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Zinc for the prevention or treatment of acute viral respiratory tract infections in adults: a rapid systematic review and meta-analysis of randomised controlled trials

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ABSTRACT

Objective To evaluate the benefits and risks of zinc formulations compared with controls for prevention or treatment of acute viral respiratory tract infections (RTIs) in adults.

Method Seventeen English and Chinese databases were searched in April/May 2020 for randomised controlled trials (RCTs), and from April/May 2020 to August 2020 for SARS-CoV-2 RCTs. Cochrane rapid review methods were applied. Quality appraisals used the Risk of Bias 2.0 and Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach.

Results Twenty-eight RCTs with 5446 participants were identified. None were specific to SARS-CoV-2. Compared with placebo, oral or intranasal zinc prevented 5 RTIs per 100 person-months (95% CI 1 to 8, numbers needed to treat (NNT)=20, moderate-certainty/quality). Sublingual zinc did not prevent clinical colds following human rhinovirus inoculations (relative risk, RR 0.96, 95% CI 0.77 to 1.21, moderate-certainty/quality). On average, symptoms resolved 2 days earlier with sublingual or intranasal zinc compared with placebo (95% CI 0.61 to 3.50, very low-certainty/quality) and 19 more adults per 100 were likely to remain symptomatic on day 7 without zinc (95% CI 2 to 38, NNT=5, low-certainty/quality). There were clinically significant reductions in day 3 symptom severity scores (mean difference, MD −1.20 points, 95% CI −0.66 to −1.74, low-certainty/quality), but not average daily symptom severity scores (standardised MD −0.15, 95% CI −0.43 to 0.13, low-certainty/quality). Non-serious adverse events (AEs) (eg, nausea, mouth/nasal irritation) were higher (RR 1.41, 95% CI 1.17 to 1.69, NNHarm=7, moderate-certainty/quality). Compared with active controls, there were no differences in illness duration or AEs (low-certainty/quality). No serious AEs were reported in the 25 RCTs that monitored them (low-certainty/quality).

Conclusions In adult populations unlikely to be zinc deficient, there was some evidence suggesting zinc might prevent RTIs symptoms and shorten duration. Non-serious AEs may limit tolerability for some. The comparative efficacy/effectiveness of different zinc formulations and doses were unclear. The GRADE-certainty/quality of the evidence was limited by a high risk of bias, small sample sizes and/or heterogeneity. Further research, including SARS-CoV-2 clinical trials is warranted.

PROSPERO registration number CRD42020182044.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ An extensive database search was conducted with no limits on language or date.
⇒ It is the first systematic review to analyse hazard ratios for symptomatic duration, day 3 mean symptom severity scores around the peak of acute respiratory illness and risks of adverse events.
⇒ The Risk of Bias 2.0 tool was used to appraise the risk of bias at the outcome level, and the Grading of Recommendations, Assessment, Development and Evaluation approach was used to appraise the quality/certainty of the evidence.
⇒ The study was limited by the rapid review methods, for example, where calibrated single reviewers were used.
⇒ Protocol changes and post hoc decisions as declared increased the risk of selective reporting bias.

BACKGROUND

Acute viral respiratory tract infections (RTIs) are ubiquitous in the community. Clinical presentations range from milder cold and influenza-like illnesses to more serious conditions such as viral pneumonia and severe acute respiratory syndrome. Infection rates vary according to viral pathogen, location, season and the host's health status and age.[1] Although most infections are self-limiting, the high incidence leads to substantial healthcare costs and broader economic impacts from school and work absenteeism.[2]

Except for influenza and SARS-CoV-2 vaccinations, prophylactic and therapeutic options are limited. Clinical practice guidelines focus

on hand hygiene, reducing inappropriate antibiotic use and symptomatic relief with over-the-counter medications.[3–5] Some guidelines recommend zinc.[5] However, systematic reviews of zinc are limited by variations in administration route or formulation, are outdated, have been withdrawn or are low quality.[6–11] The mechanisms for how zinc might work include broad spectrum antiviral properties in vitro against most of the common respiratory viruses, including coronaviruses.[12–14] Zinc is important for immunity, inflammation, haemostasis, ACE 2 activity and also assists with tissue responses to hypoxia.[13 15 16] Not surprisingly then, zinc has garnered attention during the global COVID-19 pandemic.[13 15 17] Both high-income and low- income countries have seen increased zinc supplement use and sales.[18 19] Some healthcare workers, clinicians and hospitals are already using zinc to prevent or treat SARS-CoV-2 infections.[20–31]

In response to calls for rapid evidence appraisals to inform self-care and clinical practice during the COVID-19 pandemic,[32] we developed a rapid systematic review protocol to evaluate zinc for the prevention and treatment of SARS-CoV-2 and other viral RTIs.[33 34] At the time of this review, results from COVID-19 randomised controlled trials (RCTs) were all pending. Therefore, this rapid review updates previous systematic reviews of RCTs investigating any type of zinc intervention to prevent or treat viral RTIs in adult populations.

METHODS

Protocol

This rapid review conforms with Cochrane guidance[35 36] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (online supplemental file 1: PRISMA 2020 checklist).[37] Following feedback from our content experts, who at that stage were blinded to the search results, amendments to the registered protocol[33] were made pre data extraction and a revised protocol published.[34] Postprotocol input from consumer/patient advocate representatives who were blinded to the results, led to minor changes to the rating of the importance of outcomes. Due to very serious concerns with the indirectness of the available evidence and the importance of not overstating its relevance to the pandemic, the post hoc decision was made to remove COVID-19 from the title and not Grading of Recommendations, Assessment, Development and Evaluation (GRADE) the certainty of the evidence in the context of SARS-CoV-2 prevention or treatment. Further details about amendments to the protocol and post hoc decisions are reported below.

Search strategy

A research librarian (JB) experienced with systematic review led the search (online supplemental appendix 1). PubMed, Embase, Cochrane CENTRAL, Academic Search Complete, Allied and Complementary Medicine Database, Alt Health Watch, CINAHL Plus with Full Text, Health Source, PsycINFO, China Knowledge Resource Integrated Database (CNKI), U.S. National Library of Medicine Register of Clinical Trials (ClinicalTrials.gov), International Standard Randomized Controlled Trial Number Register (ISRCTN), World Health Organization International Clinical Trials Registry Platform (WHO ICTRP), Global Coronavirus COVID-19 Clinical Trial Tracker and Chinese Clinical Trial Registry were searched from inception up to 8 May 2020, with no limit on language. This was supplemented by bibliography searches of included articles, and due to no eligible RCTs being identified in the first search additional post hoc COVID-19 focused searches were conducted up to 19 August 2020 that included the addition of covid19-trials.org, and medRxiv and bioRxiv preprint databases.

Eligibility criteria

Study design

Included were randomised and quasi-randomised controlled trials. Excluded were systematic reviews, non-randomised studies of interventions and studies without a concurrent control.

Population

Adults in any setting were included if they were at risk of contracting a viral RTI, had clinical illness with a laboratory confirmed viral RTI, or a non-specific respiratory tract illness that is predominantly caused by a viral infection, such as the common cold, non-seasonal rhinosinusitis, pharyngitis, laryngitis, influenza-like illness and healthy adults with acute bronchitis. Excluded were adults with bacterial infections and other respiratory illnesses when a viral infection was not confirmed.

Interventions and comparators

Included were interventions of any zinc conjugates, dose, duration and administration route. Excluded were co-interventions, including other nutraceuticals, herbs or pharmaceuticals unless both the intervention and control groups received the co-intervention. All types of controls and comparator groups were included.

Outcomes

A detailed list of critical (primary) and important (secondary) outcomes can be found in online supplemental appendix 2. Critical outcomes included incidence of RTIs, symptomatic survival, composite symptom severity scores, health-related quality of life (QoL) and serious and non-serious adverse events (AE). Important outcomes included the duration of symptoms and the number of different types of AEs.

Data collection and appraisal

In line with rapid review methods,[35] the first 30 title abstracts and 5 full papers were jointly screened for calibration. After which, single reviewers screened articles and a second reviewer screened the excluded articles (online supplemental appendix 2). Similarly, following calibration, single reviewers extracted data on the study design, funding, participants, interventions, comparators,

outcomes measures and effect size and direction into a piloted electronic spreadsheet that was verified by a second reviewer. For articles published in Chinese the second reviewer used Google translate to verify data extraction. Single reviewers also appraised the risk of bias (RoB) of study outcomes with the Cochrane RoB 2.0 tool[38] that was verified by a second reviewer (online supplemental appendix 3). However, discrepancies in calibration led to the post hoc decision to apply recommended systematic review methods where two reviewers independently appraise the RoB. Any disagreements or uncertainties were discussed with the other reviewers and resolved through consensus. Other review constraints included only appraising the RoB of outcomes that were meta-analysed or the primary outcome, not imputing missing data for secondary outcomes and not contacting the authors. Instead, additional information from previous systematic reviews was extracted.[7 8 39] Data from graphical reports were extracted with WebPlotDigitizer V.4.2 (online supplemental appendix 4).[40]

Statistical methods and evidence synthesis

RevMan V.5.4,[41] R software,[42 43] Microsoft Excel and GRADEpro GDT[44] were used. Studies reporting separate counts for different types of viral RTIs (eg, common cold, bronchitis, influenza-like illness) were combined to calculate the incidence of RTIs per person-months. Mean symptom severity scores were transformed to a modified Jackson common cold scale.[45 46] Means were used as a proxy for median days duration of symptoms. Data extracted from symptomatic survival curves was imputed for the first 7 days using the direct method 10 in the 'HR calculations spreadsheet' published by Tierney *et al*.[47] Results and their 95% CIs are expressed as relative risks (RR) for dichotomous outcomes, incidence rate ratios (IRR) for person-time rates, mean difference (MD) or standardised MD (SMD) for continuous outcomes and hazard ratios (HR) for time-to-event outcomes. Absolute risks/rate differences and numbers needed to treat (NNT) or harm (NNH) are also reported. The Mantel-Haenszel method was used to calculate the pooled RR, generic inverse variance method was used for MD, SMD and IRR, and O-E variance method was used for HR. Irrespective of statistical heterogeneity, due to considerable clinical and methodological diversity/heterogeneity, random effects models were used.

The Cochran Q test and I^2 statistic were used to measure heterogeneity.[36] Subgroup analyses followed published methods and was assessed with the χ^2 test.[48] A priori analyses compared age groups, RTI causes and severity, and zinc administration routes, salts and doses. Post hoc subgroup analyses compared days symptomatic prior to study enrolment and study definitions of symptomatic recovery. The three zinc dose subgroups (<50 mg daily, 50–200 mg daily, >200 mg daily of elemental zinc) were selected post hoc based on a no observed adverse effect level of 50 mg and a higher risk of more severe AEs, such as vomiting, with doses above 225 mg.[49]

For SMD the minimally important difference (MID) was set at 0.5.[50] Except for an MID of 1-day reduction in the duration of the common cold,[51] there was little consensus in the literature on the MID for the other measures of effect; therefore, these were set post hoc. For symptom severity on day 3 for mild RTIs, the MID for MD was set at 1 point on a standardised scale that was the half-way mark between two proposed MIDs (online supplemental appendix 4).[51 52] Based on a 33% probability of remaining symptomatic on day 7 without any treatment,[53] the MID for HRs was set at 1.9 (ie, NNT=5).

The GRADE approach was used to grade the certainty (quality) of the effects estimates and for the Summary of Findings table (online supplemental appendix 5).[54] When data from at least 10 studies were pooled, funnel plots were created, visually inspected for publication bias and statistically analysed using Egger's regression for continuous outcomes and the Harbord score for dichotomous outcomes. However, due to ongoing methodological uncertainties, no statistical test was used for HRs.[55 56]

Throughout the manuscript, zinc doses are reported as milligrams (mg) of elemental zinc. Further details about protocol and post hoc changes, RoB appraisal, statistical methods and GRADE-certainty assessments can be found in online supplemental appendices 3–5.

Patient and public involvement

The protocol was rapidly developed in response to a call from the WHO for rapid evidence reviews to inform self-care and clinical practice during the COVID-19 pandemic. The World Naturopathic Federation responded by setting review topics.[32] The zinc protocol was published prior to direct patient advocate involvement. Experienced Australian patient advocates have since provided input on the outcome measures and the presentation of the results and discussion.

RESULTS

From the 1360 articles and registered trials screened (online supplemental appendix 1), 28 unique RCTs, reported in 25 articles, with 5446 participants met the inclusion criteria (figure 1).[51 57–80] Three were published in Chinese language only.[77–79] Online supplemental appendix 2 lists the 95 RCTs evaluating zinc in paediatric populations, articles published in English that were excluded at full-paper screen, and the characteristics of the seven registered RCTs evaluating zinc for SARS-CoV-2, all with pending results.

