. Among these 15 studies were included in this review. The methodological quality of the included trials was rated as good, with two trials excluded because of poor quality. Eby's trial realised a number of limitations which raised concerns regarding the validity of the results. Treatment blinding in the trial has been questioned as zinc lozenges were found to be unpalatable, distorted the taste of participants and caused a higher incidence of side effects. In addition, investigators relied solely on the subjective assessment of cold symptoms; laboratory confirmation of viral infection was not conducted and analyses were only conducted on a subgroup of those originally enrolled in the trial. Eby's trial was nevertheless instructive and highlighted a number of methodological issues.

Like Eby's trial, most trials have relied on community-acquired infections. However, two trials recruited participants from volunteers experimentally inoculated with human rhinovirus (Al-Nakib 1987; Farr 1987a). While high rates of infection with human rhinovirus were attained in the later trials and most participants experienced cold symptoms, in trials relying on community-acquired infection, the infecting agent and the infection rates were generally not determined.

In trials relying on community-acquired infection, investigators relied on trial participants or family members to assess the incidence and severity of cold symptoms. Though in most of the trials information was generally provided on how compliance with the recording of symptoms was assessed, objective periodic assessments of the clinical severity of respiratory symptoms were not conducted. In the trials conducted by Al-Nakib (Al-Nakib 1987), Farr (Farr 1987a), Macknin (Macknin 1998) and Kurugol (Kurugol 2006a; Kurugol 2006b; Kurugol 2007) symptoms were assessed by trial personnel thus providing some assurance as to the validity of clinical severity scores and estimates based on such scores. Assessment of response to treatment also depended on objective measurements such as nasal mucus weight or tissue counts, which was measured in one study (Al-Nakib 1987) and the authors found that zinc gluconate reduced both of these parameters. However, as in most studies children were involved, this was not practical.

Research by Farr (Farr 1987b) suggested that in most trials the size of the placebo-blinding study used to determine whether zinc and placebo lozenges were indistinguishable was not sufficiently large to detect a significant difference. In their efforts to find a suitable matching placebo lozenge Farr showed that a false negative result may result if a small subject population (i.e. fewer than 20) is used. Given that placebo-blinding studies were only conducted in six of the 15 trials, and with the exception of three trials (Farr 1987a; Prasad 2000; Prasad 2008) the size of the placebo-matching studies in two of the remaining three trials (no information was provided on the size of placebo study conducted by Weismann (Weismann 1990)) ranged from eight to 20, the adequacy of blinding in most trials is questioned. Zinc-treated participants also experienced higher incidences of side effects, complaints or both, and in four trials, zinc-treated participants complained of altered, bad or unpalatable taste which suggests that zinc lozenges were distinct from placebo lozenges and, in this respect, blinding may have been compromised. However, the increased incidence of bad taste and nausea found by Mossad (Mossad 1996); constipation and mouth dryness found by Prasad (Prasad 2000) and bad taste, nausea, mouth, tongue or throat discomfort and diarrhoea found

by Macknin (Macknin 1998), may have been related to the use of different ligands (gluconate, acetate) rather than to zinc itself.

Much of the controversy surrounding the use of zinc lozenges in the treatment of the common cold has concerned whether formulations used in trials showing no benefit failed to release sufficient zinc ions to be effective. It has been hypothesised that there is a direct correlation between reductions in the duration of common cold symptoms and the daily dosage of all positively charged zinc species released from lozenges at physiologic pH (Eby 1995). The reanalysis of 10 double-blind, placebo-controlled zinc trials by solution chemistry methods showed a significant correlation between total daily dosages of positively-charged zinc species and a reduction in the mean duration of common colds (Eby 2004). Zinc gluconate and zinc acetate have very low chemical stability and mainly release positively charged zinc ions in aqueous solutions at physiologic pH, but stronger complexes do not (Eby 2004). Adding a strong zinc-binding ligand, such as glycine, citric acid, tartaric acid, mannitol and sorbitol, to a solution containing a zinc complex that is weakly bonded results in the sequestration of zinc to the stronger ligand, reducing or eliminating the benefits of zinc lozenges (Eby 2004). The extent to which the zinc ion was released from formulations reporting no benefit is not known. However, experimental evidence suggests that in saliva the ionisation of zinc to free zinc for some formulations may have been completely (Zarembo 1992) or partially (Farr 1988) suppressed. A formulation developed by Godfrey (Godfrey 1992) that incorporates glycine has been shown to release more than 90% of the zinc from zinc gluconate as the zinc ion. Results from trials conducted by Godfrey (Godfrey 1992) and Mossad (Mossad 1996) suggest this formulation reduced the duration and severity of respiratory symptoms; whereas the trial conducted by Macknin (Macknin 1998) and Turner (Turner 2000) suggest no effect of this formulation. The placebo-matching was inadequate; consequently the adequacy of blinding in all these four trials is questioned. Hatch et al (Hatch 1987), reported that zinc acetate releases essentially 100% of its zinc as Zn^{2+} ions at a physiological pH. Thus, use of zinc lozenges may be advantageous. Results from trials conducted by Petrus (Petrus 1998) and Prasad (Prasad 2000; Prasad 2008) suggest this formulation reduced the duration and severity of respiratory symptoms. These studies used compressed lozenges designed by George Eby that were identical in composition. In addition to zinc acetate, they contained directly compressible (agglomerated) dextrose as the tablet base, glycerol monostearate (2.5% of tablet weight) as the tablet lubricant, stevia for added sweetness, and peppermint oil for flavour, with the composition compressed to near maximal hardness for slowest dissolution. These ingredients were specifically chosen because they do not react with ionic zinc. The trials conducted by Douglas (Douglas 1987) using zinc acetate suggest no effect of this formulation. The placebo-matching and blinding were stated to be adequate in all the four trials. Three trials (Kurugol 2006a; Kurugol 2006b; Kurugol 2007) used syrup preparation of zinc (zinc sulphate) and found reduced duration and severity of respiratory symptoms without any increase in adverse effects in zinc group. Placebo-matching and adequacy of blinding was not stated in these two trials. Another trial (Vakili 2009) used tablet preparation (zinc sulphate) and found decreased incidence, fewer school absences, less antibiotic administration and no adverse effects in zinc-supplemented children. Again placebo-matching and adequacy of blinding was not stated in this trial.

The toxicology of zinc has been well characterized. The potential for elevated blood levels of zinc to disrupt copper metabolism and other nutrients preclude its long-term use in the treatment of the common cold (Pfeiffer 1980). Doses higher than 150 mg/day have also been associated with adverse effects (Chandra 1984). In addition, the higher incidence of side effects in zinc-treated participants will most likely limit the usefulness of zinc in the treatment of cold symptoms. In 11 trials (Douglas 1987; Kurugol 2006a; Kurugol 2006b; Kurugol 2007; Macknin 1998; Mossad 1996; Prasad 2000; Prasad 2008; Smith 1989; Vakili 2009; Weismann 1990) included for reporting of any or individual adverse events, the overall adverse events (OR 1.59; 95% CI 0.97 to 2.58) (P = 0.06) were higher in the intervention than in the control group, except in one trial (Vakili 2009). Among individual events, bad taste (OR 2.64; 95% CI 1.91 to 3.64) (P < 0.00001) and nausea (OR 2.15; 95% CI 1.44 to 3.23) (P = 0.002) had a significantly higher incidence in the zinc group.

Viral studies were only performed in six trials (Al-Nakib 1987; Douglas 1987; Farr 1987a; Kurugol 2006a; Kurugol 2006b; Kurugol 2007). While in-vitro studies suggest zinc inhibits viral replication and the concentration of zinc in saliva should be sufficient to induce such an effect, three trials (Al-Nakib 1987; Douglas 1987; Farr 1987a) found no effect of zinc on incidence or shedding of rhinovirus by study participants. In relation to this, trials by Farr and Douglas, found no effect of zinc in treatment of cold, while Al-Nakib found reduction in the clinical symptom score. From trial by Al-Nakib, it might be suggested that medication may have had an effect on signs and symptoms of the colds rather than on virus replication. If this is the case, it would be interesting to know whether zinc would also have the same effect on corona virus colds or, indeed, on colds caused by other respiratory viruses. This may be the future area of research in zinc and common cold trials. Trials by Kurugol (Kurugol 2006a; Kurugol 2006b; Kurugol 2007) did not study the effect of zinc on rhinovirus cold; rather they excluded colds due to influenza viruses from analysis and found that zinc is effective in the treatment of the common cold.

Part 2: results

Although most investigators required participants to record the clinical severity of symptoms each day and used similar scales against which to rate symptom severity (symptoms were rated as none, mild, moderate or severe), there was little commonality in

summary estimates used by investigators to describe the duration, incidence and severity of respiratory symptoms. Consequently for some outcomes it was not possible to pool results. In addition, there was insufficient detail provided in most published papers to determine whether trials used similar criteria for rating the severity of each symptom and therefore it was not possible to standardise clinical severity scores across all trials.

