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Zinc for preventing and treating the common cold (Protocol)

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[Intervention Protocol]

Zinc for preventing and treating the common cold

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the effects of zinc to reduce the incidence, duration and severity of the common cold when used either as a daily supplement to prevent colds or as therapy at the onset of cold symptoms or during a cold.

BACKGROUND

Description of the condition

While familiar to most people, the 'common cold' is not a precisely defined disease (Eccles 2013). Typical cold symptoms include combinations of nasal symptoms, sore throat, cough and fever. The common cold is a significant cause of absenteeism from work and school.

The common cold is usually caused by one of a number of viruses. The respiratory viruses include rhino, corona, adeno, parainfluenza, influenza and respiratory syncytial types, which together have around 200 serotypes (Eccles 2009; Turner 2010). A number of non-respiratory viruses can also cause common cold-type symptoms. However, in a third of people with cold symptoms, the aetiology remains undefined even though extensive virological tests may be carried out. Similar symptoms can also be caused by mechanical irritation of the airways and from allergy or some bacterial infections. Hence, common cold symptoms do not always imply viral aetiology.

In common cold trials, symptom-based definitions of the common cold are almost always used. However, there is no explicit combination of symptoms and symptom duration that enables conclusions to be drawn about the aetiology. There is thus no rigorous definition of the common cold and the symptoms can vary substantially. It is the person's subjective experience that prompts a visit to a physician to seek treatment or to ask for sick leave certification due to the common cold.

Most adults have one or two common cold episodes per year due to naturally occurring common colds. Laboratory studies have induced colds by inoculating high numbers of rhinovirus into the nose, which causes nearly all study volunteers to develop common cold symptoms within a few days.

Description of the intervention

Zinc is an essential nutrient for humans (Prasad 2013; Sandstead 2013). Zinc deficiency has been associated with increased susceptibility to infections (Prasad 2013). Zinc deficiency is quite common in low-income countries, but mild deficiency has also been observed in middle- and high-income countries (Prasad 2013). A

meta-analysis of six studies conducted in Bangladesh, India, Peru and South Africa concluded that zinc supplementation prevented pneumonia and that low dietary zinc levels may have practical importance in decreased resistance against infections (Lassi 2016).
To treat zinc deficiency, or marginal deficiency, zinc has been administered as tablets and as a syrup (zinc supplements).
For the treatment of the common cold, zinc has also been administered as lozenges soon after the onset of symptoms (Eby 1984). People with colds have been instructed to dissolve the lozenges slowly in the mouth several times per day. Nose gels and sprays have also been tested for treating the common cold.
In the USA, the recommended daily intake of zinc is 11 mg/day for men and 8 mg/day for women (NRC 2001). However, zinc has been administered in doses of 100 mg to 150 mg per day to some people (not for the common cold) for several months with few adverse effects (Bamford 2012; Pories 1967; Serjeant 1970). Copper deficiency has been reported as a consequence of long-term zinc supplementation (Hoffman 1988; Prasad 1978), although a six-week experiment in which 150 mg/day of zinc was administered found no effect on plasma copper levels (Samman 1987). Due to the zinc and copper interaction, 150 mg/day of zinc is currently one of the standard treatments for Wilson's disease. Most people with Wilson's disease take 150 mg doses of zinc daily for life (Ala 2007; Marcellini 2005). In the treatment of Wilson's disease, zinc has an excellent safety profile, although it caused gastric irritation in 5% to 10% of people requiring therapy (Brewer 2005). The use of high-dose zinc for long periods in people with Wilson's disease indicates that zinc does not have long-term serious adverse effects, except for copper deficiency, which is reversible.

How the intervention might work

Zinc participates in the function of about 300 enzymes and has a range of effects on the immune system (Prasad 2008; Prasad 2013). For example, zinc has been reported to inhibit the replication of rhinovirus and respiratory syncytial virus (Geist 1987; Korant 1976; Suara 2004) and to enhance the effects of interferon (Berg 2001). However, the mechanism by which zinc supplements have an effect on pneumonia is not clearly understood (Lassi 2016).
The major hypothesis in the use of zinc lozenges to treat the common cold is that the effect is due to local effects of free zinc ions in the oro-pharyngeal region (Eby 2010). However, the molecular-level mechanism of the effect of zinc lozenges for common cold treatment is not known. Although zinc might influence the local immune system, non-immune mechanisms have also been proposed to explain the effect of zinc lozenges on the common cold (Novick 1996; Novick 1997). The formulation of zinc lozenges appears to be critical (Eby 2010). Zinc binds effectively to citrate, and zinc lozenges containing citrate or citric acid do not release free zinc ions (Eby 1988; Eby 2010; Godfrey 1988; Martin 1988). Zinc acetate and zinc gluconate have been used as salts in zinc lozenges. Zinc acetate has been proposed as the better salt in zinc lozenges because acetate binds to zinc ions very weakly, whereas gluconate binds the zinc ions more effectively. Given the stronger binding, zinc gluconate has been proposed as a less suitable constituent for zinc lozenges (Eby 2010). However, it is uncertain if variation in zinc ion binding leads to significant differences at the clinical level in the treatment of the common cold.