Study characteristics

Study participants were generally healthy with clinical symptoms consistent with a mild to moderate viral RTI (online supplemental appendix 3). None were infected with the primary pathogen of interest SARS-CoV-2. Only 1[74] of the 20 RCTs[51 61–80] with community-acquired RTI reported the number of participants

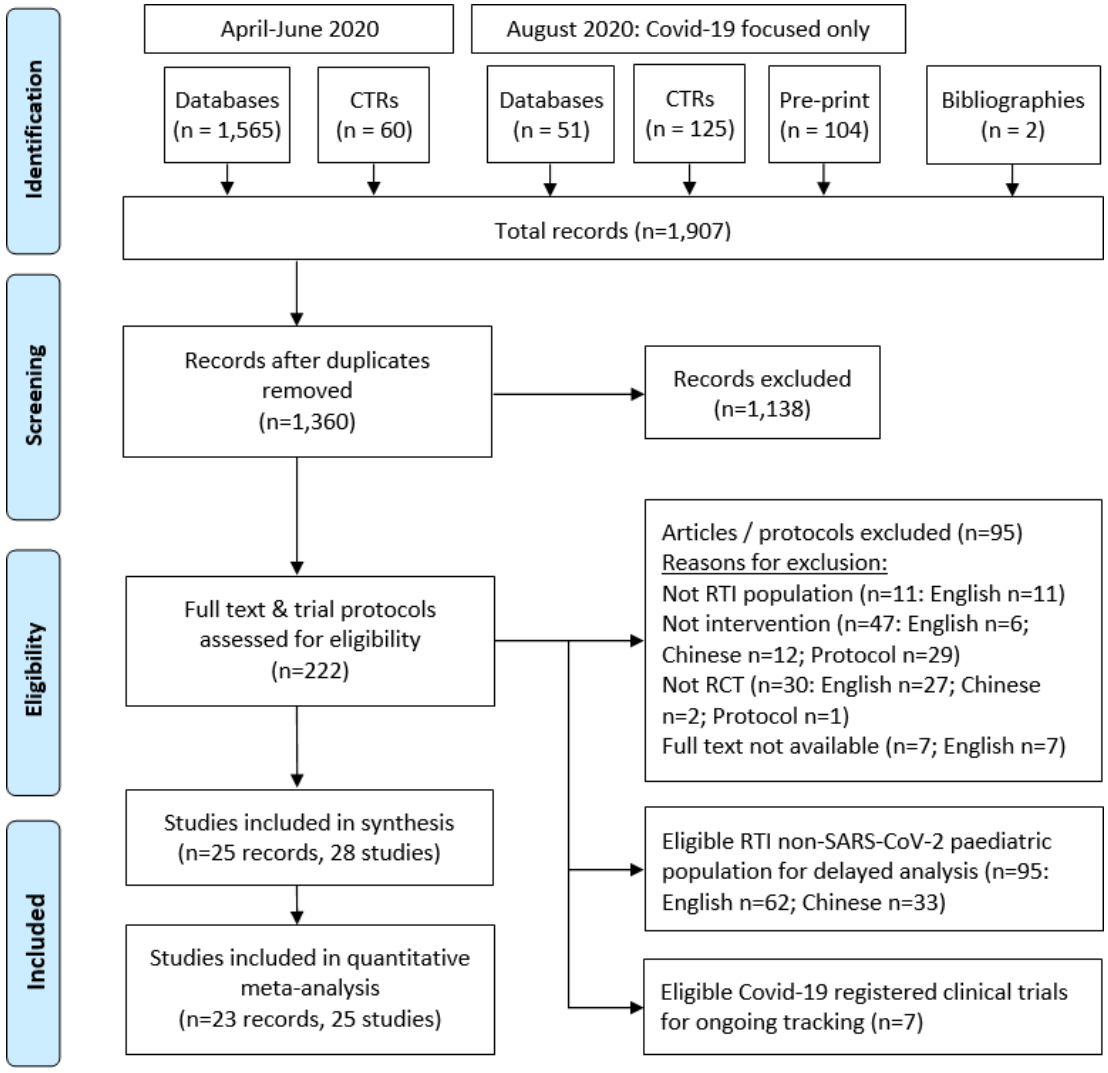

Figure 1 Search results flow chart. CTRs, clinical trial registries; RTIs, respiratory tract infections.

with a proven viral infection. Six RCTs inoculated participants with a human rhinovirus strain (HRV 2, 13, 23 or 39).[51 58–60] Most participants were younger than 65 years. Two RCTs also included older children and adolescents, notwithstanding, the mean age was around 37 years.[63 66] Two RCTs included older adults from different ethnic backgrounds in the USA, many of whom had chronic disease comorbidities and were taking long-term medication.[57 76] In another RCT, around one-third of participants had a history of asthma.[67] In the two RCTs that used oral zinc for prevention, zinc deficiency was excluded prior to enrolment.[75 76]

Most studies were single centre, two-arm RCTs (n=26)[57–78 80] and were conducted in the USA (n=19),[51 57 59–66 68 70–73 75 76] followed by western Europe (n=5),[58 67 69 80] China (n=3)[77–79] and Australia (n=1).[74] The median sample size for prevention studies was 53 (range 32–1945) and for treatment studies 78 (range 12–279). At least half reported the RCT had sufficient statistical power for the study's primary outcome(s).

All but two RCTs reported at least one result that was used in a meta-analysis of a critical or important outcome.[57 79] None of the RCTs reported mortality or other clinical outcomes relevant to severe or critical illness from acute viral RTIs or QoL outcomes. Four RCTs evaluated zinc for prevention,[75–78] and 17 RCTs for treatment[51 61–74 79 80] of symptoms consistent with a community-acquired viral RTI. Of the six RCTs that inoculated participants with HRV, four RCTs evaluated zinc for both prevention and treatment,[58–60] one RCT for treatment only[51] and one assessed the tolerability and AEs of a zinc lozenge.[58] Another RCT assessed AEs and safety of a zinc lozenge used by older adults.[57]

The most common zinc formulations were lozenges followed by nasal sprays and gels containing either zinc acetate or gluconate salts. The daily dose of prophylactic oral zinc for community-acquired infections was 15 mg[75] or 45 mg[76] for 7 or 12 months, respectively. Sublingual lozenge doses to prevent or treat HRV inoculation and community-acquired infections ranged between 45 mg and 300 mg daily and were used

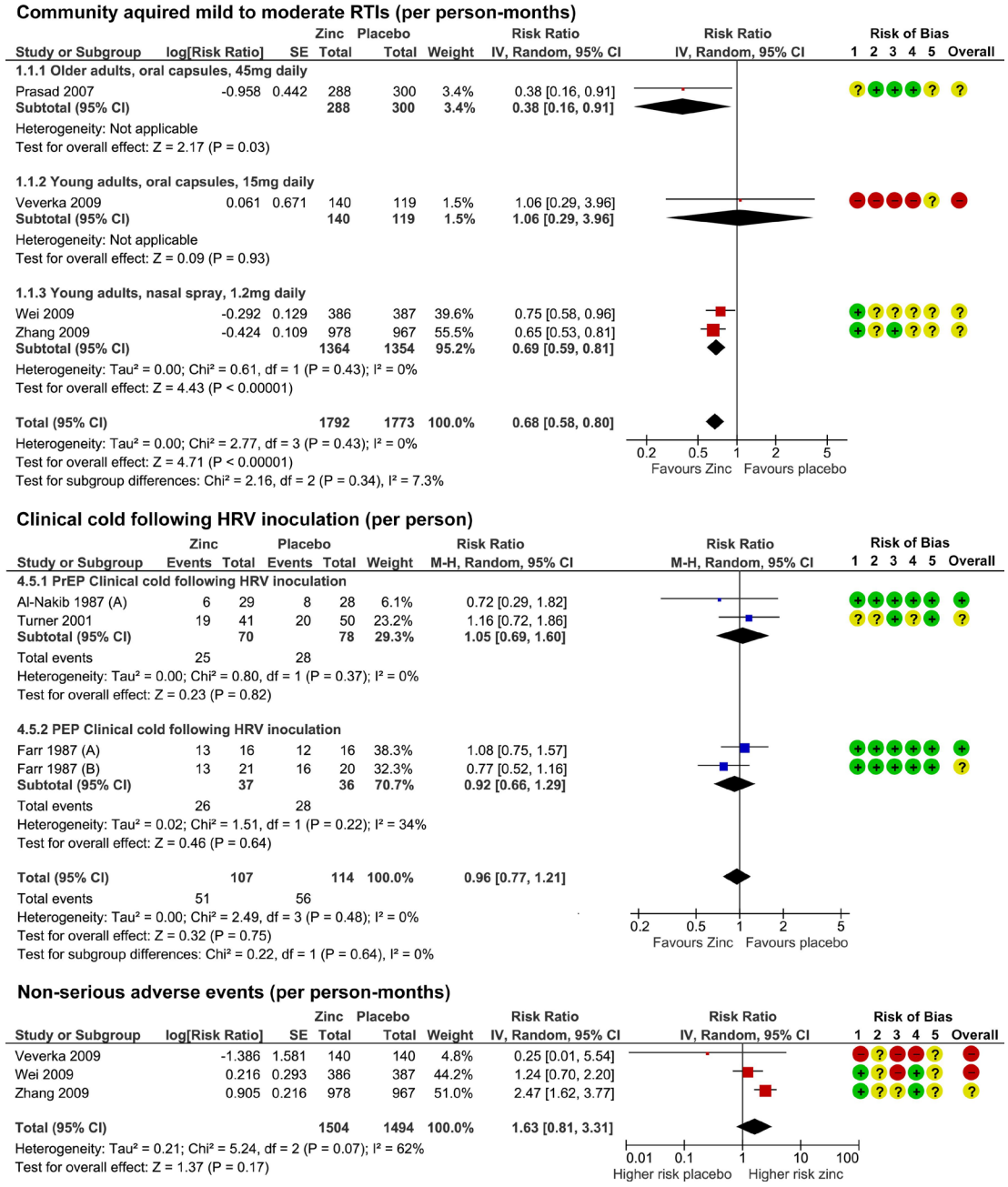

Figure 2 Prevention of respiratory tract infections (RTIs). Risk of community-acquired RTI, clinical colds from human rhinovirus (HRV) inoculation and non-serious adverse effects from prophylaxis. RoB-2 risk of bias legend: (1) randomisation process, (2) deviations from intended interventions, (3) missing outcome data, (4) measurement of the outcome, (5) selection of the reported result. M-H, Mantel-Haenszel; PEP, post-exposure prevention; PREP, pre-exposure prevention; RoB, risk of bias.

for up to 2 weeks.[51 58–61 63–67 69 71–74] Doses for topical nasal zinc to prevent or treat community-acquired infections were substantially lower (0.9–2.6 mg/day).[62 66 68 70 77–79] Twenty-five RCTs compared zinc to a placebo that was matched or partially matched. Two 4-arm RCTs used an active control lozenge containing quinine hydrochloride[51] and a 2-arm RCT used a nasal spray containing naphazoline hydrochloride.[79]

Certainty and quality of the evidence

Most of the prevention, duration, severity and AE outcomes had at least some concerns about their overall RoB (online supplemental appendix 3 and figures 2–5). Consequently, except for the prevention of RTIs following HRV inoculation[58–60] and risk of non-serious AEs with zinc compared to an active control,[60 79] the GRADE certainty/quality of evidence was downgraded by one level for RoB (online supplemental appendix 5). This included the outcomes in which some studies had a high RoB, as the estimates of effects were robust following removal of these RCTs (online supplemental appendix 4). Serious AEs and symptom severity outcomes were downgraded another

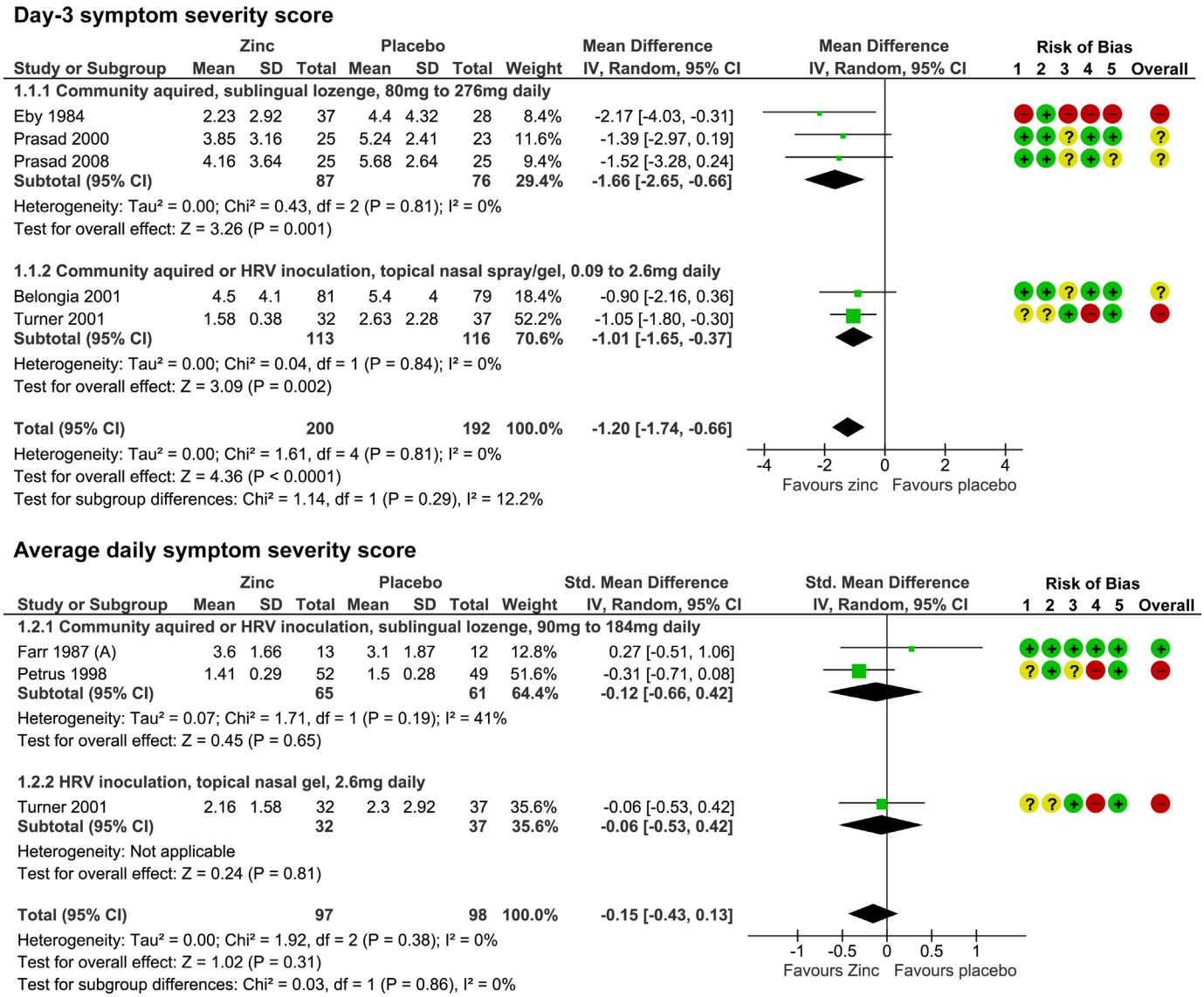

Figure 3 Symptom severity. Mean symptom severity scores following treatment for community-acquired respiratory tract infections and clinical colds from human rhinovirus (HRV) inoculation. RoB-2 risk of bias legend: (1) randomisation process, (2) deviations from intended interventions, (3) missing outcome data, (4) measurement of the outcome, (5) selection of the reported result. RoB, risk of bias.