Among 10 trials reporting the duration of cold symptoms, results could be pooled from six trials, which suggest that zinc significantly reduced the duration of cold in treated participants. Among six of these trials, two trials (Kurugol 2006a; Kurugol 2007) used syrup preparation at a daily dose of 30 mg, whereas four trials (Macknin 1998; Petrus 1998; Prasad 2000; Prasad 2008) used lozenge preparation at a daily doses varying from 90 mg to 160 mg. In the other three trials (Douglas 1987; Godfrey 1992; Mossad 1996), estimates of average cold duration were available. These three trials used lozenge preparation at a daily dose varying from 80 mg to 190 mg. The average duration of cold for zinc-treated participants was reduced by approximately 42% and 20% of that estimated for placebo-treated participants in trials conducted by Mossad and Godfrey, respectively. However, in the trial conducted by Douglas, the average duration for zinc-treated participants was found to be increased by approximately 57% of that estimated for placebo-treated participants. Results from five trials (Kurugol 2006a; Macknin 1998; Petrus 1998; Prasad 2000; Prasad 2008) could be pooled to find the time taken for resolution of individual symptoms, and the result suggests that zinc significantly shortens the duration of individual symptoms (cough, nasal drainage, nasal congestion and sore throat). In one trial (Kurugol 2007), the authors found no significant decrease in the individual symptoms in the zinc group; while in another trial (Godfrey 1992), incidence of cough and nasal symptoms (congestion, drainage) were significantly decreased in the zinc group.

Among 10 trials measuring the severity score of cold symptoms, results from five trials (Kurugol 2006a; Kurugol 2007; Petrus 1998; Prasad 2000; Prasad 2008) could be pooled. There was no significant difference between the intervention and control group for reduction in the severity of cold symptoms. Al-Nakib (Al-Nakib 1987) and Douglas (Douglas 1987) provided estimates of mean clinical scores. However, estimates were not directly comparable. In the trial by Al-Nakib, the zinc group had a significantly lower mean daily clinical score than the placebo group; the difference in scores attaining statistical significance on days four and five. However, in the trial conducted by Douglas, there were no statistically significant differences between zinc and placebo groups with respect to mean nasal, throat and cough scores. Results of the trial conducted by Godfrey (Godfrey 1992) suggested treatment with zinc reduced the frequency and severity of cold symptoms, which was noticeable by day five and significant by day seven. Among four trials (Douglas 1987; Kurugol 2006a; Kurugol 2007; Petrus 1998) measuring individual symptom scores there was a significant reduction in the cough score, with nasal and throat score being variably affected. In the trial conducted by Smith 1989, the zinc group had lower symptom severity scores on days four to seven of treatment which was statistically significant (P = 0.02); but in the trial conducted by Weismann 1990, no statistically significant differences between the two groups were found by day six of treatment (P = 0.14). Among these 10 trials, trials using syrup preparation used a daily dose of 30 mg, whereas the trials using lozenge preparation used daily doses varying from 80 mg to 276 mg.

Among the two preventive trials measuring the incidence of the common cold (Kurugol 2006b; Vakili 2009), the incidence rate ratio (IRR) of developing a cold in participants who received the intervention was lower than in the placebo group. There was marked heterogeneity, therefore we used a random-effects model for analysing this outcome. The second trial, though a randomized controlled trial (RCT), was not of good methodological quality, but this was included in the analysis as it included a large number of participants. Even after excluding this trial from analysis, the result still favoured zinc supplementation. The first trial used zinc sulfate syrup at a daily dose of 15 mg for seven months, whereas the second trial used zinc sulfate tablet at a daily dose of 10 mg for five months.

The proportion of participants that were asymptomatic after three, five and seven days of treatment was reported in the trials conducted by Mossad (Mossad 1996), Weismann (Weismann 1990) and Smith (Smith 1989), and the proportion asymptomatic after seven days of treatment was reported in all but the trials conducted by Farr (Farr 1987a) and Al-Nakib (Al-Nakib 1987). Analyses were conducted on an intention-to-treat (ITT) basis. In the trial conducted by Mossad (Mossad 1996) participants were less likely to have cold symptoms after three and five days of treatment in the zinc-treated group. The Peto ORs for days three and five were 0.37 (95% CI 0.14 to 0.92) and 0.35 (95% CI 0.16 to 0.76), respectively. In the trials conducted by Weismann (Weismann 1990) and Smith (Smith 1989), the proportion of participants asymptomatic after three and five days in the zinc and placebo groups was similar. The test for heterogeneity attained statistical significance for day five, but not day three and consequently a combined OR for day five is not appropriate. The combined Peto OR for day three was not significant 0.97 (95% CI 0.62 to 1.5). In trials conducted by Mossad (Mossad 1996), Godfrey (Godfrey 1992) and Weismann (Weismann 1990), there were fewer participants in the zinc group who had cold symptoms after seven days. Although the Peto OR 0.53 (95% CI 0.38 to 0.75) obtained by pooling results from the trials conducted by Mossad (Mossad 1996), Weismann (Weismann 1990), Godfrey (Godfrey 1992), Smith (Smith 1989) and Douglas (Douglas 1987) indicated fewer participants in the zinc group had cold symptoms after seven days of treatment, the test for heterogeneity was statistically significant and therefore we did not pool the results.

In six trials (Godfrey 1992; Kurugol 2006a; Mossad 1996; Petrus 1998; Prasad 2000; Prasad 2008) with similar study designs,

methodologies and efficacy assessments, zinc was found to be effective in reducing the duration and severity of common cold symptoms in healthy children and adults, when it was administered within 24 hours of the onset of symptoms. In another trial (Kurugol 2007) with similar study design, methodology and efficacy assessments, zinc was found to be effective in reducing the severity of common cold symptoms in healthy children (without any change in duration), when it was administered within 24 to 48 hours of the onset of symptoms. In the trial by Godfrey et al (Godfrey 1992), the authors found a significant decrease in the duration and severity of symptoms when treatment was administered within 24 hours, compared to treatment administration within 48 hours.

There are a number of potential sources of heterogeneity in results obtained from trials included in this review. Most trials relied on community-acquired infections in which the infecting agent was not identified and as such different agents may have been involved which may have differed in their sensitivity to zinc. The amount of zinc taken each day by participants varied across trials, and given that some formulations released less zinc ion than others the effective dose of zinc across trials was variable. Blinding of treatment may not have been adequately controlled in some trials, thereby increasing the potential for performance and detection bias to occur. The time from onset of cold symptoms to commencement of treatment ranged from one to three days. Given the beneficial effects noted in trials commencing treatment with zinc within 24 hours, the results from all the trials may not be comparable. Last but not the least is the fact that the lifestyle of the study population in all the trials was different and the results might have been affected to some degree by this factor.

Summary of main results

Studies reporting duration and severity of cold symptoms suggest that the intake of zinc is associated with a significant reduction in the overall duration and severity of common cold symptoms. A higher proportion of participants became asymptomatic by day seven of treatment with zinc. Duration of individual cold symptoms was also significantly reduced in the zinc group, though the individual symptom severity scores were not significantly affected by the intake of zinc. Zinc supplementation led to reduction in the incidence of common cold, decreased school absence and decreased the risk of antibiotic use when used for at least for five months. The incidence of adverse events was significantly higher in the zinc group with the syrup preparation being better tolerated than lozenges.

Overall completeness and applicability of evidence

The trials included in the analysis involved healthy children and adults of all ages (except infants) and both sexes. All 15 trials were conducted in high-income countries, where zinc deficiency is uncommon (including in young children). Therefore, the results of these trials may not be applicable to children and adults in low-income countries. In all the included trials, the main weakness of the data is that most trials, when presenting data, did not differentiate between cold due to rhinovirus and other viruses (as viral studies were not conducted in most of these trials). So it is unclear whether zinc helps those with rhinoviral cold or even cold due to other viruses. However, as rhinovirus is the most common aetiological agent of the common cold all over the world (in both low-income and high-income countries), it may be predicted that zinc might also help people living in low-income countries.

Quality of the evidence

The trial evidence included is generally of good quality, with a low risk of bias. All 15 studies were blinded, but placebo-blinding was adequately described in only six trials. In nine trials, zinc-treated participants complained of altered, bad or unpalatable taste which suggests that zinc lozenges were distinct from placebo lozenges and, in this respect, blinding may have been compromised. Allocation concealment was adequate in nine studies and unclear in five studies. Thirteen trials reported a low rate of loss to follow up. This suggests that the studies were of good quality. For all the outcomes, there was more than one study reporting the individual outcome. The majority were carefully conducted community trials, with active mechanisms to promote adherence to the intervention and both active and passive case finding.

Potential biases in the review process

All the included trials, as expected, measured the effect of zinc on the common cold. There was therefore the potential to miss trials which may have measured common cold as upper respiratory tract infection in secondary outcomes which were less publicised or less well-indexed within the electronic databases. We tried to avoid this by conducting a wide search and assessing the relevance of each paper identified in that search carefully. There are no other obvious sources of potential bias.

Agreements and disagreements with other studies or reviews

The important changes in this updated review in comparison to the previous version (Marshall 1999) include the following.

1. Intake of zinc is associated with a significant reduction in the duration and severity of common cold symptoms.
2. Duration of individual cold symptoms was also significantly reduced in the zinc group.
3. The syrup and tablet preparation of zinc is better tolerated than lozenges.
4. Zinc supplementation reduces incidence, school absenteeism and prescription of antibiotics in children with the common cold.

