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Zinc for prevention and treatment of the common cold (Protocol)

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[Intervention Protocol]

Zinc for prevention and treatment of the common cold

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ABSTRACT

Objectives

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

To assess the effectiveness and safety of zinc for the prevention and treatment of the common cold.

BACKGROUND

Description of the condition

The common cold is an acute, self-limiting respiratory illness characterised by several symptoms including nasal congestion, nasal mucus discharge, sneezing, sore throat, cough, and general malaise. The common cold is generally considered to be caused by viruses (e.g. some common rhinoviruses and coronaviruses). However, there is no minimum level or specific combination of symptoms that defines a cold, and viruses are often but not always detected in people exhibiting symptoms (Mäkelä 1998). The most bothersome symptoms of a cold may be sore throat on the first day, followed by nasal congestion and then cough on the following days (Witek 2015). These symptoms overlap with other conditions such as allergy, tonsillitis, and lower respiratory tract infection, therefore the diagnosis is partly one of exclusion and is generally based on a global clinical assessment by the patient or a healthcare provider. Whilst colds are generally limited in severity and duration, and do not lead to serious health outcomes such as hospitalisation, they do occur frequently at any time of year, and everyone is vulnerable to colds. It is estimated that children average between six and 10 colds per year, whilst adults average between two and four colds per year, thus the common cold is a public health burden (IQWiG 2020). Colds impact daily life and are a major cause of lost work productivity and school absenteeism (Dicpinigaitis 2015).

Description of the intervention

Zinc is an essential trace mineral for which the human body has no specialised storage mechanism (Rink 2000). Regular intake of small amounts is therefore necessary for the maintenance of health and optimal physiological functioning. Zinc is naturally present in some foods (e.g. red meat); is sometimes added to other foods (e.g. cereals may be fortified with zinc); and may be taken as an over-the-counter dietary supplement. According to the US Institute of Medicine (IOM), the Recommended Dietary Allowance (RDA) for adults is 8 mg/day for women and 11 mg/day for men, whilst the Tolerable Upper Intake Level (UL) for adults is 40 mg/day (IOM 2001). The World Health Organization (WHO) estimates that 31% of the world's population is at risk for zinc deficiency, a percentage that ranges between 4% and 73% in different regions of the world and is higher in low-income countries (Caulfield 2004). People who eat vegetarian or vegan diets, the elderly, and people who suffer from conditions causing poor zinc absorption or high zinc loss are also at risk (Maares 2020). The consequences of severe, moderate, and even marginal zinc deficiency are seen in multiple body systems, including immune function (Prasad 2020).

Zinc supplements exist in several forms, including zinc gluconate, zinc sulfate, zinc acetate, zinc carnosine, and zinc picolinate, which vary in percentages of elemental zinc. The bioavailability of zinc is affected by the form of zinc, whether zinc is included in a meal or alone as a supplement, and by zinc levels in the body (Maares 2020).

Whilst many people believe that zinc may be helpful in preventing or treating colds, there is currently no established intervention to prevent colds or to shorten their duration (IQWiG 2020). The risk of developing a cold can be reduced by avoiding contact with other people who have colds, and cold symptoms can be treated with over-the-counter medications such as non-steroidal anti-inflammatory drugs (NSAIDs), antihistamines, and decongestants, although these medications have potential side effects and contraindications (Harvard Health Letter 2014). The safety and efficacy of zinc for the prevention and treatment of colds is therefore of ongoing interest.

How the intervention might work

There are two main biologically plausible mechanisms for the potential effects of zinc on the common cold: 1) zinc may improve immune function (Maares 2016); and 2) zinc may interfere with the binding and replication of viruses involved in colds (Hulisz 2004; Read 2019). The mechanisms of zinc delivered by tablets, capsules, or syrups may differ from those of zinc delivered as lozenges (which are held and dissolved in the mouth, coating the tongue and throat) and those of zinc delivered as sprays or gels (which coat the nasal mucosa).