level for imprecision due to the small pooled-sample sizes (online supplemental appendix 5). There was considerable statistical heterogeneity for the zinc versus placebo duration outcomes (figure 4). The HR effect estimate was downgraded one level for inconsistency, as the heterogeneity was partially explained by clinical and methodological diversity in the subgroup and sensitivity analyses (online supplemental appendix 4) and the 95% CI mostly overlapped (figure 3). However, the mean days duration was downgraded by two levels, due to conflicting evidence from clinically important positive and negative effects, minimal overlapping of the 95% CI (figure 3) and neither the subgroup nor sensitivity analyses substantially reduced the heterogeneity (online supplemental appendix 4). At least 11 RCTs were industry funded, with a further seven receiving partial industry support (online supplemental appendix 3). Publication bias was not strongly suspected (online supplemental appendices 4, 5).

Findings from prevention studies

Community-acquired infections

When oral or topical nasal zinc was compared with placebo controls, there was moderate certainty/quality evidence of a 32% lower RR of developing mild to moderate symptoms consistent with a viral RTI (IRR 0.68, 95% CI 0.58 to 0.80) (figure 2).[75–78] Five RTIs per 100 person-months of zinc use were prevented (95% CI 1 to 8, NNT=20). The largest reductions in RR were for moderately severe symptoms consistent with an influenza-like illness (eg, elevated temperature). There was an 87% lower risk of developing moderately severe symptoms (IRR 0.13, 95%

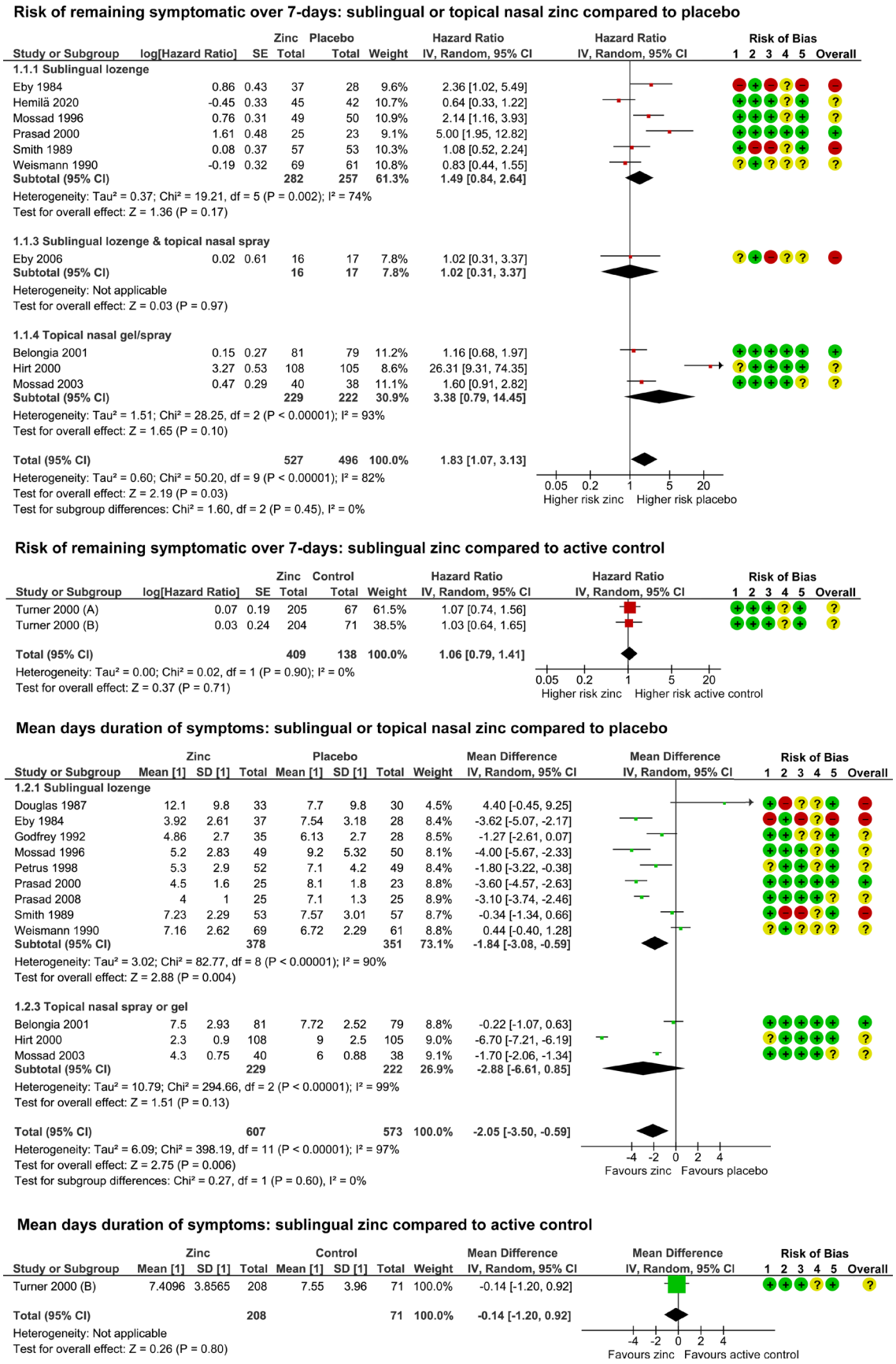

Figure 4 Duration of illness. Risk of remaining symptomatic and mean days duration following treatment for community-acquired RTI or clinical colds from HRV inoculation. RoB-2 risk of bias legend: (1) randomisation process, (2) deviations from intended interventions, (3) missing outcome data, (4) measurement of the outcome, (5) selection of the reported result. HRV, human rhinovirus; RoB, risk of bias; RTI, respiratory tract infection.

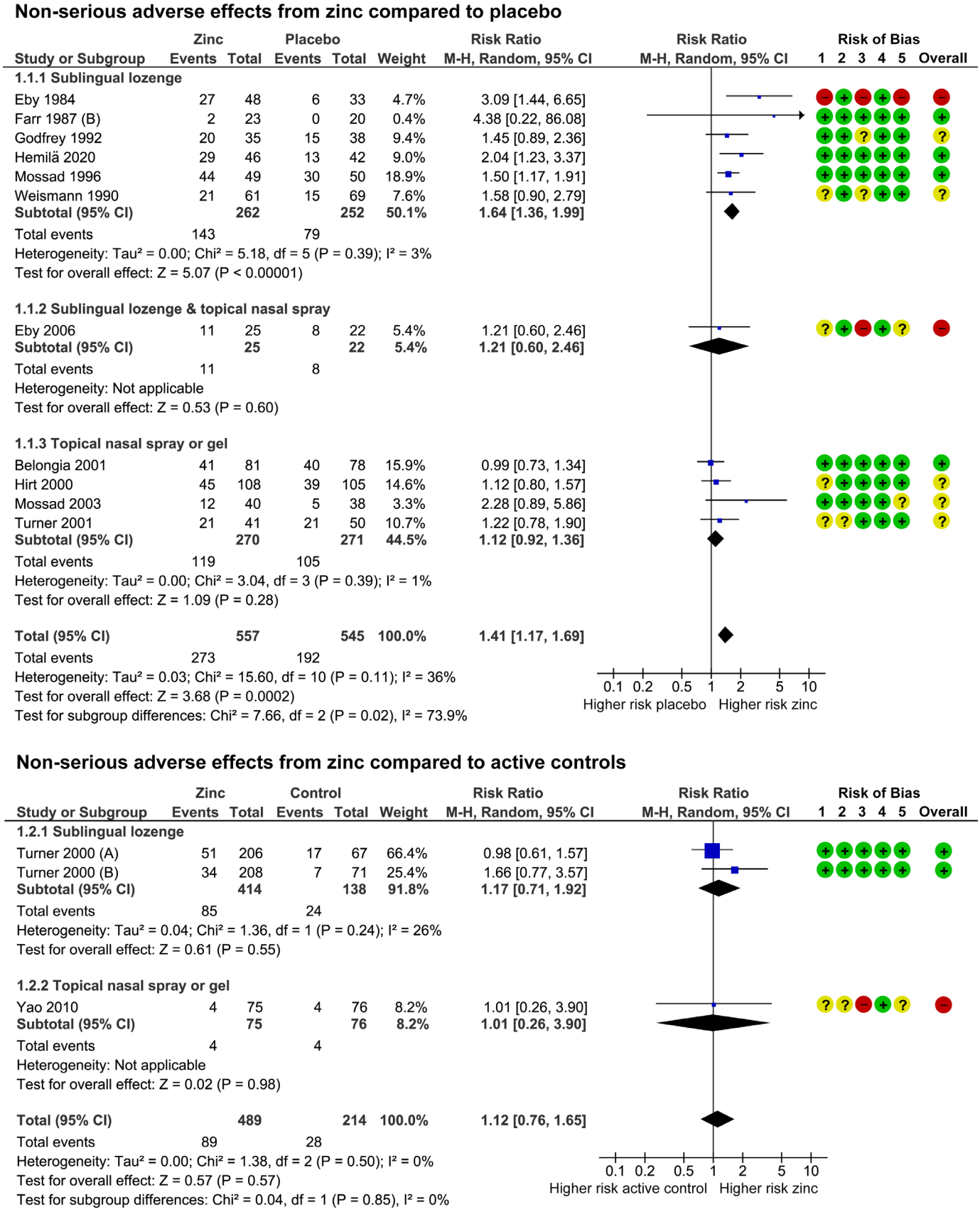

Figure 5 Adverse effects from zinc used to treat RTIs. Risk of any non-serious adverse effects during treatment of an acute respiratory tract infection. RoB-2 risk of bias legend: (1) randomisation process, (2) deviations from intended interventions, (3) missing outcome data, (4) measurement of the outcome, (5) selection of the reported result. M-H, Mantel-Haenszel; RoB, risk of bias; RTI, respiratory tract infection.

CI 0.04 to 0.38) compared with a 28% lower risk of developing milder symptoms (eg, common cold) (IRR 0.72, 95% CI 0.61 to 0.85) (moderate certainty/quality).[76–78] However, due to more people contracting mild RTIs, the absolute risk reduction/risk difference was higher. Five mild RTIs were prevented per 100 person-months (95% CI 2 to 7, NNT=20) compared with one moderate RTI per 100 person-months (95% CI 1 to 2, NNT=100) (online supplemental appendix 4).[76–78] Subgroup analysis found no significant differences according to age or zinc administration route or dose (online supplemental appendix 4).

Human rhinovirus inoculation

The effect of zinc lozenges compared with placebo for preventing RTIs caused by HRV inoculation was evaluated in two pre-exposure prevention (PrEP) RCTs with 53 participants,[58 60] and two post-exposure prevention (PEP) RCTs with 54 participants.[59] Zinc had no effect on the risk of developing a clinical cold (RR 0.96, 95% CI 0.77 to 1.21, moderate certainty/quality) (figure 2). There were no significant differences between the effects of zinc compared with placebo for either the PrEP or PEP subgroup, or in the subgroup analysis comparing the two groups (figure 2). There were similar non-significant findings for the risks of developing a laboratory confirmed infection (online supplemental appendix 4).

Adverse events

No serious AEs were reported were reported in the four RCTs that used zinc for prevention (low certainty/quality).[75–78] Anosmia (loss of sense of smell) was not reported by the 1447 participants who used a zinc nasal spray nor the 1354 participants who used a placebo spray for 1 month (low certainty/quality).[77 78] Compared with placebo, no differences in copper plasma concentration were found in the two smaller RCTs that evaluated 15 mg of oral zinc for younger adults over 7 months[75] or 45 mg for older adults over 12 months[76] (low certainty/quality). No differences in the of risk non-serious AEs from zinc compared with placebo controls were found (IRR 1.63, 95% CI 0.81 to 3.31, low certainty/quality).[75 77 78]

Findings from treatment studies

Symptom severity

Compared with placebo, a clinically important reduction of more than one point in the day 3 symptom severity scores was found for sublingual and topical nasal zinc (MD −1.21, 95% CI −1.74 to −0.66, low certainty/quality) (figure 3).[60–63 65] In contrast, no differences in average daily symptom severity scores were found (SMD −0.15, 95% CI −0.43 to 0.13, low certainty/quality).[59 60 64] Subgroup analyses found no significant differences according to zinc administration route or type of viral infection (online supplemental appendix 4).