In the review conducted by Marshall (Marshall 1999), the included studies had following missing information, for which it was not possible to pool the results across the studies, and these included: although most investigators required participants to record the clinical severity of symptoms each day and used similar scales against which to rate symptom severity (symptoms were rated as none, mild, moderate or severe), there was little commonality in the summary estimates used by investigators to describe the duration, incidence and severity of respiratory symptoms. It was therefore only possible to determine the proportion of participants who were asymptomatic after three and five days of treatment for three trials and after seven days of treatment for five trials. Except one study (Godfrey 1992), duration of symptoms was not reported in the rest of the studies. Therefore, again it was not possible to pool the results for this outcome.

A review published in 2004 by Hulisz (Hulisz 2004), which was an overview of published articles through MEDLINE (1980 to 2003), concluded that zinc effectively reduces the duration and severity of common cold symptoms when administered within 24 hours of the onset of symptoms. The author also had some concerns regarding the clinical tests of zinc for the treatment of common colds being inconsistent, primarily because of study design, blinding and lozenge contents; early formulations of lozenges being unpalatable with a higher incidence of side effects.

AUTHORS' CONCLUSIONS

Implications for practice

Evidence shows that zinc is beneficial for the common cold in healthy children and adults living in high-income countries. Pooled results from the trials showed that zinc reduced the duration and severity of common cold symptoms when used therapeutically. Zinc also reduced the incidence of the common cold, school absence and antibiotic use in healthy children when used prophylactically. We could not find any trials conducted in low-income countries, so our results cannot be applied to people living in low-income countries. Also, all the studies included healthy participants; we could not find any evidence regarding use of zinc in participants at risk of developing the common cold. Given that some formulations (especially lozenges) produced side effects and not all formulations may be effective, the use of zinc to treat common cold symptoms is presently advised with caution.

Implications for research

Morbidity associated with the common cold is not trivial. The median duration of a cold episode is 7.4 days, with 25% of cases continuing for two weeks. The burden of the common cold is even more pronounced in individuals with chronic co-morbidities or clinical risk factors, including those with asthma and chronic obstructive pulmonary disease, the elderly, those with a history of otitis media or sinusitis, and those who are immunocompromised. Asthmatic children experience more cold episodes than non-asthmatic children, which is a common risk factor for acute asthma exacerbations. Future studies should therefore focus on the role of zinc in these populations rather than healthy people, as the results would be more meaningful for them.

To date no clinical trials of zinc for the common cold have been conducted in low-income countries. The assumption is that in these countries zinc deficiency may be prevalent and the results may be far more impressive. It is therefore important that before any firm conclusion is made, trials should be conducted in these countries. Furthermore, although the economic burden of the common cold in these populations may be less the vast majority of people live in such countries, potentially making the results more meaningful.

More clinical trials reporting clinically relevant outcomes in a standard format are also needed, analysing and presenting data in a manner that is appropriate and suitable for combining with other trial data in meta-analyses. Investigators also need to recognise the difficulties that have been encountered, particularly with respect to blinding and bioavailability (with various formulations).

Although laboratory confirmation of infection is desirable, in large community-based trials the costs associated with such investigations limit the extent to which serology can be undertaken. However, unlike trials relying on experimentally-induced rhinoviral colds, findings from large community-based trials will address issues relating to the diversity of and generalisability to the common cold.

In addition, given its toxicological profile, the potential for zinc to induce adverse effects at the doses participants are required to take also needs to be determined.

ACKNOWLEDGEMENTS

We wish to thank Ian IR Marshall, the previous author of this review. We acknowledge all the help and infrastructure provided by the Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh. We acknowledge the help provided by Elizabeth Dooley, Managing Editor and Sarah Thorning, Trials Search Co-ordinator of the Cochrane Acute Respiratory Infections Group, for the EMBASE search and getting full text articles of studies. We are very grateful to the referees Durhane Wong-Rieger, Craig Mellis, Mark Jones and Paul Little for their input in improving the quality of this updated review.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Al-Nakib 1987

Methods	Double-blind, placebo-controlled randomized trial
Participants	Healthy adults 18 to 50 years
Interventions	Therapeutic trial: participants took 1 lozenge 2-hourly for 6 days Intervention group: zinc gluconate lozenges containing 23 mg zinc Placebo group: not stated Prophylactic trial : participants took 1 lozenge/2 waking hours for a total of 12 lozenges/day for 4.5 days. On the second day they were challenged with HRV-2 Intervention group: zinc gluconate lozenges containing 23 mg zinc Placebo group: not stated
Outcomes	Severity of symptoms Mean daily nasal secretions Total tissue counts Viral shedding Biochemical and haematological parameters Trial 1: urinary zinc levels
Notes	Although participants were stated to be healthy, no other exclusion criteria were stated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	High risk	
Allocation concealment?	Unclear risk	B - Unclear
Blinding? All outcomes	Low risk	
Incomplete outcome data addressed? All outcomes	Unclear risk	There were no drop-outs or withdrawals
Free of selective reporting?	High risk	
Free of other bias?	Unclear risk	The zinc and placebo lozenges were gifted by RBS Pharma, Milan

Douglas 1987

Methods	Double-blind, placebo-controlled randomized trial
Participants	Healthy adults
Interventions	Participants took 6 to 8 lozenges/day at 2nd-hourly intervals for a minimum of 3 days and maximum of 6 days if symptoms persisted. New course commenced after 2 weeks if symptoms persisted but type of treatment may differ. Consequently 33 zinc courses and 30 placebo courses Treatment group: zinc acetate lozenges containing 10 mg zinc Placebo group: lozenges contained sodium acetate
Outcomes	Duration and severity of symptoms (nasal, throat or cough) Viral cultures
Notes	Although adults were stated to be healthy, no exclusion criteria were stated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	
Allocation concealment?	Low risk	Used blocked randomisation of 4 blocks each. The code was broken twice (once in middle of study and then at the end of study)
Blinding? All outcomes	Low risk	
Incomplete outcome data addressed? All outcomes	Low risk	
Free of selective reporting?	Low risk	
Free of other bias?	Unclear risk	The zinc and placebo lozenges were provided by Fauldings Ltd

Farr 1987a

Methods	Double-blind, placebo-controlled trial
Participants	Healthy adults
Interventions	Trial 1: treatment consisted of initial loading dose of 2 lozenges 36 hours following inoculation with HRV-39, and thereafter 1 lozenge every 2 hrs for a total of 8 lozenges/day for 5 days Intervention group: zinc gluconate lozenges containing 23 mg zinc

Farr 1987a (*Continued*)

	Placebo group: lozenges contained 0.00125 mg denatonium benzoate Trial 2: treatment consisted of initial loading dose of 2 lozenges 2 hours following inoculation with HRV-13, and thereafter 1 lozenge every 2 hrs for a total of 8 lozenges/day for 7 days Intervention group: zinc gluconate lozenges containing 23 mg zinc Placebo group: 0.0025 mg denatonium benzoate
Outcomes	Severity and duration of symptoms Tissue counts Laboratory tests Infection rates
Notes	Exclusion criteria were symptoms of any respiratory illness in the week before the study, a history of hay fever, any familiarity with the taste of either denatonium benzoate or zinc, a history of any chronic disease, pregnancy, lactation or an unacceptable contraceptive method in women of child-bearing potential, and known abuse of habit-forming drugs

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	Each lozenge was wrapped in cellophane and packaged in an opaque polyethylene bottle bearing the study number, the number of subjects, the treatment day and dosing instructions
Blinding? All outcomes	Low risk	
Incomplete outcome data addressed? All outcomes	Low risk	
Free of selective reporting?	Low risk	
Free of other bias?	Unclear risk	Partly funded by Bristol Myers Products, Hillside, NJ

Godfrey 1992

Methods	Double-blind, placebo-controlled randomized trial
Participants	Participants ranged in age from 18 to 40 years
Interventions	Participants took 1 lozenge every 2 hours for up to 8 hours a day Treatment group: zinc gluconate lozenges containing 23.7 mg zinc. Placebo group: lozenges contained tannic acid, glycine and calcium saccharinate in an orange-flavoured, boiled candy base

Godfrey 1992 (*Continued*)

Outcomes	Frequency and severity of symptoms over 7 days	
Notes	Exclusion criteria were positive bacteriological throat culture, pregnancy, lactation, and diabetes mellitus	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	
Allocation concealment?	Low risk	A pharmacist, using a randomisation table provided by the study statistician, packaged containers for individual participants with lozenges according to the production run number and subject identification number
Blinding? All outcomes	Low risk	
Incomplete outcome data addressed? All outcomes	Low risk	
Free of selective reporting?	Low risk	
Free of other bias?	Unclear risk	The study was sponsored by Godfrey Science and Design, PA and by a grant from the Rorer Pharmaceutical corporation, PA, USA

Kurugol 2006a

Methods	Double-blind, placebo-controlled trial
Participants	Children aged 2 to 10 years
Interventions	Therapeutic trial: children received syrup preparation of zinc twice daily for 10 days Intervention group: zinc syrup consisted of 1.32 gm zinc sulphate in 100 cm^3 (15 mg of zinc in a 5 cm^3 spoonful) and glycerin, glucose, sunset yellow, orange essence, nipajin Placebo group: similar to above, but lacking the zinc component
Outcomes	Duration and severity of cold symptoms
Notes	Children with chronic disease, immunodeficiency disorder, asthma and history of hypersensitivity were excluded
Risk of bias	