Why it is important to do this review

Given the frequency and impact of common colds (Dicpinigaitis 2015), reducing the incidence, duration, or severity of colds would benefit public health. Zinc is a popular supplement often recommended to reduce the duration of the common cold. However, uncertainty remains surrounding overall effectiveness, and the influence of different forms, dosages, and delivery methods for different populations. Meanwhile, there is concern about the potential for permanent anosmia from intranasal zinc (D'Cruze 2009). Several previous systematic reviews have investigated zinc for the treatment or prevention of the common cold (D'Cruze 2009; Hemilä 2011; Hemila 2015; Hemila 2016; Hemila 2017a; Hemila 2017b; Jackson 1997; Moshtagh 2020; Science 2012; Wang 2020). However, Cochrane Reviews on this topic are no longer current (Marshall 2007; Singh 2015). New randomised controlled trials have been published since the most recent systematic review (Hemila 2020). It is important to incorporate the latest information about the potential benefits and harms of this popular intervention into a methodologically rigorous and up-to-date review of the evidence.

OBJECTIVES

To assess the effectiveness and safety of zinc for the prevention and treatment of the common cold.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs). We will exclude studies using quasi-randomisation because they are susceptible to selection bias. We will include studies reported as full text, those published as abstracts only, and unpublished data. We will include studies in any language.

Types of participants

We will include studies in adults and children. To assess the prevention of the common cold, we will include participants without a diagnosis of the common cold who are being followed to detect development of the common cold. We will include both naturalistic studies and challenge studies of prevention. To assess treatment of the common cold, we will include participants with a clinical diagnosis of the common cold (i.e. acute viral rhinopharyngitis), either naturally or experimentally induced. We will exclude participants with diagnoses commonly resulting from

other viruses (e.g. influenza) or commonly a result of bacterial infections (e.g. sinus infections).

Types of interventions

We will include trials comparing zinc interventions with placebo. We will also include trials comparing zinc plus any other intervention versus placebo plus the same other intervention. We will include any form (e.g. zinc gluconate, zinc acetate, zinc citrate), delivery method (e.g. intranasal, tablet, lozenge), duration, and dose of zinc. We will exclude zinc interventions in which zinc is combined with other minerals, vitamins, or herbs (e.g. a multivitamin, or mineral supplement containing zinc).

Types of outcome measures

We will collect information on the following outcomes. We will not use the presence or absence of specific outcomes as eligibility criteria for the inclusion of studies.

Primary outcomes

1. Proportion of participants developing colds (for analyses of prevention trials only), with colds as defined by each study.
2. Duration of cold (measured in days from start to resolution of the cold, as defined by each study).
3. Adverse events potentially due to zinc supplements (e.g. unpleasant taste, loss of smell, vomiting, stomach cramps, and diarrhoea).
4. Adverse events considered to be potential complications of the common cold (e.g. respiratory bacterial infections).

Secondary outcomes

1. Global severity of the cold using a global measure if available (e.g. visual analogue scale (VAS)), or by summing severity scores for individual symptoms.
2. Severity of individual cold symptoms (e.g. nasal congestion) measured on a scale.
3. Duration of individual cold symptoms (e.g. nasal congestion) measured in days from start to resolution of symptoms.
4. Days missed from work or school.

Search methods for identification of studies

Electronic searches

We will search the following databases from inception to present.

1. The Cochrane ARI group Trials Register (search via the Cochrane Register of Studies to date).
2. The Cochrane Central Register of Controlled Trials (CENTRAL) (search via the Cochrane Register of Studies to date).
3. MEDLINE (PubMed) (from 1946 to present).
4. Embase (from 1947 to present).
5. CINAHL (Cumulative Index to Nursing and Allied Health Literature) (EBSCOhost) (from 1981 to present) .
6. LILACS (Latin American and Caribbean Health Science Information database) (from 1985 to present).
7. Web of Science Core Collection:
   a. Science Citation Index Expanded (SCI-EXPANDED) (from 1900 to present).
   b. Social Sciences Citation Index (SSCI) (from 1900 to present).
   c. Arts & Humanities Citation Index (AHCI) (from 1975 to present)
   d. Conference Proceedings Citation Index - Science (CPCI-S) (from 1990 to present).
   e. Conference Proceedings Citation Index - Social Science & Humanities (CPCI-SSH) (from 1990 to present).
   f. Emerging Sources Citation Index (ESCI) (from 2005 present).