Symptom duration

During the first week of illness, participants who used sublingual or topical nasal zinc were 1.8 times more likely to recover before those who used placebo (HR 1.83, 95% CI 1.07 to 3.13, low certainty/quality) (figure 4).[61–63 66–72] An estimated 19 more adults per 100 were likely to remain symptomatic at the end of the first week if they used placebo rather than zinc (95% CI 2 to 38, NNT=5). Compared with placebo, zinc also reduced the mean duration of symptoms by 2 days (MD −2.05, 95% CI −3.50 to −0.59, very low certainty/quality) (online supplemental appendix 4).[61–65 68–74] Results from the subgroup analyses that compared zinc salts, administration routes and zinc lozenge doses were inconsistent (online supplemental appendix 4). There was low certainty/quality evidence that zinc lozenges were equivalent to an active control (HR 1.06, 95% CI 0.79 to 1.41; MD −0.14 days, −1.20 to 0.92) (figure 4).[51]

Adverse events

No serious AEs were reported in the 19 RCTs that reported AEs (low certainty/quality).[51 59–73 79] However, the risk of any type of non-serious AE was higher from zinc use compared with placebo (RR 1.41, 95% CI 1.17 to 1.69) (figure 5), with 14 more adults per 100 experiencing a non-serious AE (95% CI 9 to 20, NNH=7, moderate certainty/quality).[59 60 62 63 66–71 73] Specifically, zinc increased the risk of nausea or gastrointestinal discomfort (RR 1.46, 95% CI 1.03 to 2.06),[59 61 63 65–68 71–74] mouth irritation or soreness from sublingual lozenges (RR 1.55, 95% CI 1.05 to 2.29),[59 61 63 65 66 72 73] and taste aversion from sublingual lozenges (RR 2.11, 95% CI 1.47 to 3.04),[59 61 63 65 66 69 71 72 74] but not nasal irritation or pain from topical nasal sprays or gels (RR 1.22, 95% CI 0.72 to 2.05) (online supplemental appendix 4).[60 62 70] Zinc lozenges were more likely than nasal sprays and gels to cause any type of non-serious AE (p=0.02) (online supplemental appendix 4). There was no difference in the rates of non-serious AE from zinc lozenges compared with active controls (RR 1.12, 95% CI 0.76 to 1.65) (figure 5).[51 79]

DISCUSSION

Principal findings

This rapid systematic review and meta-analysis advances the evidence on the effects of zinc for mild to moderate RTIs in adults without zinc deficiency.[7–10 39 81 82] However, despite additional searches through to August 2020, none of the RCTs were for the primary population of interest that was SARS-CoV-2 infection as the results from the registered clinical trials were all pending.

New evidence about zinc prophylaxis found that compared with placebo, zinc reduced the risk of developing symptoms consistent with a community-acquired viral RTI. The prophylactic effects were greatest for reducing the RR of developing more severe symptoms, such as fever and influenza-like illnesses. However, only four studies were identified, and none used laboratory tests to confirm a viral infection.

When zinc was used to treat symptoms consistent with mild to moderate viral RTIs, new evidence found that

compared with placebo, there were clinically important reductions in day 3 symptom severity, but not average daily symptom severity scores. The difference in the severity results may reflect reporting bias and imprecision, as results could not be extracted for 13[58 59 66–74 79] of the 20 RCTs[58–74 79] that evaluated symptom severity, and there was only one overlapping RCT[60] in the two meta-analyses conducted. Like previous reviews,[7–10 39 81] compared with placebo there were clinically important reductions in symptomatic duration from zinc use. However, there was also an increased risk of non-serious adverse effects that may reduce the tolerability or acceptability of some zinc formulations.

In contrast to these promising findings, following human rhinovirus inoculations, compared with placebo, sublingual zinc did not reduce the risk of developing an infection or symptoms of a clinical cold, nor were there any significant effects on symptom severity or duration of illness when zinc was compared with an active control. While the number of studies and sample sizes were small, it still raises the questions about the in vitro versus in vivo antiviral effects of zinc ions, at least against rhinoviruses, and comparative effectiveness.

Strengths and weakness of the review

Limitations to the certainty (quality) of the evidence included concerns about the RoB for most prevention, severity and duration outcomes, along with imprecision in the symptom severity lowering effects and inconsistencies in the treatment effect sizes for symptomatic duration. Further details about the impact of individual studies on GRADE certainty assessment of RoB, heterogeneity, imprecision and the overall quality of the evidence can be found in online supplemental appendix 5.

The findings build on previous reviews.[7–10 39 81 82] Compared with two other systematic reviews conducted in the same period,[10 82] substantially more studies were identified in this review. This in part was due to searching non-English language databases and affirms calls to carefully consider which methods to restrict when conducting rapid reviews of traditional and complementary medicine.[83] Other strengths included being the first systematic review of zinc for RTIs to synthesise hazard ratios for symptomatic duration, day 3 mean symptom severity scores around the peak of illness and risks of AEs. RoB appraisal at the outcome level rather than the study level helped optimise GRADE-certainty assessments that were both conducted following calibration exercises. Notwithstanding, there is always a degree of judgement that may vary between reviews. For instance, when appraising the available evidence for risk of serious AEs, we rated down one level for RoB and another for imprecision. However, it might also be reasonable to judge the RoB as not serious and the overall GRADE assessment as moderate, rather than low certainty/quality evidence. The assessments of publication bias were a potential limitation. While publication bias was not strongly suspected, visual inspection of funnel plots are necessarily subjective[56] and a statistical test for hazard ratios was not performed.

Like other rapid reviews, single reviewers conducted many of the tasks that increases the risk of errors and inconsistencies. Nevertheless, we applied rigorous checks. For example, the use of a detailed data extraction form led to our reviewers being the first to notice that there were two 4-arm RCTs[51] in which the control lozenge contained an active ingredient, quinine hydrochloride that has broad-spectrum antiviral effects.[84] Reclassifying them as an active control addressed unexplained inconsistencies identified by previous reviewers.[39] Sensitivity analysis confirmed that the inclusion of these two RCTs, both with non-significant findings, did not substantially change the effect estimates for symptom duration (online supplemental appendix 4). We also determined that two earlier reviews[9 11] had incorrectly included the day 4 symptom severity scores from two RCTs[61 65] in their meta-analysis of average daily symptom severity. When these are removed, we found the effect of zinc was no longer significant.

Finally, while all protocol changes were declared, this increases the risk of selective reporting bias. Initiating the rapid review in the early stages of the COVID-19 pandemic necessitated rapid protocol development and registration. To help mitigate bias we sought blinded advice from our content experts and consumer/patient advocates and post hoc decisions were conservative with the rationale reported. Notably, while the published amendments[34] to the protocol inclusion/exclusion criteria led to RCTs that inoculated participants with HRV also being included, the additional findings did not favour zinc. Post hoc decisions also ensured that the very serious indirectness of the available evidence was not overstated in the context of SARS-CoV-2 prevention or treatment.

Is zinc more than a dietary supplement?

The role of zinc in viral RTIs appears to extend beyond supplementing nutritional intake to prevent or treat zinc deficiency.[85] The two RCTs that used prophylactic oral zinc excluded zinc deficiency prior to enrolment.[75 76] While none of the other RCTs excluded deficiency, the risk was low as participants were generally healthy and the three RCTs conducted in China all used a low dose intranasal zinc spray (1.15 mg daily)[77–79] that is unlikely to have substantial systemic effects.[86] The rationale for topical intranasal and sublingual zinc is based on the in vitro effects of zinc ions that can inhibit viral replication, stabilise cell membranes and reduce mucosal inflammation.[14 86] However, other mechanisms may also be at play, at least for sublingual and oral administration as activation of T lymphocytes, monocytes and granulocytes has been observed in healthy young adult males within 24–48 hours of taking 15 mg of oral zinc daily.[87]

Implications for clinicians and consumers

Zinc is readily available for consumers to self-prescribe. The marginal benefits, strain specificity, drug resistance and potential risks of other over-the-counter and

prescription medications[88–98] makes zinc a viable 'natural' alternative for the self-management of non-specific RTIs. It also provides clinicians with a management option for patients who are desperate for faster recovery times and might be seeking an unnecessary antibiotic prescription.

However, clinicians and consumers need to be aware that considerable uncertainty remains regarding the clinical efficacy of different zinc formulations, doses and administration routes,[39 67 81 86] and the extent to which efficacy might be influenced by the ever changing epidemiology of the viruses that cause RTIs. The largest body of evidence comes from sublingual lozenges and zinc gluconate and acetate salts, suggesting these are suitable choices. Yet, this does not mean that other administration routes and zinc salts are less effective. The new evidence on the prophylactic effects of low dose nasal sprays[77 78] adds weight to the otherwise inconclusive findings from the handful of RCTs evaluating zinc nasal sprays or gels for acute treatment.[62 66 68 70 79] A minimum therapeutic dose for zinc is also yet to be determined. An earlier review suggested the minimum dose for sublingual lozenges is 75 mg.[8] However, our analysis does not support this conclusion. Further, a daily oral dose of 15 mg has been shown to upregulate lymphocytes within days,[87 99] so it is plausible that much lower doses might also be effective.

The minimum time frame in which zinc should be started is also unclear. Most of the RCTs included in this review commenced zinc within 24 hours from the onset of symptoms and some guidelines have claimed that zinc 'only works if you start taking them within 24 hours'.[5] Yet, in the post hoc subgroup analyses, the duration of illness was also reduced in the subset of RCTs in which participants commenced zinc up to 3 days from the onset of symptoms. Further, in a preliminary analysis for one of the included RCTs, the investigators briefly report that the significant reduction in the duration of symptoms remained when participants with symptoms of up to 10 days duration were included in the analysis.[63]

Alongside potential benefits, consumers also seek detailed information about adverse effects and tolerability. Zinc was found to increase the risk of non-serious AEs. No serious AEs were reported, suggesting the risk is low. However, it cannot be ruled out as RCTs, especially those with small samples, are not well placed to identify rare events. If the rule of three is applied to determine maximum risk,[100] then the upper 95% CI for a serious AE from prophylactic zinc would be 1.7/1000 person-months and for therapeutic zinc, 2.9/1000 participants. Indeed, postmarketing surveillance has identified cases of long-lasting anosmia associated with a zinc gluconate nasal gel.[101 102] Reassuringly, a loss of smell was not reported by any of the 1364 young adults who used nasal sprays for 1 month. Notwithstanding, anosmia is an early SARS-CoV-2 symptom, so any use of topical nasal zinc during the pandemic should be carefully considered and monitored.

Copper deficiency is another concern. Plasma copper levels and other laboratory parameters were stable following 15 mg and 45 mg for 7 months and 12 months, respectively.[75 76] However, contamination of the zinc intervention was found in one RCT,[75] both RCTs were small and may be underpowered to detect a difference, only a single marker of copper status was measured,[103] and intestinal absorption of zinc is influenced by a variety of factors including diet, medications, chronic diseases and increasing age.[15 17]

Implications for research

Given the limited therapeutic options for preventing and treating viral RTIs, further research is indicated to better understand zinc's mechanisms of action, the optimum administration routes, formulations and dose, the minimum time-frame in which zinc should be started following an acute infection and the duration of therapy.

Except for one RCT that evaluated the effects of zinc on cognitive function,[58 80] the symptomatic and functional impact on the participants' QoL was not assessed. These outcomes are important to patients. Questionnaires like the Wisconsin Upper Respiratory Symptom Survey-24 that assess both symptom severity and QoL are therefore recommended.[104]

The review findings align with calls for more immunonutrition research, particularly in populations with a higher SARS-CoV-2 risk.[17 105] Results from seven RCTs evaluating various zinc doses, salts and administration routes for the prevention or treatment of SARS-CoV-2 are all pending. These RCTs will continue to be tracked and the review periodically updated and reported until there is moderate certainty/quality in the evidence, or no results are pending. However, based on the limited information reported in the protocols, some of the choices for zinc interventions appear to be arbitrary. Future SARS-CoV-2 clinical trials should consider replicating the RCTs with positive results for other viral RTIs and consider focusing on high-risk groups. Trials also need to determine if zinc requires a carrier or an ionophore, such as hydroxychloroquine,[28] and compare the risks and benefits. According to our review findings and preliminary in vitro SARS-CoV research,[12] it is plausible that zinc may be effective when used on its own.

CONCLUSIONS

In adult populations in which zinc deficiency is unlikely, our review found when zinc was used for prophylaxis, there was a lower risk of contracting a clinical illness consistent with a community-acquired viral RTI, but not following direct HRV inoculation. When used for treatment, zinc was found to shorten the duration of symptoms and reduce day 3 symptomatic severity, but not overall daily symptom severity. While there was an increased risk of non-serious AEs that may limit tolerability for some, the risk of serious AEs was low. Limitations to the GRADE certainty/quality assessments of the available evidence included a high RoB and/or small sample sizes in primary studies, and considerable heterogeneity in the duration effect estimates. We were unable to answer

questions about the comparative efficacy, effectiveness and acceptability of different zinc formulations and doses, and their mechanisms of action. Prior to recommending zinc, patient preferences, financial and opportunity costs, and availability of different zinc interventions should be considered. Clarification of the efficacy and mechanism of zinc in viral respiratory infections, including SARS-CoV-2 infections, warrants further research.