Why it is important to do this review

The common cold causes significant global morbidity, but identifying simple and effective preventive or therapeutic agents has been elusive. Even modest benefits for defined populations could be an important advantage from a public health perspective. In a survey of people with the common cold in the USA, about half had received antibiotics (Barnett 2014), although antibiotics are not usually of any benefit, since the common cold is caused mostly by viruses. Indiscriminate use of antibiotics can be harmful at both individual and population levels. Alternative treatment options such as zinc are therefore worth investigating.
Previous systematic reviews of zinc and the common cold have various shortcomings. Caruso 2007 used vote counting, that is counting the number of positive and negative studies, and had a number of other inadequacies (Hemilä 2013). Eby 2010 found dose-dependent effects of zinc lozenges on the common cold, but did not take into account variation in study size or calculate confidence intervals for the effect. Science 2012 combined zinc lozenge trials with zinc tablet and syrup trials, although zinc tablets and syrups were not intended to be dissolved in the oro-pharyngeal region, leading to the problem of combining 'apples with oranges' (Hemilä 2012). Since zinc tablets and syrups appear to have a different mechanism of effect to zinc lozenges, we will analyse them separately. A Cochrane Review on zinc and the common cold had a number of problems and was withdrawn (Hemilä 2015; Singh 2015). Given the issues with previous reviews, a thorough review is now warranted.

OBJECTIVES

To assess the effects of zinc to reduce the incidence, duration and severity of the common cold when used either as a daily supplement to prevent colds or as therapy at the onset of cold symptoms or during a cold.

METHODS

Criteria for considering studies for this review

Types of studies

We will include parallel-group randomised controlled trials (RCTs) including the first period of cross-over studies and cluster-RCTs if there are 10 or more clusters. We will include studies reported as full text, those published as abstracts only, and unpublished data. We will restrict our review to placebo-controlled trials. The common cold is a subjective experience, and there can be great variation among people in how they classify their symptoms and when they consider themselves to have recovered. However, as such subjective variation applies similarly to both intervention and placebo group participants, it should not lead to any bias. Subjectivity in the assessment of common cold symptoms can increase inaccuracy, which can lead to false-negative findings, but is unlikely to lead to false-positive findings in studies with adequate blinding.

Types of participants

We will include adults and children of either gender and any age. We will define children as people aged up to 18 years and adults as those aged 18 years and over. We will define older adults as those aged 65 years and over. We will not exclude studies with participants who have comorbidities.

We will include prevention trials that involved participants who did not have common cold symptoms before the intervention started.

We will include treatment trials that involved participants who had cold symptoms before the intervention started.

We will include studies in which participants had either natural common colds or induced common colds. We will analyse prevention trials and treatment trials data separately. We will also analyse natural common colds and induced common colds separately.

Types of interventions

We will include trials investigating oral zinc (tablets and syrups but not lozenges) versus placebo, zinc lozenges versus placebo, and nasal zinc administration versus placebo.

There will be no limitation on zinc dose administered by any route or duration of therapy.

We will not exclude studies with co-interventions.

Types of outcome measures

Because common cold is not a precisely defined disease, we will describe the definitions for the common cold applied in the included studies in 'Characteristics of included studies' tables in the review.

Primary outcomes

1. Incidence of colds during regular supplementation will be assessed as the proportion of participants experiencing one or more colds during the study period.
2. Duration of the common cold (i.e. time from cold onset to recovery).
3. Rate of recovery (i.e. how many participants recover on a given day) from the common cold.
4. Adverse effects (e.g. taste disturbances and stomach irritation).

Secondary outcomes

1. Severity of the common cold. Symptom severity is often measured on a scale, one scale for each symptom. The severity scores for each symptom are summed to provide a total severity score for a specific day. We will compare the average severity in the zinc groups with the average severity in the placebo groups.
2. Complications of the common cold (e.g. otitis, sinusitis, and exacerbation of asthma).