We will use Peer Review of Electronic Search Strategies (PRESS) to peer review the search strategy described in Appendix 1 for searching MEDLINE (McGowan 2016). We will combine the peer-reviewed MEDLINE search with the Cochrane Highly Sensitive Search Strategy for randomised trials: sensitivity and precision-maximising version (2008 revision) (Lefebvre 2019).

We will also conduct a search of ClinicalTrials.gov (www.clinicaltrials.gov) and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (apps.who.int/trialsearch/). We will not impose any language or publication restrictions.

Searching other resources

We will check the reference lists of all relevant review articles identified through our electronic searches for additional studies. We will check reference lists of all primary studies for additional references. We will contact experts in the field to identify any additional unpublished material.

Data collection and analysis

Selection of studies

Two review authors (LSW, CH) will independently screen the titles and abstracts of all studies identified as a result of the searches for inclusion in the review. We will retrieve the full-text study reports/publication for those studies deemed relevant based on the title and abstract, and two review authors (LSW, CH, or SN) will independently and in duplicate screen the full texts and identify studies for inclusion based on the a priori defined eligibility criteria, and identify and record reasons for exclusion of the ineligible studies. Any disagreements will be resolved through discussion or by consulting a third review author (MK or EL) if necessary. If information about relevant inclusion and exclusion criteria in the study report is unclear, we will attempt to contact study authors for clarification. 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).

Data extraction and management

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

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, severity of condition, diagnostic criteria for the common cold, baseline zinc status and how this was measured, smoking history, and inclusion 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 (LSW, MK) will independently and in duplicate extract outcome data from the included studies. We will note in the 'Characteristics of included studies' table (see Table 1) if outcome data are not reported in a useable way. Any disagreements will be resolved by consensus or by involving a third review author (CH or SN). One review author (LSW) will transfer data into the Review Manager Web file (RevMan Web 2020). We will double-check that data are entered correctly by comparing the data presented in the systematic review with the study reports. A second review author (SN or EL) will spot-check study characteristics for accuracy against the trial report. For relevant analyses, one review author (MK) will transfer the data into R (R Core Team 2021).

Assessment of risk of bias in included studies

Two review authors (LSW, CH) will independently and in duplicate assess the risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019). Any disagreements will be resolved by discussion or by involving another review author (MK or SN). We will assess 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 rate each potential source of bias as low, high, 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 and incomplete outcome data 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 review.

Measures of treatment effect

We will enter the outcome data for each study into the data tables in Review Manager Web to calculate the treatment effects (RevMan Web 2020). We will use risk ratios (RR) for dichotomous outcomes and mean differences (MD) for continuous outcomes on the same scale. For continuous outcomes where different scales measure the same underlying construct (e.g. severity of a symptom), we will use standardised mean differences (SMD). We will report 95% confidence intervals (CI) for all effects.

We will undertake meta-analyses only where this is meaningful, that is if the treatments, participants, and the underlying clinical question are similar enough for pooling to make sense. Because the likely mechanisms and potential adverse effects of oral and intranasal zinc differ, we will analyse trials of oral zinc (including tablets, capsules, syrups, or lozenges) separately from trials of intranasal zinc (including sprays or gels). If statistical pooling is not appropriate, we will produce a narrative summary.