Kurugol 2006a (*Continued*)

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	
Allocation concealment?	Low risk	A statistical consultant programmed a computer-generated randomisation code and prepared the packages of medication
Blinding? All outcomes	Low risk	
Incomplete outcome data addressed? All outcomes	Low risk	
Free of selective reporting?	Low risk	
Free of other bias?	Low risk	Berko Ilac Company, Turkey, supplied the active and placebo medications and digital thermometers. The company did not participate in designing the study, collecting and analysing the data, or in writing the report

Kurugol 2006b

Methods	Double-blind, placebo-controlled trial
Participants	Children aged 2 to 10 years
Interventions	Prophylactic trial: children received syrup preparation of zinc once daily for 7 months. Intervention group: zinc syrup consisted of 1.32 gm zinc sulphate in 100 cm^3 (15 mg of zinc in a 5 cm^3 spoonful) and glycerin, glucose, sunset yellow, orange essence, nipajin Placebo group: similar to above, but lacking the zinc component
Outcomes	Number of colds per study child Cold-related school absence Concomitant antibiotic use
Notes	Children with chronic disease, immunodeficiency disorder, asthma and history of hypersensitivity were excluded

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	

Kurugol 2006b (*Continued*)

Allocation concealment?	Low risk	A statistical consultant programmed a computer-generated randomisation code and prepared the packages of medication
Blinding? All outcomes	Low risk	
Incomplete outcome data addressed? All outcomes	Low risk	
Free of selective reporting?	Low risk	
Free of other bias?	Low risk	Berko Ilac Company, Turkey, supplied the active and placebo medications, and digital thermometers. The company did not participate in designing the study, collecting and analysing the data, or in writing the report

Kurugol 2007

Methods	Double-blind, placebo-controlled trial
Participants	Children aged 1 to 10 years
Interventions	Participants were asked to take 1 spoonful syrup twice a day for 10 days Treatment group: zinc syrup consisted of 1.32 g of zinc sulfate in 100 ml (15 mg of zinc in 5 mL spoonful) and glycerin, glucose, sunset yellow, orange essence and nipajin as preservative Placebo group: identical to above, but lacking the zinc component
Outcomes	Duration and severity of cold symptoms
Notes	Exclusion criteria were: common cold symptoms for > 48 hours, immunodeficiency disorder, chronic disease, recent acute respiratory disease (diagnosed by a physician in the previous 2 weeks), zinc allergy, allergic disease or non-allergic rhinitis, positive culture for group A *Streptococcus* and a positive cell culture for influenza A or B viruses

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	
Allocation concealment?	Low risk	A statistical consultant programmed a computer-generated randomisation code and prepared the packages of medication. The packages were identical in appearance except for the

Kurugol 2007 (*Continued*)

		randomisation numbers. The packages were randomly distributed by the study nurse
Blinding? All outcomes	Low risk	
Incomplete outcome data addressed? All outcomes	Low risk	
Free of selective reporting?	Low risk	
Free of other bias?	Low risk	Medications (active and placebo) and digital thermometers were supplied by Berko Ilaç, Turkey. The company did not participate in designing the study, collecting and analysing the data, or in writing the report

Macknin 1998

Methods	Double-masked, placebo-controlled trial
Participants	Students aged 6 to 16 years in grades 1 through to 12
Interventions	Students asked to take zinc lozenges, 10 mg, orally dissolved, 5 times a day (in grades 1 to 6) or 6 times a day (in grades 7 to 12) until their cold symptoms had been completely resolved for 6 hours Treatment group: zinc gluconate lozenges containing 10 mg zinc in a 3.75 gm hard candy that also contained sucrose, corn syrup, glycine Placebo group: lozenges contained calcium lactate pentahydrate instead of zinc and had similar composition as above
Outcomes	Duration of resolution and severity of symptoms
Notes	Subjects were excluded if they had an oral temperature greater than 37.7 ºC, had previously taken the zinc preparation, were pregnant, had a known immune deficiency, any acute illness other than common cold (e.g. pneumonia, gastroenteritis) or cold symptoms lasting more than 24 hours

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	
Allocation concealment?	Low risk	A computer-generated randomisation code was provided to the pharmacist, who held the code and prepared the packages of medication

Macknin 1998 (*Continued*)

Blinding? All outcomes	Low risk	
Incomplete outcome data addressed? All outcomes	Low risk	
Free of selective reporting?	Low risk	
Free of other bias?	Unclear risk	The study was supported by a grant from the Quigley Corporation, Doylestown, Pa

Mossad 1996

Methods	Double-blind, placebo-controlled trial
Participants	Participants were older than 18 years of age
Interventions	Subjects took 1 lozenge 2-hourly for every waking hour Treatment group: zinc gluconate lozenges containing 13.3 mg zinc Placebo group: lozenges contained 5% calcium lactate
Outcomes	Duration and severity of cold symptoms
Notes	Exclusion criteria were pregnancy, immune deficiency or symptoms of the common cold for more than 24 hours prior to interview. Subjects were assessed for non-adherence to treatment; reasons for non-adherence were: participants had taken antibiotics, condition diagnosed by physician to be other than the common cold, participants filled in diaries from memory, or insufficient lozenges were taken (i.e. fewer than 4 per day for the first 4 days)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	
Allocation concealment?	Low risk	A statistical consultant prepared a computer-generated randomisation code and the packages of medication
Blinding? All outcomes	Low risk	
Incomplete outcome data addressed? All outcomes	Low risk	
Free of selective reporting?	Low risk	

Mossad 1996 (*Continued*)

Free of other bias?	Low risk	The study was supported by grants from the General Pediatrics Research Fund and the Departments of Infectious Diseases and General Pediatrics of the Cleveland Clinic Foundation

Petrus 1998

Methods	Double-blind, placebo-controlled trial
Participants	Participants were 18 to 54 years of age
Interventions	Participants were instructed to use a lozenge every 1.5 hours while awake during day 0, then 1 lozenge every 2 hours while awake on following days while symptoms were present for 14 days or 6 hours after disappearance of last symptoms Treatment group: zinc acetate lozenges containing 9 mg zinc in a 2.7 g dextrose base Placebo group: lozenges contained sucrose octaacetate (0.169 mg)
Outcomes	Duration and severity of symptoms
Notes	Participants were excluded if they had a serious illnesses, organ transplants or disability (including HIV infection)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	High risk	
Blinding? All outcomes	Low risk	
Incomplete outcome data addressed? All outcomes	Low risk	
Free of selective reporting?	Low risk	
Free of other bias?	Unclear risk	Funded by Weider Nutrition International, Salt Lake City, Utah

Prasad 2000

Methods	Double-blind, placebo-controlled trial
Participants	Participants were older than 18 years of age

Prasad 2000 (*Continued*)

Interventions	Participants were asked to use 1 lozenge every 2 to 3 hours while awake for as long as they had symptoms Treatment group: zinc acetate lozenges containing 12.8 mg zinc Placebo group: lozenges contained 0.25 mg of sucrose octaacetate, 6 mg of peppermint oil, 16 mg silica gel, 3877.75 mg dextrose DC and 100 mg glycerol monostearate
Outcomes	Duration of symptoms Plasma levels of zinc and pro inflammatory cytokines
Notes	Exclusion criteria were pregnancy, underlying immunodeficiency, chronic illness, symptoms of common cold for more than 24 hours, or had previously used zinc lozenges to treat common cold

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	A research consultant prepared the randomisation code and the packages of medication
Blinding? All outcomes	Low risk	
Incomplete outcome data addressed? All outcomes	Low risk	
Free of selective reporting?	Low risk	
Free of other bias?	Low risk	Funded partly by George and Patsy Eby Research Foundation. The research foundation had no role in the collection, analysis, or interpretation of the data or in the decision to publish the study

Prasad 2008

Methods	Double-blind, placebo-controlled trial
Participants	Participants were older than 18 years of age
Interventions	Participants were asked to use one lozenge every 2 to 3 hours while awake for as long as they had symptoms Treatment group: zinc acetate lozenges containing 13.3 mg zinc in a hard candy that contained 3.8 g of sucrose and corn syrup Placebo group: lozenges contained 0.25 mg of sucrose octaacetate

Prasad 2008 (*Continued*)

Outcomes	Duration of symptoms Plasma levels of zinc and pro inflammatory cytokines
Notes	Exclusion criteria were pregnancy, underlying immunodeficiency, chronic illness, symptoms of common cold for more than 24 hours, or had previously used zinc lozenges to treat common cold

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	A research consultant prepared the randomisation code and the packages of medication
Blinding? All outcomes	Low risk	
Incomplete outcome data addressed? All outcomes	Low risk	
Free of selective reporting?	Low risk	
Free of other bias?	Low risk	Funded by National Institutes of Health; George and Patsy Eby Foundation, Austin, Texas (unrestricted research funds to Wayne State University for partial support)