We will analyse measures of effect separately for prophylactic oral zinc (excluding lozenge) trials, prophylactic zinc lozenge trials, oral zinc (excluding lozenge) therapeutic trials, zinc lozenge therapeutic trials, and nasal zinc administration trials.

Search methods for identification of studies

Electronic searches

We will search the following databases from inception to present:

- Cochrane Central Register of Controlled Trials (CENTRAL), which contains the Cochrane Acute Respiratory Infection Group Specialised Register;
- PubMed; and
- Embase (Elsevier).

We will use the search strategy described in Appendix 1 to search PubMed. We will modify this search appropriately for other databases and clinical trials registers.

We will also search ClinicalTrials.gov (www.clinicaltrials.gov) and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (apps.who.int/trialsearch/).

Searching other resources

We will check reference lists of all primary studies and review articles for additional references. We will contact experts in the field to identify additional unpublished material.

Data collection and analysis

Selection of studies

Two review authors (HH, EC) will independently screen titles and abstracts identified as a result of the searches to select potentially eligible trials). We will retrieve the full-text study reports/publications, and two review authors (HH, EC) will independently screen the full texts and identify studies for inclusion, and identify and record reasons for exclusion of the ineligible studies. Any disagreements will be resolved through discussion. We will identify and exclude duplicates and collate multiple reports of the same study so that each study rather than each report is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram and 'Characteristics of excluded studies' table (Moher 2009). We will include studies reported as full text, those published as abstract only, and unpublished data. We will not impose any language restrictions.

Data extraction and management

We will use a data collection form for study characteristics and outcome data that has been piloted on at least one study in the review. One review author (HH) will extract the following study characteristics from the included studies.

1. Methods: study design, total duration of study, details of any 'run in' period, number of study centres and location, study setting, withdrawals, and date of study.
2. Participants: N, mean age, age range, gender, diagnostic criteria, inclusion criteria, and exclusion criteria.
3. Interventions: intervention, comparison, concomitant medications, and excluded medications.
4. Outcomes: primary and secondary outcomes specified and collected, and time points reported.
5. Notes: funding for trial, and notable conflicts of interest of trial authors.

Two review authors (HH, EC) will independently extract outcome data from the included studies. We will note in the 'Characteristics of included studies' table if outcome data are not reported in a usable format. We will resolve disagreements by consensus. One review author (HH) will transfer data into the Review Manager 5 file (Review Manager 2014). Both review authors (HH, EC) will double check that data are entered correctly by comparing the data presented in the systematic review with those in the study reports, and they will check study characteristics against the trial reports and data collection forms for accuracy.

Assessment of risk of bias in included studies

Two review authors (HH, EC) will independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Any disagreements will be resolved by discussion. We will assess the risk of bias according to the following domains.

1. Random sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
4. Blinding of outcome assessment.
5. Incomplete outcome data.
6. Selective outcome reporting.
7. Other bias.

We will grade each potential source of bias as high, low, or unclear and provide a quote from the study report together with a justification for our judgement in the 'Risk of bias' table. We will summarise the 'Risk of bias' judgements across different studies for each of the domains listed. We will consider blinding separately for different key outcomes, where necessary. Where information on risk of bias relates to unpublished data or correspondence with a trialist, we will note this in the 'Risk of bias' table.

When considering treatment effects, we will take into account the risk of bias for the studies that contribute to that outcome.

Assessment of bias in conducting the systematic review

We will conduct the review according to this published protocol and report any deviations from it in the 'Differences between protocol and review' section of the systematic review.

Measures of treatment effect

We will enter the outcome data for each study into the data tables in Review Manager 5 to calculate the treatment effects (Review Manager 2014).

We will calculate the risk ratio (RR) for dichotomous outcomes. We will calculate the effect of zinc on common cold duration in days, and we will calculate the pooled mean difference (MD) estimate. Because duration is a time-related outcome, we will also conduct survival analysis in accordance with guidance in Section 9.2.6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Survival analysis enables visual inspection and formal analysis of possible time-dependent variations in treatment effects. Survival analysis is not confounded by censored data or outlier participants who had particularly long colds. In contrast, outliers may decrease the statistical power of a t-test when examining cold duration, because these data inflate the standard deviation estimates.

Unit of analysis issues

If there are several zinc arms for a single placebo group, we will divide the placebo group for the zinc arms if we show several zinc arms in the same analysis table. If we find cross-over trials, we will include data for the first observation period. Because the common cold is contagious and different groups of people have different

levels of incidence, we will include cluster-randomised trials only if there are 10 or more clusters. In such cases, we will conduct the analysis at the same level as the allocation, using a summary measurement from each cluster.