Unit of analysis issues

We do not expect to find relevant studies with non-standard designs (e.g. cross-over or cluster-randomised trials). However, if we find otherwise eligible studies employing these designs, we will follow the guidance in Chapter 23 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019). Since cross-over trials are most suitable for trials on the treatment of stable, chronic conditions, we will analyse only the first period of any identified cross-over trials. For cluster-randomised trials, we will ensure that our analyses take into account that the unit of allocation is the cluster rather than the individual participant.

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). We will note all attempts to contact trialists, and the results of these attempts, in the 'Characteristics of studies' table for that study. If numerical outcome data are missing, such as standard deviations (SD) or correlation coefficients, and we are unable to obtain these from the trial 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 2019). If these values cannot be estimated, we will discuss the impact of the missing data in the Discussion section.

For each outcome, we will conduct our analyses to the greatest degree possible using the intention-to-treat (ITT) principle. We will define the denominator as the number randomised minus any participants whose outcome is known to be missing. We will identify the levels of attrition, and explore the impact of excluding studies with attrition of 20% or greater on the overall assessment of results by a sensitivity analysis.

Assessment of heterogeneity

We will assess and measure the presence and extent of between-study variation (heterogeneity) in each meta-analysis (Higgins 2019). We will use the Chi^2 test to assess whether the observed variation between effect estimates is compatible with chance alone ($P < 0.10$), and the I^2 statistic to describe the percentage of the variability in effect estimates due to heterogeneity rather than

chance. We will consider an I^2 statistic of 50% or higher as indicative of substantial heterogeneity. We recognise that the I^2 measurement must be interpreted in the context of the size and direction of effect estimates and the evidence of the existence of heterogeneity, and that there is uncertainty in the I^2 measurement when there are few studies in a meta-analysis (Higgins 2019). If we identify substantial heterogeneity, we will report it and explore possible causes for it by prespecified subgroup analysis.

Assessment of reporting biases

If we are able to pool more than 10 trials, we will create and examine a funnel plot to explore possible small-study and publication biases. We will also investigate discrepancies between reporting in studies and their corresponding protocols as a source of publication bias.

Data synthesis

We will pool data from studies that we judge to be clinically homogeneous using Review Manager Web software (RevMan Web 2020). We will perform a meta-analysis if more than one study provides useable data for any single comparison. For analyses in which a single time point is present, we will use the random-effects model to carry out meta-analyses because we expect variation in participants, settings, interventions, and measurement of outcomes such that a fixed-effect model would not be appropriate. For outcomes with multiple time points, we will use a mixed-effects meta-analysis, the implementation of which will be guided by past works (Ishak 2007; Musekiwa 2016; Sera 2019). Specific implementations will be guided by model parsimony and model information (i.e. the Akaike Information Criterion).

Subgroup analysis and investigation of heterogeneity

We consider the following factors to be potential causes of heterogeneity in the effects of the intervention: formulation, form, and dose of the zinc intervention; the presence of intervention components that may reduce the bioavailability of zinc; the presence of zinc deficiency amongst participants; and the age (children, adults, elderly) of participants. We plan to carry out the following subgroup analyses for the primary outcomes in the case of sufficient data:

1. different oral formulations of product (i.e. syrup versus capsules or tablets versus lozenges);
2. different forms of zinc (e.g. zinc gluconate, zinc acetate, zinc citrate);
3. different doses of zinc (e.g. < 75 mg versus 75 mg or higher);
4. zinc interventions with and without components that are thought to potentially reduce bioavailability of zinc (e.g. mannitol or sorbitol, citric acid);
5. different participant age groups (e.g. age < 18, adults 18 to 65, age > 65); and
6. participants with and without zinc deficiency at baseline.

We will not require a minimum number of studies to prepare forest plots comparing subgroups. We will use the Chi^2 test to test for subgroup interactions in Review Manager Web when there are at least 10 trials overall and at least two trials in each subgroup (RevMan Web 2020).

Sensitivity analysis

We plan to explore the robustness of effect estimates by carrying out the following sensitivity analyses, if sufficient data are available.