Smith 1989

Methods	Double-blind, placebo-controlled trial
Participants	Participants were older than 18 years
Interventions	Participants took a loading dose of 4 lozenges then took 2 every 2 hours for 7 days or 24 hours after disappearance of last symptoms Treatment group: zinc gluconate lozenges containing 11.5 mg zinc Placebo group: lozenges contained sucrose octaacetate
Outcomes	Duration and severity of symptoms
Notes	Participants were excluded if they had a serious acute or chronic medical condition, seasonal allergies, productive cough, required antibiotic therapy or had taken any treatment for symptoms within 8 hours of baseline assessment

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Smith 1989 (*Continued*)

Blinding? All outcomes	Low risk	
Incomplete outcome data addressed? All outcomes	Low risk	
Free of selective reporting?	Low risk	
Free of other bias?	Unclear risk	The study was supported by a grant from McNeil Consumer Products Company

Vakili 2009

Methods	Double-blind, placebo-controlled trial
Participants	School children aged 6.5 to 10 years
Interventions	Participants took tablet daily for 6 days a week for 5 months Treatment group: zinc sulfate tablets containing 10 mg zinc Placebo group: not defined
Outcomes	Occurrence and duration of common cold
Notes	The subjects were free of chronic diseases, such as sickle cell disease or protein-energy malnutrition

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	High risk	
Incomplete outcome data addressed? All outcomes	Low risk	
Free of selective reporting?	Low risk	
Free of other bias?	Low risk	This study was supported by grant of vice president for research, Mashhad University of Medical Sciences

Weismann 1990

Methods	Double-blind, placebo-controlled randomized trial
Participants	Participants were aged 18 to 65 years
Interventions	Participants took 1 lozenge at 1 to 1.5-hourly intervals Treatment group: zinc gluconate lozenges (in maltitol syrup) containing 4.5 mg zinc Placebo group: lozenges contained maltitol syrup with natural flavour
Outcomes	Overall assessment of clinical condition assessed by participants using a visual analogue scale
Notes	No exclusion criteria stated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	High risk	
Allocation concealment?	Unclear risk	B - Unclear
Blinding? All outcomes	Low risk	
Incomplete outcome data addressed? All outcomes	Low risk	
Free of selective reporting?	Low risk	
Free of other bias?	Unclear risk	The lozenges were manufactured and supplied by a firm

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

Study	Reason for exclusion
Eby 1984	The trial was rated of poor methodological quality. A higher incidence of side effects and complaints in the zinc group may have reduced compliance with treatment (no information was provided on whether compliance with treatment was assessed). Intention-to-treat analyses were not conducted; analyses were only conducted on a subset of those originally enrolled in the trial. The trial relied on subjective assessment of symptoms by subjects. Inclusion criteria were not adequately addressed and therefore there may have been potential for selection bias to occur. In addition, no information was provided on how allocation to treatment groups was concealed, the power of the study was not stated and viral studies were not conducted
McElroy 2003	Poor methodological quality. Not a randomized trial

(*Continued*)

Potter 1993	Poor methodological quality. Not a randomized trial
Turner 2000	Poor methodological quality. Not a randomized trial
Veverka 2009	Poor methodological quality. Measured upper respiratory tract infection as a whole (common cold and seasonal flu)

DATA AND ANALYSES

Comparison 1. Primary outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duration of cold symptoms	6	762	Std. Mean Difference (IV, Random, 95% CI)	-0.97 [-1.56, -0.38]
2 Severity of cold symptoms	5	513	Std. Mean Difference (IV, Random, 95% CI)	-0.39 [-0.77, -0.02]
3 Incidence of common cold	2	1522	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.47, 0.88]

Comparison 2. Secondary outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants symptomatic after 3 days of treatment	3	340	Odds Ratio (M-H, Random, 95% CI)	0.81 [0.27, 2.42]
2 Number of participants symptomatic after 5 days of treatment	3	340	Odds Ratio (M-H, Random, 95% CI)	0.78 [0.32, 1.95]
3 Number of participants symptomatic after 7 days of treatment	5	476	Odds Ratio (M-H, Random, 95% CI)	0.45 [0.20, 1.00]
4 Time to resolution of cough	4	453	Std. Mean Difference (IV, Random, 95% CI)	-0.55 [-1.04, -0.05]
5 Time to resolution of nasal congestion	5	605	Std. Mean Difference (IV, Fixed, 95% CI)	-0.25 [-0.41, -0.09]
6 Time to resolution of nasal drainage	5	599	Std. Mean Difference (IV, Random, 95% CI)	-0.32 [-0.62, -0.01]
7 Time to resolution of sore throat	4	430	Std. Mean Difference (IV, Fixed, 95% CI)	-0.24 [-0.44, -0.03]
8 Change in cough symptom score	1	101	Std. Mean Difference (IV, Fixed, 95% CI)	-2.84 [-3.40, -2.28]
9 Change in nasal symptom score	2	314	Std. Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.42, 0.30]
10 School absenteeism (days)	2	394	Std. Mean Difference (IV, Random, 95% CI)	-0.37 [-0.70, -0.04]
11 Antibiotic use	2	394	Odds Ratio (M-H, Fixed, 95% CI)	0.27 [0.16, 0.46]
12 Any adverse event	5	796	Odds Ratio (M-H, Random, 95% CI)	1.59 [0.97, 2.58]
13 Bad taste	9	1062	Odds Ratio (M-H, Fixed, 95% CI)	2.64 [1.91, 3.64]
14 Nausea	8	932	Odds Ratio (M-H, Fixed, 95% CI)	2.15 [1.44, 3.23]
15 Constipation	7	874	Odds Ratio (M-H, Fixed, 95% CI)	1.60 [0.82, 3.10]
16 Diarrhoea	6	764	Odds Ratio (M-H, Fixed, 95% CI)	1.89 [0.92, 3.89]
17 Abdominal pain	6	824	Odds Ratio (M-H, Fixed, 95% CI)	1.31 [0.83, 2.07]
18 Dry mouth	7	874	Odds Ratio (M-H, Fixed, 95% CI)	1.37 [0.95, 1.99]
19 Mouth irritation	7	822	Odds Ratio (M-H, Fixed, 95% CI)	1.15 [0.77, 1.73]

Analysis 1.1. Comparison 1 Primary outcomes, Outcome 1 Duration of cold symptoms.

Review: Zinc for the common cold

Comparison: 1 Primary outcomes

Outcome: 1 Duration of cold symptoms

Study or subgroup	Intervention N	Mean(SD)	Control N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Kurugol 2006a	97	4.7 (0.8)	97	5.3 (0.7)		18.0 %	-0.80 [-1.09, -0.50]
Kurugol 2007	60	5.5 (1.97)	60	6.5 (1.97)		17.5 %	-0.50 [-0.87, -0.14]
Macknin 1998	125	8.5 (2.85)	124	8.5 (2.85)		18.2 %	0.0 [-0.25, 0.25]
Petrus 1998	52	4.4 (1.4)	49	5.1 (2.8)		17.4 %	-0.32 [-0.71, 0.08]
Prasad 2000	25	4.5 (1.6)	23	8.1 (1.8)		14.7 %	-2.08 [-2.80, -1.37]
Prasad 2008	25	4 (1.04)	25	7.12 (1.26)		14.2 %	-2.66 [-3.43, -1.88]
Total (95% CI)	**384**		**378**			**100.0 %**	**-0.97 [-1.56, -0.38]**

Heterogeneity: $Tau^2 = 0.48$; $Chi^2 = 68.88$, df = 5 ($P<0.00001$); $I^2 = 93\%$

Test for overall effect: $Z = 3.22$ ($P = 0.0013$)

Analysis 1.2. Comparison 1 Primary outcomes, Outcome 2 Severity of cold symptoms.

Review: Zinc for the common cold

Comparison: 1 Primary outcomes

Outcome: 2 Severity of cold symptoms

Study or subgroup	Intervention N	Mean(SD)	Control N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Kurugol 2006a	97	0.2 (4.92)	97	0.4 (5.9)		24.0 %	-0.04 [-0.32, 0.24]
Kurugol 2007	60	0.3 (4.64)	60	0.7 (6.97)		22.2 %	-0.07 [-0.43, 0.29]
Petrus 1998	52	1.41 (0.29)	49	1.5 (0.28)		21.3 %	-0.31 [-0.71, 0.08]
Prasad 2000	25	2.7 (2)	23	5.4 (1.9)		15.5 %	-1.36 [-1.99, -0.73]
Prasad 2008	25	3.45 (5)	25	5.61 (2.5)		17.0 %	-0.54 [-1.10, 0.03]
Total (95% CI)	**259**		**254**			**100.0 %**	**-0.39 [-0.77, -0.02]**

Heterogeneity: $Tau^2 = 0.13$; $Chi^2 = 16.10$, df = 4 ($P = 0.003$); $I^2 = 75\%$

Test for overall effect: $Z = 2.05$ ($P = 0.040$)

Analysis 1.3. Comparison 1 Primary outcomes, Outcome 3 Incidence of common cold.