Dealing with missing data

We will contact investigators or study sponsors to verify key study characteristics and to obtain missing numerical outcome data where possible (e.g. when a study is identified as abstract only). Where this is not possible, and the missing data are thought to introduce serious bias, we will explore the impact of excluding such studies in the overall assessment of results by a sensitivity analysis. If numerical outcome data such as standard deviations or correlation coefficients are missing and cannot be obtained from the authors, we will calculate them from other available statistics such as P values according to the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Assessment of heterogeneity

We will use the I^2 statistic to estimate heterogeneity among the trials in each analysis. We will also use the Chi^2 test to calculate the P value for the heterogeneity. We will consider an I^2 value of 50% or more to represent a substantial level of heterogeneity, though heterogeneity is not a dichotomous issue (Higgins 2003).
If we identify substantial heterogeneity, we will report this and explore possible causes in prespecified subgroup analyses.

Assessment of reporting biases

We will construct funnel plots, but will interpret them cautiously, since there are a number of problems with the use of funnel plots in the assessment of publication bias (Ioannidis 2007; Lau 2006; Sterne 2011; Terrin 2005). We will also narratively consider the possibility of publication bias in the Discussion section.

Data synthesis

We will pool data from studies judged to be clinically homogeneous using Review Manager 5 software (Review Manager 2014). If more than one study provides usable data for any single comparison, we will perform fixed-effect meta-analysis.

GRADE and 'Summary of findings' table

We will create one 'Summary of findings' table with different sections for prophylactic oral zinc (not lozenge) trials, prophylactic zinc lozenge trials, oral zinc (not lozenge) therapeutic trials, zinc lozenge therapeutic trials, and nasal zinc administration trials. We will use the following outcomes: incidence and duration of the common cold and adverse effects in zinc prophylactic trials; duration of the common cold and adverse effects in oral zinc therapeutic trials; duration of the common cold and adverse effects in nasal zinc therapeutic trials.
We will use the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of a body of evidence as it relates to the studies that contribute data to the meta-analyses for the prespecified outcomes (Atkins 2004). We will use methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), using GRADEpro GDT software (GRADEpro GDT 2015). We will justify all decisions to down- or upgrade the quality of studies using footnotes, and we will make comments to aid the reader's understanding of the review where necessary.

Subgroup analysis and investigation of heterogeneity

We plan to conduct subgroup analysis to investigate the preventive effects of zinc for people in low-income countries compared with those in middle- and high-income countries. We will use the World Bank 2017 classification to determine countries' income status.
In the analysis of treatment effects, we intend to perform subgroup analyses for children, adults, and older adults where possible.
We will also explore the effects of zinc lozenges for:

1. dose of elemental zinc per day: < 75 mg versus ≥ 75 mg; and
2. zinc acetate lozenges versus zinc gluconate lozenges in zinc lozenge trials with doses ≥ 75 mg/day.

We will use the Chi^2 test to test for subgroup interactions in Review Manager 5 (Review Manager 2014).
If there are several studies that are clinically so similar that they can be considered to measure the same effect, we may consider carrying out meta-regression to simultaneously analyse several subgroup variables. However, meta-regression is not a valid approach if there are fewer than 10 trials, as described in Section 9.6.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Sensitivity analysis

We plan to perform sensitivity analyses excluding trials:

- with methodological shortcomings leading to inadequate randomisation or blinding; and
- those with missing data that required imputation.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. MEDLINE search strategy

("Zinc Acetate"[Mesh] OR "Zinc Compounds"[Mesh] OR "Zinc"[Mesh] OR Zinc[tiab] OR Galzin[tiab] OR Zincteral[tiab)
AND
("Common Cold"[Mesh] OR "Rhinovirus"[Mesh] OR Cold[tiab] OR Colds[tiab] OR Rhinovirus[tiab] OR Rhinoviruses[tiab] OR Coryza[tiab] OR Catarrh[tiab] OR Catarrhs[tiab] OR "Respiratory infection"[tiab] OR "Respiratory infections"[tiab])

CONTRIBUTIONS OF AUTHORS

HH drafted the protocol and EC participated in its revisions. HH is the guarantor of the review.

DECLARATIONS OF INTEREST

Harri Hemilä: None known.

Elizabeth Chalker: None known.

SOURCES OF SUPPORT

Internal sources

- None, Other.

External sources

- None, Other.