1. Excluding trials with high or unclear risk of selection bias (i.e. random sequence generation or allocation concealment, or both).
2. Excluding trials with 20% or greater attrition.
3. Using endpoint outcome data versus change outcome data.
4. Using adjusted outcome data versus unadjusted outcome data.

Summary of findings and assessment of the certainty of the evidence

We will create a summary of findings table for prevention and a summary of findings table for treatment, using the following outcomes: proportion of participants developing colds (for analyses of prevention trials only); duration of colds; global severity of colds; adverse events potentially due to zinc supplements; and adverse events considered to be potential complications of the common cold. 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 which contribute data to the meta-analyses for the prespecified outcomes (Atkins 2004). We will use the methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019), employing GRADEpro GDT software (GRADEpro GDT). We will justify all decisions to down- or upgrade the quality of studies using footnotes, and will make comments to aid the reader's understanding of the review where necessary.

We will describe the overall strength of the evidence, implications for further research, clinical importance of the results, impact of contextual factors, and considerations of equity in summarising and discussing the results of the review.

ACKNOWLEDGEMENTS

The Methods section of this protocol is based on a standard template developed by the Cochrane Airways Group and adapted by the Cochrane Acute Respiratory Infections Group. We gratefully acknowledge helpful comments on the protocol from the following peer reviewers: Professor Craig Mellis, University of Sydney, NSW, Australia; Professor Timothy Kenealy, Dept of Medicine and Dept of General Practice and Primary Health Care, University of Auckland, Auckland, New Zealand; Professor Robert Ware; Dr M Dulce Estêvão, School of Health, University of Algarve, Portugal; and Associate Professor Johannes van der Wouden.

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ADDITIONAL TABLES

Table 1. 'Characteristics of included studies' table template

Methods	Study design (*e.g. parallel randomised controlled trial (RCT), cross-over RCT, cluster-RCT*) Study duration: *date of first recruitment to last follow-up*
Participants	**Inclusion criteria** Setting: *e.g. outpatient, inpatient, multicentre, national/international* Country: *list all countries* Relevant health status: Number: treatment (N = x); control (N = x) Age (mean, standard deviation (SD)/median, range) Treatment group: Control group:

Table 1. 'Characteristics of included studies' table template *(Continued)*

	Sex (M/F): treatment (N/N M/F); control (N/N M/F) *Any other relevant info, such as comorbidities* **Exclusion criteria**
Interventions	**Treatment group** *Intervention* Dose, duration, frequency, administration *Other relevant info* **Control group** *Intervention (e.g. placebo, no treatment)* Dose, duration, frequency, administration *Other relevant info*
Outcomes	**Primary outcomes** *<list>* **Secondary outcomes** *<list>* *Note: we will describe the methods used to measure the outcomes and include the range and direction of outcomes when this is not obvious.*
Notes	Declaration of interest: Funding source: Contact with study authors for additional information: Other:

APPENDICES

Appendix 1. MEDLINE search strategy

(zinc[tiab] OR zn[tiab] OR zinc[mesh] OR “zinc compounds”[mesh] OR “zinc acetate”[mesh])

AND

(common cold*[tiab] OR rhinovirus*[tiab] OR rhinitis[tiab] OR coryza[tiab] OR catarrh[tiab] OR upper respiratory infection*[tiab] OR upper respiratory tract infection*[tiab] OR uri[tiab] OR urti[tiab] OR upper airway infection*[tiab] OR cold virus*[tiab] OR colds[tiab] OR “common cold”[mesh] OR “rhinovirus”[mesh] OR “rhinitis”[mesh] OR “respiratory tract infections”[mesh])

AND

((randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR clinical trials as topic[mesh: noexp] OR randomly[tiab] OR trial[ti])

NOT

(Animals[mh] NOT humans[mh]))

CONTRIBUTIONS OF AUTHORS

LSW, CH, MK, SN, AGS, and EL drafted the protocol.

DECLARATIONS OF INTEREST

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