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PRISMA 2020 Main Checklist

Topic	No.	Item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Introduction
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Introduction
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Methods
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Methods Appendix 1
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Methods – Search strategy Appendix 1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Methods – Eligibility criteria, Data collection and appraisal
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Methods – Data collection and appraisal

Topic	No.	Item	Location where item is reported
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Methods – Eligibility criteria: Outcomes Appendix 2 Results – Study characteristics
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Methods – Eligibility criteria, Statistical methods and evidence synthesis Appendix 3 & 4
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Methods – Data collection and appraisal Appendix 3
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Methods – Eligibility criteria, Statistical methods and evidence synthesis Appendix 4
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item 5)).	Methods – Data collection and appraisal
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Methods – Data collection and appraisal Appendix 4
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Methods – Data collection and appraisal
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Methods – Data collection and appraisal Appendix 4
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Methods – Data collection and appraisal Appendix 4

Topic	No.	Item	Location where item is reported
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Methods – Data collection and appraisal Appendix 4
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Methods – Data collection and appraisal Appendix 4
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Methods – Data collection and appraisal Appendix 5
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Results - intro Figure 1 Appendix 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Appendix 2
Study characteristics	17	Cite each included study and present its characteristics.	Results – Study characteristics Appendix 3
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Figures 2-5 Appendix 3
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Figures 2-5 Appendix 4
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Results – Findings from prevention studies, Findings from treatment studies Appendix 3 & 5
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Results – Findings from prevention studies, Findings from treatment studies Appendix 4 & 5

Topic	No.	Item	Location where item is reported
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Appendix 4
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Appendix 4
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Appendix 4 & 5
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Results – Findings from prevention studies, Findings from treatment studies Appendix 5
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Discussion – all sections
	23b	Discuss any limitations of the evidence included in the review.	Discussion - Strengths and weakness of the review Appendix 5
	23c	Discuss any limitations of the review processes used.	Discussion - Strengths and weakness of the review Box 1
	23d	Discuss implications of the results for practice, policy, and future research.	Discussion - Implications for clinicians and consumers, Implications for research Conclusions
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Methods – Protocol
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Methods – Protocol

Topic	No.	Item	Location where item is reported
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Methods – Protocol Appendix 4
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	End
Competing interests	26	Declare any competing interests of review authors.	End
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	End

PRIMSA Abstract Checklist

Topic	No.	Item	Reported?
TITLE			
Title	1	Identify the report as a systematic review.	Yes
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	Yes
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	Yes
Synthesis of results	6	Specify the methods used to present and synthesize results.	Yes
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	Yes
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes
OTHER			
Funding	11	Specify the primary source of funding for the review.	Yes
Registration	12	Provide the register name and registration number.	Yes

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. MetaArXiv. 2020, September 14. DOI: 10.31222/osf.io/v7gm2. For more information, visit: www.prisma-statement.org

Appendix 1: Search strategies

CONTENTS

1 DATABASE SEARCH STRATEGIES

Rapid Review of Zinc for the Prevention or Treatment of COVID-19 and Other Coronavirus-related Respiratory Tract Infections in Humans

1.1 Initial Searches, April-June 2020

1.1.1 Main Databases

Database: PubMed

Searched: 8 May 2020

Results: n=546

Search:

(Coronaviridae[mh] OR Coronavir* OR nCov OR covid OR Coronaviridae Infections[mh] OR Middle East Respiratory Syndrome Coronavirus[mh] OR "Middle East Respiratory Syndrome" OR MERS OR "Severe Acute Respiratory Syndrome" OR “Severe acute respiratory syndrome-related coronavirus”

OR “Severe Acute Respiratory failure” OR “Acute febrile respiratory syndrome” OR SARS OR Respiratory Tract Infections[mh] OR “Lower respiratory infection” OR “viral respiratory” OR pneumonia OR “flu -like illness” OR bronchitis OR “Common cold” OR Rhinitis OR laryngitis OR “Respiratory Infections” OR “Infections, respiratory” OR “Infections, Respiratory Tract” OR “Infections, Upper Respiratory” OR “Upper Respiratory Tract” OR “Infections, Lower Respiratory Infections” OR “Lower Respiratory Infections” OR “Lung Inflammation” OR “Lobar Pneumonia” OR “Lobar Pneumonitis” OR “Pulmonary Inflammation”)

AND

(Zinc[mh] OR zinc OR zn)

AND

(randomized controlled trial[pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals [mh] NOT humans [mh])

Database: Embase (via Ovid)

Searched: 29 April 2020

Results: n=268

Search:

1) (exp Coronaviridae/ OR exp Coronaviridae infection/ OR exp Middle East respiratory syndrome coronavirus/ OR exp respiratory tract infection/ OR (Coronavir* OR nCov OR covid OR “Middle East Respiratory Syndrome” OR MERS OR “Severe Acute Respiratory Syndrome” OR “Severe acute respiratory syndrome-related coronavirus” OR “Severe Acute Respiratory failure” OR “Acute febrile respiratory syndrome” OR SARS OR “Lower respiratory infection*” OR “viral respiratory” OR pneumonia OR “flu-like illness” OR bronchitis OR “Common cold” OR Rhinitis OR laryngitis OR “Respiratory Infection*” OR “Respiratory Tract Infection*” OR “Upper Respiratory Infection*” OR “Upper Respiratory Tract” OR “Lung Inflammation” OR “Lobar Pneumonia” OR “Lobar Pneumonitis” OR “Pulmonary Inflammation”).ti,ab,kw.)
2) (exp zinc/ OR (zinc OR zn).ti,ab,kw.)
3) (exp dietary supplement/ OR (supplement* OR deficiency OR additive* OR vitamin*).ti,ab,kw.)
4) 2 AND 3
5) (crossover-procedure/ OR double-blind procedure/ OR randomized controlled trial/ OR single-blind procedure/ OR (random* OR factorial* OR crossover* OR cross over* OR placebo* OR (doubl* adj blind*) OR (singl* adj blind*) OR assign* OR allocat* OR volunteer*).tw.
6) 1 AND 4 AND 5

Database: EBSCOhost (Academic Search Complete, Allied and Complementary Medicine Database(AMED), Alt HealthWatch, CINAHL Plus with Full Text, Health Source and PsycINFO)

Searched: 27 April 2020

Results: n=231

Search:

Coronaviridae OR Coronavir* OR nCov OR covid OR Coronaviridae Infections OR Middle East Respiratory Syndrome Coronavirus OR "Middle East Respiratory Syndrome" OR MERS OR "Severe Acute Respiratory Syndrome" OR “Severe acute respiratory syndrome-related coronavirus” OR “Severe Acute Respiratory failure” OR “Acute febrile respiratory syndrome” OR SARS OR Respiratory Tract Infections[mh] OR “Lower respiratory infection” OR “viral respiratory” OR pneumonia OR “flu -like illness” OR bronchitis OR “Common cold” OR Rhinitis OR laryngitis OR “Respiratory Infections” OR “Infections, respiratory” OR “Infections, Respiratory Tract” OR “Infections, Upper Respiratory” OR “Upper Respiratory Tract” OR “Infections, Lower Respiratory Infections” OR “Lower Respiratory Infections” OR “Lung Inflammation” OR “Lobar Pneumonia” OR “Lobar Pneumonitis” OR “Pulmonary Inflammation”

AND

Zinc OR zinc OR zn OR dietary supplements OR supplement* OR deficiency OR additive* OR vitamin*

AND

Randomi*ed controlled trial OR controlled clinical trial OR randomi*ed OR placebo OR drug therapy OR randomly OR trial OR groups OR “comparative effectiveness” NOT animals

Database: CKNI (Chinese Knowledge Database)

Searched: 24 April 2020

Results: n=193

Search:

1. SU=新型冠状病毒(Xinxing Guanzhuang Bingdu, Coronavirus) OR 新冠病毒(Xinguan Bingdu, COVID-19 or SARS-Cov-2 or 2019-nCov) OR 新型冠状病毒肺炎(Xinxing Guanzhuang Bingdu Feiyan, Coronavirus pneumonia) OR 新冠肺炎(Xinguan Feiyan, Coronavirus pneumonia) OR SARS-CoV OR SARS OR MERS OR MERS-CoV OR 中东呼吸道综合征(Zhongdong Huxidao Zonghezheng, MERS OR MERS-CoV) OR 呼吸道感染(Huxidao Ganran, Respiratory Infections) OR 肺部感染(Feibu Ganran, Lung Inflammation) OR 肺炎(Feiyan, Pneumonia) OR 肺部炎症(Feibu Yanzheng, Pulmonary Inflammation)

1 找到 179,602 条结果

2. 1 AND SU=锌 (Xin, Zinc) OR 补锌 (Buxin, diet supplementation)

1 AND 2 找到 322 条结果

3. 2 AND AB= 临床观察 (Linchuang Guancha, clinical observation) OR 临床研究 (Linchuang Yanjiu, clinical trial) OR 临床试验 (Linchuang Shiyan, clinical trial) OR 临床对照 (Linchuang Duizhao, clinical control) OR 对照 (Duizhao, control) OR 比较研究 (Bijiao Yanjiu, comparative study) OR 随机 (Suiji, random*) OR 随机对照试验(Suiji Duizhao Shiyan, Randomi?ed Controlled Trials) OR 单盲(Danmang, single blind procedure) OR 双盲 (Shuangmang, double blind prodecure) OR 盲法(Mangfa, blind procedure) OR 三盲(Sanmang, triple blind procedure) OR 交叉(Jiaocha, crossover procedure) OR 安慰剂 (Anweiji, placebo)

1 AND 2 AND 3 找到 193 条结果

Note: SU=subject, AB=abstract

Database: Cochrane Central Register of Controlled Trials (CENTRAL)

Searched: 6 May 2020

Results: n=327

Search:

(Coronaviridae[mh] OR Coronavir* OR nCov OR covid OR Coronaviridae Infections[mh] OR Middle East Respiratory Syndrome Coronavirus[mh] OR "Middle East Respiratory Syndrome" OR MERS OR "Severe Acute Respiratory Syndrome" OR “Severe acute respiratory syndrome-related coronavirus” OR “Severe Acute Respiratory failure” OR “Acute febrile respiratory syndrome” OR SARS OR Respiratory Tract Infections[mh] OR “Lower respiratory infection” OR “viral respiratory” OR pneumonia OR “flu -like illness” OR bronchitis OR “Common cold” OR Rhinitis OR laryngitis OR “Respiratory Infections” OR “Infections, respiratory” OR “Infections, Respiratory Tract” OR “Infections, Upper Respiratory” OR “Upper Respiratory Tract” OR “Infections, Lower Respiratory Infections” OR “Lower Respiratory Infections” OR “Lung Inflammation” OR “Lobar Pneumonia” OR “Lung Inflammation” OR “Lobar Pneumonitis” OR “Pulmonary Inflammation”)

AND

(Zinc[mh] OR zinc OR zn)

1.1.2 Clinical Trial Registries

Database: U.S. National Library of Medicine Register of Clinical Trials (ClinicalTrials.gov)

Searched: 5 May 2020

Results: n=14

Search: “zinc”

Condition: Coronavir* OR nCov OR covid OR "2019-nCoV infection”

Other terms: zinc OR zn

Databases: International Standard Randomized Controlled Trial Number Register (ISRCTN), and World Health Organization International Clinical Trials Registry Platform (WHO ICTRP)

Searched: 5 May 2020

Results: n= 12

Search:

Condition: Coronavir* OR nCov OR covid OR "2019-nCoV infection"

Other terms: zinc OR zn

Database: Chinese Clinical Trial Registry

Searched: 29 April 2020

Results: n=0

Search:

1. 干预措施 Intervention = 锌 (Xin, Zinc) OR 补锌 (Buxin, diet supplementation) AND 研究类型 Study type= 干预性研究 (Ganyuxing Yanjiu, Interventional Study) 13

2. 1 AND (((注册题目 Public title= 新型冠状病毒(Xinxing Guanzhuang Bingdu, Coronavirus) OR 新冠病毒(Xinguan Bingdu, COVID-19 or SARS-Cov-2 or 2019-nCov) OR 新型冠状病毒肺炎(Xinxing Guanzhuang Bingdu Feiyan, Coronavirus pneumonia) OR 新冠肺炎(Xinguan Feiyan, Coronavirus pneumonia) OR SARS-CoV OR SARS OR MERS OR MERS-CoV OR 中东呼吸道综合征(Zhongdong Huxidao Zonghezheng, MERS OR MERS-CoV) OR 呼吸道感染(Huxidao Ganran, Respiratory Infections) OR 肺部感染(Feibu Ganran, Lung Inflammation) OR 肺炎(Feiyan, Pneumonia) OR 肺部炎症(Feibu Yanzheng, Pulmonary Inflammation)) OR (正式学科名 Scientific title= Coronavirus OR 新型冠状病毒(Xinxing Guanzhuang Bingdu, Coronavirus) OR 新冠病毒(Xinguan Bingdu, COVID-19 or SARS-Cov-2 or 2019-nCov) OR 新型冠状病毒肺炎(Xinxing Guanzhuang Bingdu Feiyan, Coronavirus pneumonia) OR 新冠肺炎(Xinguan Feiyan, Coronavirus pneumonia) OR SARS-CoV OR SARS OR MERS OR MERS-CoV OR 中东呼吸道综合征(Zhongdong Huxidao Zonghezheng, MERS OR MERS-CoV) OR 呼吸道感染(Huxidao Ganran, Respiratory Infections) OR 肺部感染(Feibu Ganran, Lung Inflammation) OR 肺炎(Feiyan, Pneumonia) OR 肺部炎症(Feibu Yanzheng, Pulmonary Inflammation))) 0