Review: Zinc for the common cold

Comparison: 1 Primary outcomes

Outcome: 3 Incidence of common cold

Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Kurugol 2006b	121/281	160/281		48.8 %	0.76 [0.64, 0.90]
Vakili 2009	170/480	310/480		51.2 %	0.55 [0.48, 0.63]
Total (95% CI)	**761**	**761**		**100.0 %**	**0.64 [0.47, 0.88]**

Total events: 291 (Intervention), 470 (Control)

Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 8.39$, df = 1 (P = 0.004); $I^2 = 88\%$

Test for overall effect: Z = 2.76 (P = 0.0058)

Analysis 2.1. Comparison 2 Secondary outcomes, Outcome 1 Number of participants symptomatic after 3 days of treatment.

Review: Zinc for the common cold

Comparison: 2 Secondary outcomes

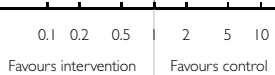
Outcome: 1 Number of participants symptomatic after 3 days of treatment

Study or subgroup	Intervention n/N	Control n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Mossad 1996	34/50	43/50		42.6 %	0.35 [0.13, 0.94]
Smith 1989	55/57	49/53		24.8 %	2.24 [0.39, 12.80]
Weismann 1990	57/61	64/69		32.6 %	1.11 [0.29, 4.35]
Total (95% CI)	**168**	**172**		**100.0 %**	**0.81 [0.27, 2.42]**

Total events: 146 (Intervention), 156 (Control)

Heterogeneity: $Tau^2 = 0.48$; $Chi^2 = 4.08$, df = 2 (P = 0.13); $I^2 = 51\%$

Test for overall effect: Z = 0.39 (P = 0.70)



Analysis 2.2. Comparison 2 Secondary outcomes, Outcome 2 Number of participants symptomatic after 5 days of treatment.

Review: Zinc for the common cold

Comparison: 2 Secondary outcomes

Outcome: 2 Number of participants symptomatic after 5 days of treatment

Study or subgroup	Intervention n/N	Control n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Mossad 1996	23/50	36/50		32.9 %	0.33 [0.14, 0.76]
Smith 1989	45/57	36/53		32.2 %	1.77 [0.75, 4.18]
Weismann 1990	40/61	48/69		34.9 %	0.83 [0.40, 1.74]
Total (95% CI)	**168**	**172**		**100.0 %**	**0.78 [0.32, 1.95]**

Total events: 108 (Intervention), 120 (Control)

Heterogeneity: $Tau^2 = 0.48$; $Chi^2 = 7.61$, df = 2 (P = 0.02); $I^2 = 74\%$

Test for overall effect: Z = 0.52 (P = 0.60)

Analysis 2.3. Comparison 2 Secondary outcomes, Outcome 3 Number of participants symptomatic after 7 days of treatment.

Review: Zinc for the common cold

Comparison: 2 Secondary outcomes

Outcome: 3 Number of participants symptomatic after 7 days of treatment

Study or subgroup	Intervention n/N	Control n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Douglas 1987	19/33	12/30		18.9 %	2.04 [0.75, 5.56]
Godfrey 1992	5/35	17/38		17.3 %	0.21 [0.07, 0.65]
Mossad 1996	9/50	29/50		19.9 %	0.16 [0.06, 0.40]
Smith 1989	24/57	29/53		21.7 %	0.60 [0.28, 1.28]
Weismann 1990	31/61	48/69		22.2 %	0.45 [0.22, 0.93]
Total (95% CI)	**236**	**240**		**100.0 %**	**0.45 [0.20, 1.00]**

Total events: 88 (Intervention), 135 (Control)

Heterogeneity: $Tau^2 = 0.60$; $Chi^2 = 15.99$, df = 4 (P = 0.003); $I^2 = 75\%$

Test for overall effect: Z = 1.96 (P = 0.050)

Analysis 2.4. Comparison 2 Secondary outcomes, Outcome 4 Time to resolution of cough.

Review: Zinc for the common cold

Comparison: 2 Secondary outcomes

Outcome: 4 Time to resolution of cough

Study or subgroup	Intervention N	Mean(SD)	Control N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Kurugol 2006a	97	2.9 (1.6)	97	3.2 (2)		28.8 %	-0.16 [-0.45, 0.12]
Macknin 1998	72	7 (8.65)	89	7.5 (7.21)		28.2 %	-0.06 [-0.37, 0.25]
Prasad 2000	25	3.1 (2.55)	23	6.3 (3.43)		21.5 %	-1.05 [-1.66, -0.44]
Prasad 2008	25	2.16 (1.7)	25	5.08 (2.97)		21.5 %	-1.19 [-1.79, -0.58]
Total (95% CI)	**219**		**234**			**100.0 %**	**-0.55 [-1.04, -0.05]**

Heterogeneity: $Tau^2 = 0.20$; $Chi^2 = 17.20$, df = 3 (P = 0.00064); $I^2 = 83\%$

Test for overall effect: Z = 2.17 (P = 0.030)

Analysis 2.5. Comparison 2 Secondary outcomes, Outcome 5 Time to resolution of nasal congestion.

Review: Zinc for the common cold

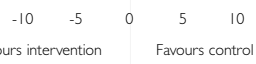
Comparison: 2 Secondary outcomes

Outcome: 5 Time to resolution of nasal congestion

Study or subgroup	Intervention N	Mean(SD)	Control N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
Kurugol 2006a	97	1.2 (0.8)	97	1.4 (1)		32.3 %	-0.22 [-0.50, 0.06]
Macknin 1998	103	7.5 (2.53)	109	8 (5.2)		35.4 %	-0.12 [-0.39, 0.15]
Petrus 1998	52	4.2 (2.88)	49	6.5 (4.9)		16.2 %	-0.57 [-0.97, -0.17]
Prasad 2000	25	3.3 (2.55)	23	4.7 (3.43)		7.8 %	-0.46 [-1.03, 0.12]
Prasad 2008	25	2.2 (2.02)	25	2.56 (2.88)		8.3 %	-0.14 [-0.70, 0.41]
Total (95% CI)	**302**		**303**			**100.0 %**	**-0.25 [-0.41, -0.09]**

Heterogeneity: $Chi^2 = 4.09$, df = 4 (P = 0.39); $I^2 = 2\%$

Test for overall effect: Z = 3.11 (P = 0.0019)



Analysis 2.6. Comparison 2 Secondary outcomes, Outcome 6 Time to resolution of nasal drainage.

Review: Zinc for the common cold

Comparison: 2 Secondary outcomes

Outcome: 6 Time to resolution of nasal drainage

Study or subgroup	Intervention N	Mean(SD)	Control N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Kurugol 2006a	97	3 (1.5)	97	3.2 (1.8)		24.8 %	-0.12 [-0.40, 0.16]
Macknin 1998	99	7.5 (7.61)	107	7 (5.17)		25.1 %	0.08 [-0.20, 0.35]
Petrus 1998	52	4.2 (2.88)	49	6.6 (4.9)		20.4 %	-0.60 [-1.00, -0.20]
Prasad 2000	25	4.1 (2)	23	5.8 (3.43)		14.6 %	-0.60 [-1.18, -0.02]
Prasad 2008	25	3 (1.63)	25	4.56 (3.01)		14.9 %	-0.63 [-1.20, -0.07]
Total (95% CI)	**298**		**301**			**100.0 %**	**-0.32 [-0.62, -0.01]**

Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 12.13$, df = 4 (P = 0.02); $I^2 = 67\%$

Test for overall effect: Z = 2.04 (P = 0.041)

Analysis 2.7. Comparison 2 Secondary outcomes, Outcome 7 Time to resolution of sore throat.

Review: Zinc for the common cold

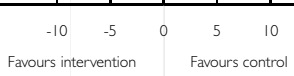
Comparison: 2 Secondary outcomes

Outcome: 7 Time to resolution of sore throat

Study or subgroup	Intervention N	Mean(SD)	Control N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Std. Mean Difference IV,Fixed,95% CI
Kurugol 2006a	97	1.8 (1.4)	97	2.4 (1.8)		-0.37 [-0.65, -0.09]
Macknin 1998	64	4.5 (2)	74	4.5 (2.15)		0.0 [-0.33, 0.33]
Prasad 2000	25	2 (1.78)	23	3 (3.18)		-0.39 [-0.96, 0.19]
Prasad 2008	25	1.96 (1.83)	25	3.24 (0)		0.0 [0.0, 0.0]
Total (95% CI)	**211**		**219**			**-0.24 [-0.44, -0.03]**

Heterogeneity: $Chi^2 = 3.04$, df = 2 (P = 0.22); $I^2 = 34\%$

Test for overall effect: Z = 2.29 (P = 0.022)



Analysis 2.8. Comparison 2 Secondary outcomes, Outcome 8 Change in cough symptom score.

Review: Zinc for the common cold

Comparison: 2 Secondary outcomes

Outcome: 8 Change in cough symptom score

Study or subgroup	Intervention N	Mean(SD)	Control N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
Petrus 1998	52	1.28 (0.07)	49	1.51 (0.09)		100.0 %	-2.84 [-3.40, -2.28]
Total (95% CI)	**52**		**49**			**100.0 %**	**-2.84 [-3.40, -2.28]**

Heterogeneity: not applicable

Test for overall effect: Z = 9.97 (P < 0.00001)

Analysis 2.9. Comparison 2 Secondary outcomes, Outcome 9 Change in nasal symptom score.

Review: Zinc for the common cold

Comparison: 2 Secondary outcomes

Outcome: 9 Change in nasal symptom score

Study or subgroup	Intervention N	Mean(SD)	Control N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Std. Mean Difference IV,Fixed,95% CI
Kurugol 2006a	97	0 (0)	97	0.3 (4.92)		0.0 [0.0, 0.0]
Kurugol 2007	60	0.1 (2.32)	60	0.3 (3.87)		-0.06 [-0.42, 0.30]
Total (95% CI)	**157**		**157**			**-0.06 [-0.42, 0.30]**

Heterogeneity: Chi^2 = 0.0, df = 0 (P = 1.00); I^2 =0.0%

Test for overall effect: Z = 0.34 (P = 0.73)

Analysis 2.10. Comparison 2 Secondary outcomes, Outcome 10 School absenteeism (days).

Review: Zinc for the common cold

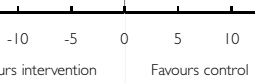
Comparison: 2 Secondary outcomes

Outcome: 10 School absenteeism (days)

Study or subgroup	Intervention N	Mean(SD)	Control N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Kurugol 2006b	97	0.9 (2.1)	97	1.3 (1.9)		50.0 %	-0.20 [-0.48, 0.08]
Vakili 2009	100	0.55 (1.09)	100	1.35 (1.79)		50.0 %	-0.54 [-0.82, -0.26]
Total (95% CI)	**197**		**197**			**100.0 %**	**-0.37 [-0.70, -0.04]**

Heterogeneity: Tau² = 0.04; Chi² = 2.77, df = 1 (P = 0.10); I² =64%

Test for overall effect: Z = 2.17 (P = 0.030)



Analysis 2.11. Comparison 2 Secondary outcomes, Outcome 11 Antibiotic use.

Review: Zinc for the common cold

Comparison: 2 Secondary outcomes

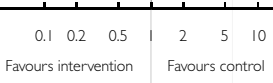
Outcome: 11 Antibiotic use

Study or subgroup	Intervention n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Kurugol 2006b	5/97	18/97		31.2 %	0.24 [0.08, 0.67]
Vakili 2009	20/100	47/100		68.8 %	0.28 [0.15, 0.53]
Total (95% CI)	**197**	**197**		**100.0 %**	**0.27 [0.16, 0.46]**

Total events: 25 (Intervention), 65 (Control)

Heterogeneity: Chi² = 0.07, df = 1 (P = 0.79); I² =0.0%

Test for overall effect: Z = 4.80 (P < 0.00001)



Analysis 2.12. Comparison 2 Secondary outcomes, Outcome 12 Any adverse event.

Review: Zinc for the common cold

Comparison: 2 Secondary outcomes

Outcome: 12 Any adverse event

Study or subgroup	Intervention n/N	Control n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Kurugol 2006a	35/100	33/100		25.3 %	1.09 [0.61, 1.96]
Kurugol 2007	15/60	16/60		18.8 %	0.92 [0.40, 2.08]
Macknin 1998	106/123	99/124		22.6 %	1.57 [0.80, 3.09]
Mossad 1996	44/49	31/50		13.4 %	5.39 [1.82, 15.99]
Weismann 1990	21/61	15/69		19.8 %	1.89 [0.87, 4.12]
Total (95% CI)	**393**	**403**		**100.0 %**	**1.59 [0.97, 2.58]**

Total events: 221 (Intervention), 194 (Control)

Heterogeneity: $Tau^2 = 0.16$; $Chi^2 = 8.21$, df = 4 (P = 0.08); $I^2 = 51\%$

Test for overall effect: Z = 1.85 (P = 0.064)

Analysis 2.13. Comparison 2 Secondary outcomes, Outcome 13 Bad taste.

Review: Zinc for the common cold

Comparison: 2 Secondary outcomes

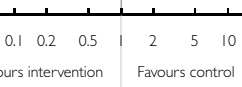
Outcome: 13 Bad taste

Study or subgroup	Intervention n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Douglas 1987	8/30	1/28		1.6 %	9.82 [1.14, 84.60]
Kurugol 2006a	8/100	9/100		17.9 %	0.88 [0.32, 2.38]
Kurugol 2007	9/60	6/60		11.0 %	1.59 [0.53, 4.78]
Macknin 1998	74/123	47/124		40.3 %	2.47 [1.48, 4.13]
Mossad 1996	39/49	15/50		6.5 %	9.10 [3.62, 22.86]
Prasad 2000	13/25	6/23		6.5 %	3.07 [0.91, 10.37]
Prasad 2008	15/25	13/25		11.2 %	1.38 [0.45, 4.25]
Smith 1989	6/57	2/53		4.0 %	3.00 [0.58, 15.57]
Weismann 1990	3/61	0/69		1.0 %	8.32 [0.42, 164.31]
Total (95% CI)	**530**	**532**		**100.0 %**	**2.64 [1.91, 3.64]**

Total events: 175 (Intervention), 99 (Control)

Heterogeneity: Chi^2 = 15.85, df = 8 (P = 0.04); I^2 =50%

Test for overall effect: Z = 5.89 (P < 0.00001)



Analysis 2.14. Comparison 2 Secondary outcomes, Outcome 14 Nausea.

Review: Zinc for the common cold

Comparison: 2 Secondary outcomes

Outcome: 14 Nausea

Study or subgroup	Intervention n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Douglas 1987	6/30	0/28		1.2 %	15.12 [0.81, 282.27]
Kurugol 2006a	6/100	5/100		14.2 %	1.21 [0.36, 4.11]
Kurugol 2007	5/60	4/60		11.1 %	1.27 [0.32, 4.99]
Macknin 1998	36/123	20/124		42.6 %	2.15 [1.16, 3.99]
Mossad 1996	10/49	2/50		4.8 %	6.15 [1.27, 29.75]
Prasad 2000	0/25	1/23		4.6 %	0.29 [0.01, 7.59]
Prasad 2008	3/25	1/25		2.7 %	3.27 [0.32, 33.84]
Smith 1989	14/57	8/53		18.9 %	1.83 [0.70, 4.80]
Total (95% CI)	**469**	**463**		**100.0 %**	**2.15 [1.44, 3.23]**

Total events: 80 (Intervention), 41 (Control)

Heterogeneity: $Chi^2 = 6.50$, df = 7 (P = 0.48); $I^2 = 0.0\%$

Test for overall effect: Z = 3.72 (P = 0.00020)

Analysis 2.15. Comparison 2 Secondary outcomes, Outcome 15 Constipation.

Review: Zinc for the common cold

Comparison: 2 Secondary outcomes

Outcome: 15 Constipation

Study or subgroup	Intervention n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Kurugol 2006a	1/100	2/100		14.1 %	0.49 [0.04, 5.55]
Kurugol 2007	5/60	4/60		26.1 %	1.27 [0.32, 4.99]
Macknin 1998	2/123	2/124		14.0 %	1.01 [0.14, 7.27]
Mossad 1996	1/49	0/50		3.4 %	3.12 [0.12, 78.55]
Prasad 2000	6/25	0/23		2.8 %	15.67 [0.83, 295.88]
Prasad 2008	2/25	1/25		6.6 %	2.09 [0.18, 24.61]
Smith 1989	6/57	5/53		33.0 %	1.13 [0.32, 3.94]
Total (95% CI)	**439**	**435**		**100.0 %**	**1.60 [0.82, 3.10]**

Total events: 23 (Intervention), 14 (Control)

Heterogeneity: $Chi^2 = 4.04$, df = 6 (P = 0.67); $I^2 = 0.0\%$

Test for overall effect: Z = 1.38 (P = 0.17)

Analysis 2.16. Comparison 2 Secondary outcomes, Outcome 16 Diarrhoea.

Review: Zinc for the common cold

Comparison: 2 Secondary outcomes

Outcome: 16 Diarrhoea

Study or subgroup	Intervention n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Kurugol 2006a	2/100	2/100		17.5 %	1.00 [0.14, 7.24]
Kurugol 2007	2/60	1/60		8.6 %	2.03 [0.18, 23.06]
Macknin 1998	13/123	5/124		39.8 %	2.81 [0.97, 8.15]
Mossad 1996	2/49	2/50		17.0 %	1.02 [0.14, 7.55]
Prasad 2000	2/25	1/23		8.6 %	1.91 [0.16, 22.63]
Prasad 2008	1/25	1/25		8.6 %	1.00 [0.06, 16.93]
Total (95% CI)	**382**	**382**		**100.0 %**	**1.89 [0.92, 3.89]**

Total events: 22 (Intervention), 12 (Control)

Heterogeneity: Chi^2 = 1.50, df = 5 (P = 0.91); I^2 =0.0%

Test for overall effect: Z = 1.74 (P = 0.083)

Analysis 2.17. Comparison 2 Secondary outcomes, Outcome 17 Abdominal pain.