1.2 Search Update: Covid-19 Focused Only, June 2020

1.2.1 Clinical Trial Registries

Database: U.S. National Library of Medicine Register of Clinical Trials (ClinicalTrials.gov)

Searched: 17 June 2020

Results: n=15

Search:

Condition: “COVID-19” OR “SARS-CoV-2” OR “severe acute respiratory syndrome coronavirus 2” OR “2019-nCoV” OR “2019 novel coronavirus” OR “Wuhan coronavirus”

Other terms: zinc OR zn

Study type: Interventional (Clinical trial)

Databases: International Standard Randomized Controlled Trial Number Register (ISRCTN), and World Health Organization International Clinical Trials Registry Platform (WHO ICTRP)

Searched: 17 June 2020

Results: n=19

Search:

Condition: Coronavir* OR nCov OR covid OR "2019-nCoV infection”

Other terms: zinc OR zn

1.3 Search Update: Covid-19 Focused Only, August 2020

1.3.1 Main Databases

Database: PubMed

Searched: 19 August 2020

Results: n=16

Search:

(Coronaviridae[mh] OR Coronavir* OR nCov OR covid OR Coronaviridae Infections[mh] OR "Severe Acute Respiratory Syndrome" OR “Severe acute respiratory syndrome-related coronavirus” OR “Severe Acute Respiratory failure” OR “SARS”)

AND

(Zinc[mh] OR zinc OR zn)

AND

(randomized controlled trial[pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals [mh] NOT humans [mh])

Filters: from 2020 – 2020

Database: Embase (Ovid)

Searched: 19 August 2020

Results: n=2

Search:

1) (exp Coronaviridae/ OR exp Coronaviridae infection/ OR (Coronavir* OR nCov OR covid "Severe Acute Respiratory Syndrome" OR "Severe acute respiratory syndrome-related coronavirus" OR "Severe Acute Respiratory failure" OR SARS
2) (exp zinc/ OR (zinc OR zn).ti,ab,kw.)
3) (exp dietary supplement/ OR (supplement* OR deficiency OR additive* OR vitamin*).ti,ab,kw.)
4) 2 AND 3
5) (crossover-procedure/ OR double-blind procedure/ OR randomized controlled trial/ OR single-blind procedure/ OR (random* OR factorial* OR crossover* OR cross over* OR placebo* OR (doubl* adj blind*) OR (singl* adj blind*) OR assign* OR allocat* OR volunteer*).tw.
6) 1 AND 4 AND 5

Limited to 'past year'

Database: EBSCOhost (Academic Search Complete, Allied and Complementary Medicine Database(AMED), Alt HealthWatch, CINAHL Plus with Full Text, Health Source and PsycINFO)

Searched: 17 August 2020

Results: n=20

Search:

(Coronaviridae OR Coronavir* OR nCov OR covid OR Coronaviridae Infections OR "Severe Acute Respiratory Syndrome" OR "Severe acute respiratory syndrome-related coronavirus" OR "Severe Acute Respiratory failure" OR SARS)

AND

(Zinc OR zn)

AND

(Randomi*ed controlled trial OR controlled clinical trial OR randomi*ed OR placebo OR drug therapy OR randomly OR trial OR groups OR "comparative effectiveness")

Database: CKNI (Chinese Knowledge Database)

Searched: 11 August 2020

Results: n=0

Search:

Xinxing Guanzhuang Bingdu [su] (COVID-19 OR 2019-nCov OR SARS-Cov-2 OR Coronavirus) OR Xinguan Bingdu [su] (COVID-19 OR 2019-nCov OR SARS-Cov-2 OR Coronavirus) OR Xinxing Guanzhuang Bingdu [ti/ab] (COVID-19 OR 2019-nCov OR SARS-Cov-2 OR Coronavirus) OR Xinguan Bingdu [ti/ab] (COVID-19 OR 2019-nCov OR SARS-Cov-2 OR Coronavirus) OR Xinxing Guanzhuang Bingdu Feiyan [su] (coronavirus pneumonia) OR Xinguan Feiyan [su] (coronavirus pneumonia) Xinxing Guanzhuang Bingdu Feiyan [ti/ab] (coronavirus pneumonia) OR Xinguan Feiyan [ti/ab] (coronavirus pneumonia)

OR SARS-CoV [su] OR SARS [su] OR SARS-CoV [ti/ab] OR SARS [ti/ab])

AND

(Xin [su] (Zinc) OR Buxin [su] diet supplementation) OR (Xin [ti/ab] (Zinc) OR Buxin [ti/ab] diet supplementation)

AND

(Suiji [ft] (randomized controlled trials OR random*)) OR (linchuang shiyan [ti/ab] (clinical trial)) OR (shiyan [ti/ab] (trial)) OR (linchuang guancha [ti/ab] (clinical observation)) OR (linchuang yanjiu [ti/ab] (clinical investigation)) OR (anweiji [ti/ab] (placebo)) OR (duizhao [ti/ab] (control*))

Filters: from 2020 – 2020

Database: Cochrane Central Register of Controlled Trials (CENTRAL)

Searched: 17 August 2020

Results: n=13

Search:

(Coronaviridae[mh] OR Coronavir* OR nCov OR covid OR Coronaviridae Infections[mh] OR "Severe Acute Respiratory Syndrome" OR “Severe acute respiratory syndrome-related coronavirus” OR “Severe Acute Respiratory failure” OR “SARS”)

AND

(Zinc[mh] OR zinc OR zn)

Filters: from 2020 – 2020

1.3.2 Clinical Trial Registries

Database: U.S. National Library of Medicine Register of Clinical Trials (ClinicalTrials.gov)

Searched: 7 August 2020

Results: n=14

Search:

Condition: "COVID-19" OR "SARS-CoV-2" OR "severe acute respiratory syndrome coronavirus 2" OR "2019-nCoV" OR "2019 novel coronavirus" OR "Wuhan coronavirus"

Other terms: zinc OR zn

Study type: Interventional (Clinical trial)

First posted: 01 May 2020

Databases: International Standard Randomized Controlled Trial Number Register (ISRCTN), and World Health Organization International Clinical Trials Registry Platform (WHO ICTRP)

Searched: 7 August 2020

Results: n=29

Search:

Condition: Coronavir* OR nCov OR covid OR "2019-nCoV infection"

Other terms: zinc OR zn

Database: www.covid19-trials.org

Searched: 7 August 2020

Results: n=22

Search:

Terms: zinc OR zn

Database:Chinese Clinical Trial Registry

Searched: 11 August 2020

Results: n=0

Search:

1. 干预措施 Intervention = 锌 (Xin, Zinc) OR 补锌 (Buxin, diet supplementation) AND 研究类型 Study type= 干预性研究 (Ganyuxing Yanjiu, Interventional Study)

2. 1 AND (((注册题目 Public title= 新型冠状病毒(Xinxing Guanzhuang Bingdu, Coronavirus) OR 新冠病毒(Xinguan Bingdu, COVID-19 or SARS-Cov-2 or 2019-nCov) OR 新型冠状病毒肺炎(Xinxing Guanzhuang Bingdu Feiyan, Coronavirus pneumonia) OR 新冠肺炎(Xinguan Feiyan, Coronavirus pneumonia) OR SARS-CoV OR SARS OR MERS OR MERS-CoV OR 中东呼吸道综合征(Zhongdong Huxidao Zonghezheng, MERS OR MERS-CoV) OR 呼吸道感染(Huxidao Ganran, Respiratory Infections) OR 肺部感染(Feibu Ganran, Lung Inflammation) OR 肺炎(Feiyan, Pneumonia) OR 肺部炎症(Feibu Yanzheng, Pulmonary Inflammation)) OR (正式学科名 Scientific title= Coronavirus OR 新型冠状病毒(Xinxing Guanzhuang Bingdu, Coronavirus) OR 新冠病毒(Xinguan Bingdu, COVID-19 or SARS-Cov-2 or 2019-nCov) OR 新型冠状病毒肺炎(Xinxing Guanzhuang Bingdu Feiyan, Coronavirus pneumonia) OR 新冠肺炎(Xinguan Feiyan, Coronavirus pneumonia) OR SARS-CoV OR SARS OR MERS OR MERS-CoV OR 中东呼吸道综合征(Zhongdong Huxidao Zonghezheng, MERS OR MERS-CoV) OR 呼吸道感染(Huxidao Ganran, Respiratory Infections) OR 肺部感染(Feibu Ganran, Lung Inflammation) OR 肺炎(Feiyan, Pneumonia) OR 肺部炎症(Feibu Yanzheng, Pulmonary Inflammation))) 0

1.3.3 Preprint Repositories

Database: BioRxiv (https://www.biorxiv.org)

Searched: 7 August 2020

Results: n=50

Search:

Term "((COVID) OR (SARS)) AND (ZINC) AND (TRIAL)" and posted between "01 Jan, 2020 and 07 Aug, 2020"

Database: MedRxiv (https://www.medrxiv.org)

Searched: 7 August 2020

Results: n=54

Search:

Term "((COVID) OR (SARS)) AND (ZINC) AND (TRIAL)"

1.3.4 Other Sources

Bibliographies

Searched: 15 July 2020

Results: n=2

Appendix 2: Outcomes included, Covid-19 RCTs, Paediatric RTI RCTs, Excluded RCTs

CONTENTS

1 Critical and important outcomes

All studies
Critical
1. Change in health-related quality of life score
2. Number of participants with a severe adverse event
3. Number of participants with any adverse effects
4. Number of withdrawals from the study due to an adverse event
Important
5. Number of participants who experienced different types of adverse effects*
Prevention of viral respiratory tract infections (RTIs)
Critical

1. Number of participants with one or more RTIs (per person or person-months/years)
2. Number of RTIs (episodes)
3. All-cause mortality

Important

4. Number of RTI symptomatic days per person or episode
5. Severity of RTI symptoms*
6. Proportion of participants with complications from RTIs, including non-respiratory*
7. Proportion of participants with RTIs requiring hospital admission

Treatment of mild to moderate viral respiratory tract infections

Critical

1. Symptomatic survival (i.e. remaining symptomatic) from onset of symptoms
2. Symptom severity score at the time when symptoms most commonly peak for the specific viral infection (e.g. day 3 of symptoms for common cold [61])
3. Average daily symptom severity score during the study period
4. Complication-free survival (not progressing to severe/critical illness, non-respiratory complications*, or all-cause mortality) up to 60 days from onset of symptoms

Important

5. Number of days from onset of symptoms to symptomatic recovery from RTI or other non-respiratory complications
6. Number of days from onset of symptoms to negative PCR result
7. Number of participants with complications (e.g. progressing to severe/critical, non-respiratory complications, or deceased from any cause) during the study period
8. Number of participants requiring hospital admission

Treatment of severe to critical viral respiratory tract infections (RTI)

Critical

1. Overall survival (all-cause mortality) up to 60 days from study enrolment
2. All-cause mortality rate up to 60 days during study period
3. Complication-free survival (not progressing from severe to critical, requiring mechanical ventilation, or all-cause mortality) up to 60 days from study enrolment
4. Number of participants with complications (e.g. progressing from severe to critical, requiring mechanical ventilation, non-respiratory complications*, deceased from any cause) during the study period
5. Symptomatic survival (i.e. remaining symptomatic, including from non-respiratory complications*) from onset of illness

Important

6. Number of days on mechanical ventilation
7. Number of days requiring critical/intensive care
8. Number of days from study enrolment to symptomatic recovery from RTI or other non-respiratory complications
9. Number of days from study enrolment to negative PCR
10. Number of days from study enrolment to absorption/resolution of pulmonary infiltration

* added post-protocol following blinded feedback from consumer advocates

2 Studies pending results: Randomized control trials (RCTs) investigating zinc for SARS-CoV-2, registered on clinical trial registries.

2.1 Coronavirus 2019 (COVID-19) - Using Ascorbic Acid and Zinc Supplementation (COVIDAtoZ)

Registration no.	NCT04342728
Registration date	8 April 2020
Completion date	30 December 2020
Location	US
Setting	Community health clinics and hospital outpatients, Ohio and Florida
Design	Multicentre, open label RCT, 4 arms
Sample size	N=520
Demographics	Adults, including women of child-bearing potential
Inclusion criteria	Confirmed diagnosis of SARS-CoV-2 not requiring hospitalisation
Exclusion criteria	1. SARS-CoV-2 detected during hospitalisation 2. Pregnant and lactating 3. CKD 4. Liver disease (waiting transplant) 5. Calcium oxalate stones
Zinc intervention (elemental dose)	1. Zinc gluconate 50mg (7mg)/day for 28 days 2. Zinc gluconate 50mg (7mg)/day + vitamin C 8000mg /day for 28 days
Comparator	1. Usual (standard) care 2. Vitamin C alone
Primary Outcomes	Days to 50% reduction of symptoms
Secondary Outcomes	1. Symptom resolution (fever, cough, shortness of breath, fatigue) 2. Total symptom score on day 5 3. Hospitalisation 4. Adjunctive medicines 5. Adverse events
Follow-up time	28 days

2.2 High-dose intravenous zinc (HDIVZn) as adjunctive therapy in COVID-19 positive critically ill patients: A pilot randomized controlled trial

Registration no.	ACTRN12620000454976
Registration date	8 April 2020
Completion date	NI
Location	Australia
Setting	Austin Hospital, Victoria
Design	Pilot RCT
Sample size	N=160
Demographics	Adults
Inclusion criteria	Hospitalised with confirmed SARS-CoV-2 infection (PCR or other laboratory confirmed) of any duration. SaO2: ≤94% or Pao2:Fio2 ≤ 300 mg Hg. Ventilated or non-ventilated.
Exclusion criteria	1.CKD 2. Pregnant or lactating

	3. Allergy to Zinc 4. Severe hepatic impairment 5. eGFR ≤ 30 mL/min/1.73 m2 6. Organ transplant 7. CPR within 14 days 8. DNR or DNI orders 9. Imminent or inevitable death 10. Dialysis 11. HIV infection 12. Known or suspected history of oxalate nephropathy or hyperoxaluria, scurvy, chronic iron overload, G-6PD deficiency
Zinc intervention (elemental dose)	Zinc 0.5mg/kg/day intravenous infusion (saline 250ml/day) over 3-6 hrs for 7 days
Comparator	Saline solution 250ml/day infused over 3-6 hrs for 7 days
Primary Outcomes	For non-ventilated patients: mean change in the worst (highest) level of oxygenation (flow in litres/min). For ventilated patients: mean change in the worst (lowest) PaO2:FiO2(mmHg). Feasibility: blinding; drug availability; GCP; protocol compliance; costs; SOP
Secondary Outcomes	1.Mortality 2.Duration of mechanical ventilation 3.Duration of oxygen therapy
Follow-up time	28 days

2.3 HCQ and Zinc in the Prevention of COVID-19 Infection in Military Healthcare Workers (COVID-Milit)

Registration no.	NCT04377646
Registration date	4 May 2020
Completion date	31 July 2020 (not confirmed)
Location	Tunisia
Setting	Tunisia Military Academy
Design	Multicentre, double-blind RCT, 3 arms
Sample size	N = 660
Demographics	Military professionals aged 18-65
Inclusion criteria	At risk of infection by SARS-CoV-2 at 2 levels
Exclusion criteria	1. Allergy to medications 2. Heart rhythm disturbances 3. Severe hepatic impairment 4. Retinal pathology 5. Epilepsy 6. Myasthenia 7. Psoriasis 8. Methemoglobinemia 9. Porphyria 10. Pregnant or lactating women 11. Concomitant treatments
Zinc intervention (elemental dose)	Zinc capsules 15mg/day + HCQ 400mg on day 1 and 2 and HCQ 400mg/week for 2 months
Comparator	1. Placebo zinc, 1 per day for 28 days + HCQ 400mg on day 1 and 2 and 400mg/week for 2 months

	2. Placebo zinc, 1 each day + placebo HCQ on day 1 and 2 and weekly for 2 months
Primary Outcomes	Incidence of SARS CoV2 infection
Secondary Outcomes	1. Incidence of any COVID-19 related symptoms 2. Adverse events
Follow-up time	28 days

2.4 Hydroxychloroquine, Azithromycine and Zinc for the treatment of SARS-Cov2 infection in Senegal. (ESHAZ trial)

Registration no.	PACTR202005622389003
Registration date	14 May 2020
Completion date	NI
Location	Senegal
Setting	Community health centre – Centre for epidemic treatment, Aerogare Yoff, Health District of Yoff, Dakar
Design	RCT three arms
Sample size	N= 384
Demographics	Adults
Inclusion criteria	Patients confirmed SARS-CoV-2 infection less than 72 hours prior to randomisation without chronic disease and without danger signs (e.g. respiratory distress, requiring mechanical ventilation or supplemental oxygen, encephalitic disorders and/or renal function failure.
Exclusion criteria	1.Known allergy to any of the study medication 2.Pregnancy or breastfeeding 3.ECG abnormality at admission 4.Patients with ALAT/ASAT higher than 3 times the upper limit of normal on admission 5.Patients with known chronic kidney diseases 6.Patients with known retinal diseases.
Zinc intervention (elemental dose)	Zinc tablets: 20mg per day for 7 days
Comparator	1.Hydroxychloroquine: 600 mg daily for 6 days plus Azythromycine: 500 mg on day 1 followed by 250 mg daily from day 2 to day 5 2.Hydroxychloroquine: 400 mg daily for 6 days (200 mg twice per day) plus Azythromicine: 500 mg on day 1 followed by 250 mg from day 2 to day 5
Primary Outcomes	Percentage with undetectable viral load 7 days after treatment initiation.
Secondary Outcomes	Time to first PCR negative after treatment initiation. Biochemical parameters from baseline to day 7 after treatment initiation. Haematological parameters from baseline to day 7 after treatment initiation. Proportion with ECG abnormality after treatment initiation
Follow-up time	7 days

2.5 The effect of zinc on the treatment and clinical course of patients with SARS-cov2 (COVID-19)

Registration no.	IRCT20180425039414N2
Registration date	31 May 2020
Completion date	NI
Location	Iran
Setting	Amin Hospital, Isfahan
Design	Open label RCT, 2 arms
Sample size	N=80
Demographics	Adults
Inclusion criteria	Hospitalised with confirmed SARS-CoV-2 infection (RT, PCR and CT scan of the lungs). Blood oxygen levels: 90-3%; Breathing rate 20-24 breaths/min; Heart rate 100-130 bpm
Exclusion criteria	1.Intubation 2.Blood oxygen below 90% Breathing rate equal to 30 or more breaths per minute 3. Allergic to interventions 4.Cardiogenic pulmonary oedema associated shortness of breath 5.Pregnancy and lactation 6. Oxygen therapy at home 7. End stage lung, malignant, G6PD deficiency, diabetic ketoacidosis, cardiac arrhythmia
Zinc intervention (elemental dose)	Zinc tablets 440mg/day + HCQ sulphate tablets 400mg every 12 hours on day 1 and 200mg every 12 hours during hospitalisation
Comparator	HCQ sulphate tablets 400mg every 12 hours on day 1 and 200mg every 12 hours during hospitalisation.
Primary Outcomes	Clinical course defined as: 1. Resolution of symptoms (fever, shortness of breath, cough), SaO2 and hemodynamic parameters 2. Mortality 3. Days in hospital
Secondary Outcomes	None
Follow-up time	During hospitalisation

2.6 Zinc with chloroquine/hydroxychloroquine in treatment of COVID-19

Registration no.	NCT04447534
Registration date	23 June 2020
Completion date	1 October 2020
Location	Egypt
Setting	Tanta university hospital
Design	Phase 3, RCT double blind
Sample size	N= 200
Demographics	Adults (aged over 18 years) any gender
Inclusion criteria	Patients with positive COVID-19
Exclusion criteria	Contraindications or hypersensitivity to chloroquine.
Zinc intervention (elemental dose)	Zinc with Chloroquine NI
Comparator	Chloroquine alone
Primary Outcomes	The number of patients with mortality

	The number of patients with negative PCR
Secondary Outcomes	
Follow-up time	Two weeks
2.7 To study the role of Zinc combined with standard treatment for COVID-19	
Registration no.	CTRI/2020/07/026340
Registration date	2 July 2020
Completion date	NI
Location	India
Setting	Hospital
Design	RCT
Sample size	N= 100
Demographics	Adults
Inclusion criteria	Diagnosed with COVID-19
Exclusion criteria	1.Pregnant or lactating women 2. End stage CKD 3. Patients with dementia, learning disability, mental health needs 4. Unable to understand the procedures and protocol 5. Deemed unfit for the study according to the investigator
Zinc intervention (elemental dose)	Zinc sulphate 100mg once daily plus standard treatment NI
Comparator	Standard treatment alone
Primary Outcomes	Symptom severity reduction Duration of hospitalisation, ICU admission, ventilator requirement, complications, discharge timepoint: Baseline, day 1, day 5, day 7, day 14 or till discharge
Secondary Outcomes	Symptom resolution
Follow-up time	Day 1, day 5, day 7, day 14 or till discharge

6GPD Glucose-6-phosphate dehydrogenase deficiency**; CKD:** chronic kidney disease; **CPR** cardiopulmonary resuscitation; **CT** computerized tomography; **DNR** do not resuscitate; **DNI** do not intubate; **eGFR** estimated Glomerular Filtration Rate; **GCP:** Good Clinical Practice **FiO2** fraction of inspired oxygen**; HCQ:** hydroxychloroquine: **ICU:** intensive care unit; **NI:** no information**; PaO2** Partial pressure of oxygen; **PCR:** Polymerase Chain Reaction; **RCT:** randomised controlled trial; **RT** Rapid Test; **SaO2** Oxygen saturation; **SOP** standard operating procedures

3 Articles pending analysis: Randomized control trials (RCTs) investigating zinc for treatment or prevention of viral respiratory tract infections in children or adolescents

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4 Articles published in English that were excluded at full-paper screening

Each article is cited once and was categorised in the following order.

4.1 Reason for exclusion: study design

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Appendix 3: Characteristics of studies, funding of studies, risk of bias

CONTENTS

Table 1: Characteristics of studies

Study ID	**Country** **Setting** **Study design**	**Participants** **Age (mean ±SD)** ***Risk factors****	**Zinc Intervention (elemental dose/day)** **No. enrolled (CAA)**	**Comparator** **No. enrolled (CAA)**	**Outcomes assessed** ***Follow-up time***
SAFETY / TOLERABILITY ***Zinc verses placebo control***					
Silk 2005 [1]	US Community Single centre 2-arm RCT	Older adults Age: 60-91 years (68.4 ±7 yrs) *chronic diseases n=66*	Lozenge: zinc gluconate glycine (Cold-Eeze®) Zinc dose: <79.8mg/day *for 6 days* N=NI (33)	Placebo lozenge: NI *for 6 days* N=NI (33)	1. AEs: PRO assessed on day 7 and 14 2. Medications: day 7 and 14 3. Vital signs: day 1 and 7 4. AEs: laboratory tests (full blood count, electrolytes, kidney function, urine chemistry) on day 7 *14 days*
Al Nakib 1987 (C) [2]	UK Isolation unit Single centre 2-arm RCT	Healthy adults Age: 18-50 years (Zinc 31.5 yrs; Control 29.4 yrs) HRV-2 inoculation (n=10), placebo saline inoculation (n=8)	Lozenge: 23mg zinc gluconate 1 every 2 waking hours up to 12 daily (279mg) *from 24 hours prior to inoculation, for 5 days* N=7 (7)	Placebo lozenge: matched appearance, excipients 1 every 2 waking hours *from 24 hours prior to inoculation, for 5 days* N=11 (11)	1. Tolerability – taste 2. AEs (biochemical, haematological changes) *day 3-4*
PREVENTION ONLY ***Zinc verses placebo control***					
Prasad 2007 [3]	US Community Single centre 2-arm RCT	Older adults Age: 55-87 years (Zinc 65 ±9 yrs, Control 68 ±7 yrs) *>70 years age n=19* *influenza vaccine n=37* *chronic diseases n=9* *medications n=17*	Capsule: 15mg zinc gluconate 2 morning, 1 night 45mg / day *for 12 months* N=25 (24)	Placebo capsule: matched appearance, excipients 2 morning, 1 night *for 12 months* N=25 (25)	Incidence rate: 1. Any infection[4] 2. URTI: rhinitis, sinusitis, or bronchitis 3. Tonsillitis 4. Common cold: based on 7 symptoms 5. Cold sores 6. Flu-like illness 7. Fever (self-recall and nurse practitioner assessed)

		ethnicity: African American n=12, Hispanic n=1 Zinc deficiency excluded			8. Ex vivo generation of inflammatory markers and T cell cytokine production at 6 and 12 months 9. Plasma molecular markers of oxidative stress at 6 months 10. Plasma zinc at 12 months 11. AEs: plasma copper at 12 months *12 months*
Veverka 2009 [5]	US Air Force Academy Single centre 2-arm RCT	Healthy adults (Zinc 18.5 ±.9 yrs, Control 18.6 ±.8 yrs) Zinc deficiency excluded	Capsule: 15mg zinc gluconate 1 daily (15mg) *for 7 months* N=20 (15)	Placebo capsule: matched appearance 1 daily *for 7 months* N=20 (15)	1. Incidence: URTI, physician diagnosed 2. Incidence: Common cold according to weekly self-recall of 8 symptoms, 0-3 scale, as per Takkouche criteria[6] 2. Duration: weeks with self-reported symptoms 3. Plasma zinc at 7 months 4. AEs: plasma copper at 7 months 4. AEs: reported (ad hoc) for 7 months *7 months*
Wei 2009 [7]	China Army boot camp Single centre 2-arm RCT 2 parallel samples	Healthy males 18-22 years (Zinc 18.0 ±0.4 yrs, Control 18.0 ±0.4 yrs)	Nasal spray: zinc gluconate 0.29mg / spray 2 sprays, twice a day (1.15mg) *for 1 month* N=447 (386)	Placebo nasal spray: matched colour, smell, excipients 2 sprays, twice a day *for 1 month* N=454 (387)	Incidence of: 1. URTI: ≥2 days duration and ≥3 of 15 symptoms including appetite, nausea, vomiting or diarrhoea 2. Flu-like illness: fever >38.0C and sore throat or cough 3. AEs: PRO assessed daily *1 month*
Zhang 2009 [8]	China Community Single centre 2-arm RCT 4 parallel samples	Healthy adult college students (Zinc 19 ±1.5 yrs, Control 19 ±1.6 yrs)	Nasal spray: zinc gluconate 0.29mg / spray 2 sprays, twice a day (1.15mg) *for 1 month* N=1,000 (978)	Placebo nasal spray: matched excipients 2 sprays, twice a day *for 1 month* N=1,000 (967)	Incidence of: 1. URTI: ≥2 days duration and ≥3 of 11 symptoms 2. Flu-like illness: fever >37.8C and sore throat or cough (cited United States CDC definition) 3. AEs: PRO assessed daily *1 month*
PREVENTION & TREATMENT ***Zinc verses placebo control***					
Al Nakib 1987 (A) [2]	UK Isolation unit Single centre 2-arm RCT	Healthy adults Age: 18-50 years (Zinc 31.5 yrs Control 29.4 yrs) HRV-2 inoculation Clinical cold: investigator assessed	Lozenge: 23mg zinc gluconate 1 every 2 waking hours up to 12 daily (279mg) *from 24 hours prior to inoculation, for 5 days* N=29 (29) prevention N=6 (6) treatment	Placebo lozenge: matched appearance, excipients 1 every 2 waking hours *from 24 hours prior to inoculation, for 5 days* N=28 (28) prevention N=8 (8) treatment	1. Incidence: viral infection (HRV-2) isolated nasal swabs on day 3 and 7 and/or 4-fold rise in antibody titre on day 21 2. Incidence: clinical cold, investigator rated mild, moderate or severe 3. Severity: 4 symptoms, 0-3 scale, investigator rated daily for 6 days 4. Severity: daily nasal viral titres for 6 days 5. Severity: daily nasal mucus weight for 6 days 6. Severity: daily total tissue-count for 6 days 7. Zinc concentration: urine-analyses day 3-4 *21 days*
Farr 1987 (A) [9]	US Hotel isolation Single centre 2-arm RCT	Healthy adults (Zinc 21.4 ±2.4 yrs. Control 20.6 ±1.9 yrs.) Clinical cold following HRV-39	Lozenge: 23mg zinc gluconate (citric acid) up to 8 / day (184mg)	Placebo lozenge: citric acid, matched appearance. up to 8 / day *from 36 hours after inoculation for 5 days*	1. Incidence: viral infection (HRV-39) isolated nasal swabs on days 2 to 7 and/or 4-fold rise in antibody titre on day 21 2. Incidence clinical cold,[10] investigator rated