Review: Zinc for the common cold

Comparison: 2 Secondary outcomes

Outcome: 17 Abdominal pain

Study or subgroup	Intervention n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Kurugol 2006a	2/100	0/100		1.5 %	5.10 [0.24, 107.62]
Kurugol 2007	7/60	6/60		16.4 %	1.19 [0.37, 3.77]
Macknin 1998	36/123	32/124		69.8 %	1.19 [0.68, 2.08]
Mossad 1996	3/49	1/50		2.9 %	3.20 [0.32, 31.83]
Prasad 2000	0/25	2/23		7.9 %	0.17 [0.01, 3.71]
Smith 1989	3/57	0/53		1.5 %	6.87 [0.35, 136.25]
Total (95% CI)	**414**	**410**		**100.0 %**	**1.31 [0.83, 2.07]**

Total events: 51 (Intervention), 41 (Control)

Heterogeneity: Chi^2 = 4.36, df = 5 (P = 0.50); I^2 =0.0%

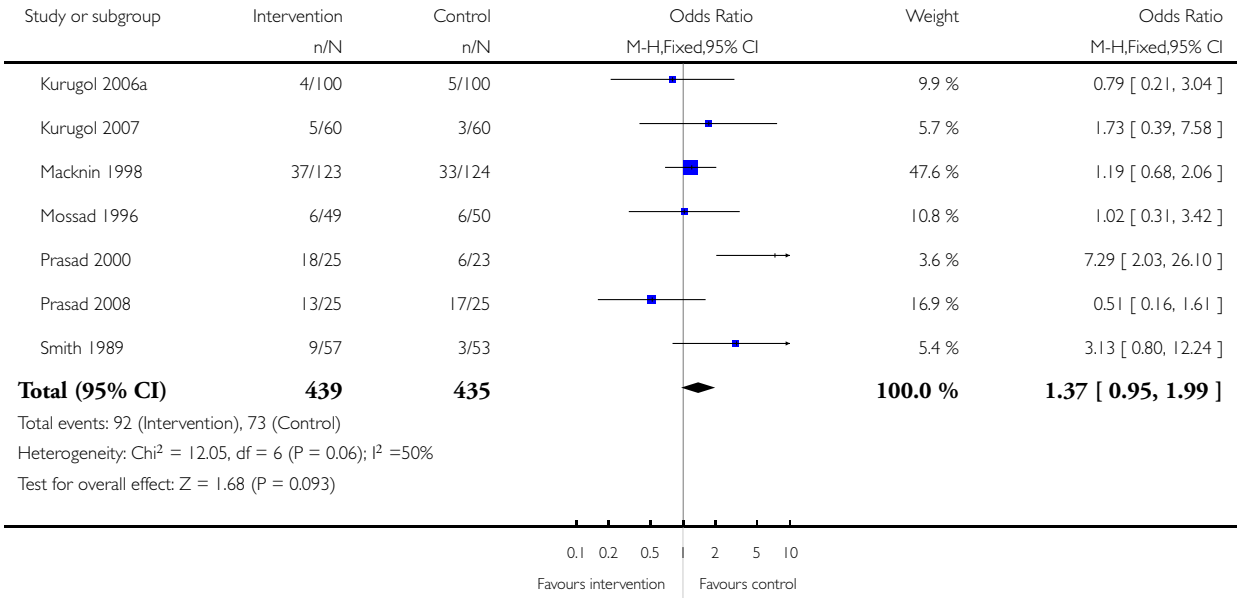
Test for overall effect: Z = 1.16 (P = 0.25)

Analysis 2.18. Comparison 2 Secondary outcomes, Outcome 18 Dry mouth.

Review: Zinc for the common cold

Comparison: 2 Secondary outcomes

Outcome: 18 Dry mouth

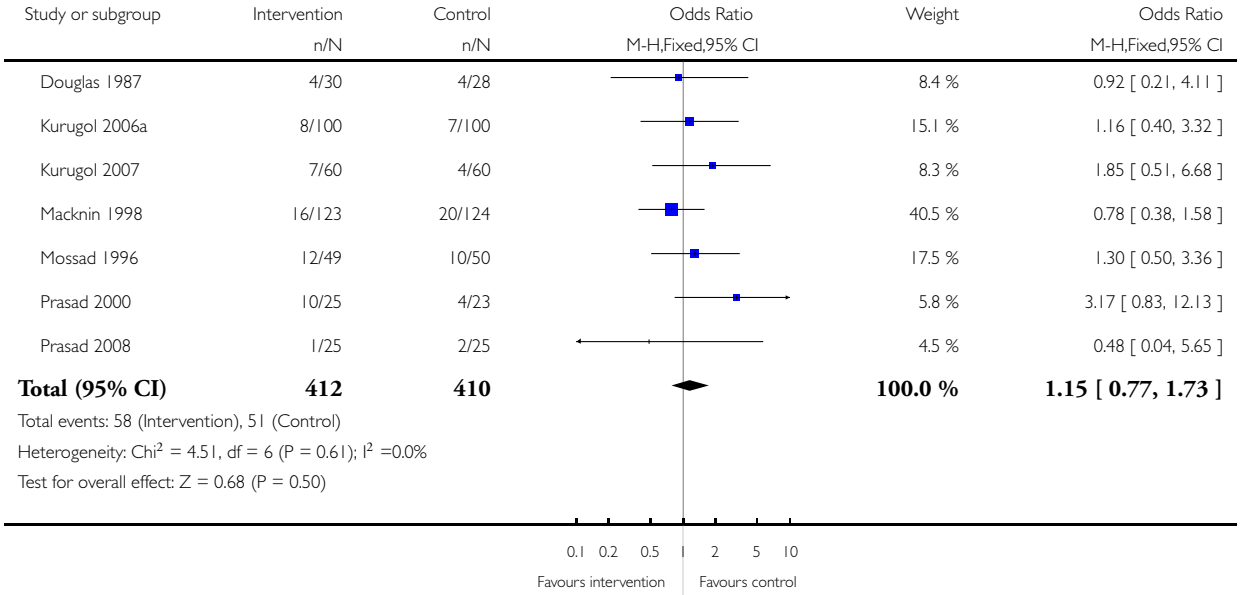


Analysis 2.19. Comparison 2 Secondary outcomes, Outcome 19 Mouth irritation.

Review: Zinc for the common cold

Comparison: 2 Secondary outcomes

Outcome: 19 Mouth irritation



APPENDICES

Appendix 1. EMBASE.com search strategy

24. #20 AND #23
23. #21 OR #22
22. random*:ab,ti OR placebo*:ab,ti OR factorial*:ab,ti OR crossover*:ab,ti OR 'cross over':ab,ti OR 'cross-over':ab,ti OR volunteer*:ab,ti OR assign*:ab,ti OR allocat*:ab,ti OR ((doubl* OR singl*) NEAR/2 (blind* OR mask)):ab,ti
21. 'randomized controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp
20. #13 AND #19
19. #14 OR #15 OR #16 OR #17
18. 'trace element':ab,ti OR 'trace elements':ab,ti OR 'trace mineral':ab,ti OR 'trace minerals':ab,ti
17. micronutrient*:ab,ti
16. 'trace element'/de
15. zinc:ab,ti OR zn:ab,ti
14. 'zinc'/exp
13. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12
12. urti:ab,ti OR uri:ab,ti
11. 'upper respiratory tract infection':ab,ti OR 'upper respiratory tract infections':ab,ti OR 'upper respiratory infection':ab,ti OR 'upper respiratory infections':ab,ti

10. 'upper respiratory tract infection'/de
9. rhinit*:ab,ti
8. 'rhinitis'/de
7. coryza:ab,ti
6. rhinovir*:ab,ti
5. 'rhinovirus infection'/de
4. 'rhinovirus'/exp
3. 'common cold symptom'/exp
2. 'common cold':ab,ti OR 'common colds':ab,ti
1. 'common cold'/exp

WHAT'S NEW

Last assessed as up-to-date: 31 May 2010.

Date	Event	Description
29 June 2010	New citation required and conclusions have changed	A new team of review authors have updated this previously withdrawn review. In the previous review, the role of zinc for the common cold was inconclusive, as the results could not be pooled due to the paucity of trials measuring clinically relevant outcomes. In this updated review we were able to undertake pooling of results due to the addition of new trials and we found that zinc is beneficial for the common cold.
1 June 2010	New search has been performed	Searches conducted. We included eight new trials (Kurugol 2006a; Kurugol 2006b; Kurugol 2007; Macknin 1998; Petrus 1998; Prasad 2000; Prasad 2008; Vakili 2009) and excluded three new trials (McElroy 2003; Turner 2000; Veverka 2009) in this update.

HISTORY

Protocol first published: Issue 1, 1999

Review first published: Issue 2, 1999

Date	Event	Description
17 June 2008	Amended	Converted to new review format
4 May 2006	Amended	Review withdrawn
24 February 1999	New search has been performed	Review first published Issue 2, 1999

CONTRIBUTIONS OF AUTHORS

Dr Meenu Singh (MS) and Dr Rashmi Ranjan Das (RRD) jointly prepared and edited the review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, India.

External sources

- No sources of support supplied

NOTES

There was a change in authorship between the first published version of the review and this updated version. Ian IR Marshall was the review author of both the protocol and review published in *The Cochrane Library* in 1999. The review was withdrawn and taken over by the current review authors (Meenu Singh and Rashmi Ranjan Das) for updating.

INDEX TERMS

Medical Subject Headings (MeSH)

Common Cold [*drug therapy]; Dosage Forms; Zinc [administration & dosage; *therapeutic use]

MeSH check words

Humans