		inoculation: symptoms as per Jackson criteria,[10] or subjective belief of having a cold	*from 36 hours after inoculation for 5 days* N=13 (13) cold symptoms	N=12 (12) cold symptoms	3. Duration: viral shedding on days 2-7 4. Severity: 7 symptoms, 0-3 scale,[10] investigator rated daily on days 1-7, self-reported on days 8-14 5. Severity: nasal mucus weight on days 1-7 6. Severity: daily tissue counts on days 1-5 7. Serum zinc and biochemistry, blood count, urinalysis on day 7 8. AEs: serum copper on day 7 9. AEs: daily PRO assessed daily on days 1-7 and exit interview between day 8 to 14 *21 days*
Farr 1987 (B) [9]	US Hotel isolation Single centre 2-arm RCT	Healthy adults (Zinc 21.1 ±2.2 yrs. Control 21.1 ±2.8 yrs.) Clinical cold following HRV-13 inoculation: symptoms as per Jackson criteria,[10] or subjective belief of having a cold	Lozenge: 23mg zinc gluconate (citric acid) up to 8 / day (184mg) *from 2 hours after inoculation for 7 days* N=NI (13) treatment	Placebo lozenge: matched appearance up to 8 / day *from 2 hours after inoculation for 7 days* N=NI (16) treatment	1. Incidence: viral infection (HRV-39) isolated nasal swabs on days 2 to 7 and/or 4-fold rise in antibody titre on day 21 2. Incidence clinical cold,[10] investigator rated 3. Duration: viral shedding on days 2-8 4. Severity: 7 symptoms, 0-3 scale,[10] investigator rated twice daily for 7 days, and self-rated following discharge on days 9-14 5. Severity: daily viral nasal titres days 2-8 6. Severity: nasal mucus weights for 7 days 7. Serum zinc and biochemistry, blood count, urinalysis on day 7 8. AEs: serum copper on day 7 9. AEs: PRO assessed daily for 7 days 7 *days*
Turner 2001 [11]	US Community Single centre 2-arm RCT	Healthy adults inoculated with HRV-23 (n=56) or HRV-39 (n=35)	Nasal gel: zinc gluconate (Zicam®) 33 mM 120 µL / squirt 2 squirts 5 x day (2.6mg) *from 3 days prior to inoculation for 5 days* N=41 (41) prevention N=30 (30) treatment	Placebo nasal gel: matched appearance, excipients 2 squirts 5 x day *from 3 days prior to inoculation for 5 days* N=50 (50) prevention N=36 (36) treatment	1. Incidence: viral infection (HRV23 or HRV39) isolated from nasal lavage on days 0-5, or 4-fold rise in antibody titre on day 21 2. Incidence: clinical cold total, investigator assessed symptom score ≥6 plus 3 days rhinorrhoea, or self-determined diagnosis 3. Severity: 8 symptoms, 0-4 scale, investigator rated daily for 5 days 4. Severity: nasal viral titre, daily for 5 days 5. AEs: PRO assessed daily for 5 days *21 days*
TREATMENT ONLY ***Zinc verses active control***					
Turner 2000 (A)[12]	US Hotel isolation Multi centre 4-arm RCT	Healthy adults Age: 18-65 years HRV-39 inoculation Clinical cold: total daily symptom score ≥3 within 48 hrs of inoculation,	Lozenge: Arm-1 zinc gluconate 13.3mg (Cold-Eeze®), Arm-2 zinc acetate 5mg, Arm-3 zinc acetate 11.5mg 1 every 2 waking hours	Placebo lozenge: unmatched, quinine hydrochloride, tannic acid, sucrose octaacetate, sugar, glucose syrup 1 every 2 waking hours	1. Duration: time up to 14 days, until two consecutive symptom scores ≤1 within 24 hours 2. Severity: 7 symptoms, 0-4 scale, self-rated twice daily for up to 14 days 3. Severity: viral IL-8 concentrations in nasal lavage, daily for 5 days (post hoc, at one centre only)

		investigator assessed. (N=273 randomised, confirmed HRV infection n=118)	up to 6 daily (79.8mg) *from 24-48 hours after inoculation until asymptomatic or for 14 days* N=NI (Arm-1=69, Arm-2=66, Arm-3=70)	*from 24-48 hours after inoculation until asymptomatic or for 14 days* N=NI (67)	4. AEs: PRO assessed from day 1 of intervention for up to 14 days *19 days*
Turner 2000 (B)[12]	US Community Multi centre 4-arm RCT	Healthy adults Age: 18-65 years Common cold: ≥ 2 of 10 symptoms for ≤ 36 hours, investigator assessed (N=281 randomised)	Lozenge: Arm-1 zinc gluconate 13.3mg (Cold-Eeze®), Arm-2 zinc acetate 5mg, Arm-3 zinc acetate 11.5mg 1 every 2 waking hours up to 6 / day (79.8mg) *until asymptomatic or for 14 days* N=NI (Arm-1=68, Arm-2=72, Arm-3=68)	Placebo lozenge: unmatched, tannic acid, sucrose octaacetate, sugar, glucose syrup, quinine hydrochloride 1 every 2 waking hours *until asymptomatic or for 14 days* N=NI (71)	1. Duration: time up to 14 days, until two consecutive symptom scores ≤1 within 24 hours 2. Severity: 7 symptoms, 0-4 scale, self-rated twice daily for up to 14 days 3. AEs: PRO assessed from day 1 for up to 14 days *14 days*
Yao 2005[13]	China Multi-centre 2-arm RCT	Healthy adults Age: 18-65 years (Zinc 37.3 ±13.1 yrs Control 35.9 ±13.2 yrs) Common cold: ≥ 2 of 8 symptoms for ≤ 36 hours	Nasal spray: zinc gluconate 1 spray every 2 hours 5 x day (zinc dose uncertain) *for 3 days until asymptomatic or up to 5 days* N=75 (70)	Nasal spray: naphazoline hydrochloride 2 sprays every 4 hours for 3 times daily *for 3 days until asymptomatic or up to 5 days* N=76 (73)	1. Duration: days until asymptomatic for each symptom, up to 5 days 2. Duration: number of participants asymptomatic for each symptom by day 5 3. Severity: 8 symptoms, 0-3 scale, self-rated daily for up to 5 days 4. Severity: number of participants ≥ 50% improvement in total symptom score over 5 days 5. AEs: Laboratory tests (blood and urine biochemistry, full blood count) 6. AEs: PRO assessed daily for up to 5 days *5 days*
TREATMENT ONLY ***Zinc verses placebo control***					
Al Nakib 1987 (B) [2 14]	UK Isolation unit Single centre 2-arm RCT	Healthy adults Age: 18-50 years HRV-2 inoculation Common cold: onset <24 hours after inoculation	Lozenge: 23mg zinc gluconate 1 every 2 waking hours up to 12 per day (276mg) *from 24 hours after inoculation, for 6 days* N=6 (6)	Placebo lozenge: citric acid, matched appearance. 1 every 2 waking hours *from 24 hours after inoculation for 6 days* N=6 (6)	1. Severity: 4 symptoms, 0-3 scale, investigator rated on days 2-7 2. Severity: nasal mucus weight on days 2-7 3. Severity: total issue count on days 2-7 4. Severity: viral shedding on days 3 and 7 5. Severity: psychomotor performance assessed with 4-choice reaction time task before inoculation and when symptomatic. *7 days*
Belongia 2001 [15]	US Community Single centre 2-arm RCT	Healthy adults (Zinc 40 ±11 yrs. Control 38 ±11 yrs.) Common cold: 2 of 8 symptoms for 24 hours, or 1 symptom for ≤	Nasal spray: zinc sulfate heptahydrate (isotonic) 0.011mg / spray 2 sprays 4 x day (0.09mg)	Placebo nasal spray: matched excipients 2 sprays 4 x day *until asymptomatic or for 14 days* N=79 (79)	1. Duration: days until symptom score ≤ 1 for 2 consecutive days, up to 14 days 2. Severity: 8 symptoms, 0-3 scale,[10] self-rated twice daily for up to 14 days

		48 hours (Rhinovirus n=6, Parainfluenza virus n=1, Respiratory syncytial virus n=2) *Medications n=91*	*until asymptomatic or for 14 days* N=81 (81)		3. Severity: daily decongestant medication over 14 days or until asymptomatic 4. Medication use: decongestants, cough medicines, combination cold medication over 14 days 4. AEs: PRO assessed twice daily up to 14 days *14 days*
Douglas 1987 [16]	Australia Community Single centre 2-arm RCT	Healthy adults (Zinc 30.7 yrs. Control 35.6 yrs.) URTI: ≥ 2 of 8 symptoms for 24 hours, or 1 symptom for 48 hrs (Rhinovirus n=6, Influenza A n=2, Adenovirus n=1, negative viral culture n=51)	Lozenge: 10mg zinc acetate (tartaric acid, sodium bicarbonate) 1 every 2 waking hours up to 8 per day (80mg) Av. daily dose: ~64mg[17] *from symptom onset for 3 days* *until asymptomatic or 6 days* N=35 (33)	Placebo lozenge: sodium acetate 1 every 2 waking hours *from symptom onset for 3 days* *until asymptomatic or 6 days* N=35 (30)	1. Duration: days until asymptomatic 2. Severity: 8 symptoms, 0-3 scale,[10] self-rated daily for 3 days until asymptomatic or up to 6 days 3. Duration: days with symptoms over 6 months (winter in 1984) 4. AEs: PRO assessed on day 14 following each RTI episode and at 6 months *6 months*
Eby 1984 [18]	US Community Single centre 2-arm RCT	Healthy children & adults Age: 11-62 years (Zinc: 35.6 ±2.2 yrs. Control: 38 ±2.8 yrs.) UTRI: symptoms ≤ 72 hours, physician diagnosed	Lozenge: 23mg zinc gluconate (dicalcium phosphate, cellulose, sodium starch glycolate, magnesium stearate) 2 every 2 waking hours up to 12 daily (276mg) Av. daily dose:~207mg[17] *until asymptomatic for 6 hours or for 7 days* N=54 (37)	Placebo lozenge: matched appearance, excipients 2 every 2 waking hours up to 12 daily *until asymptomatic for 6 hours or for 7 days* N=39 (28)	1. Duration: days until asymptomatic, up to 7 days 2. Severity: 10 symptoms, 0-3 scale, self-rated daily for up to 7 days (results not reported) 3. AEs: PRO assessed daily for up to 7 days, reviewed by physician at day 7 *7 days*
Eby 2006 [19]	US Community Single centre 2-arm RCT	Healthy older children & adults Age: 9-66 years (Zinc 38.8 yrs. Control 37.4 yrs.) Common cold: ≥2 of 10 symptoms and ≥1 nasal symptom, for ≤ 72 hours, physician diagnosed	Lozenge: 37mg zinc orotate and Nasal spray: zinc gluconate 10mM / spray 1 lozenge every 2 - 3 hours and 6 sprays every 15 - 30 minutes when awake (300mg) *until asymptomatic or for 7 days* N = 25 (17)	Placebo lozenge: calcium lactate, matched for appearance, excipients 1 lozenge every 2 - 3 hours and 6 sprays every 15 - 30 minutes when awake *until asymptomatic or for 7 days* N = 22 (16)	1. Duration: days until asymptomatic, up to 7 days 2. Severity: 10 symptoms, 0-3 scale, self-rated daily for up to 7 days 3. AEs: PRO assessed for up to 6 days, reviewed by physician at 7 days *7 days*
Godfrey 1992 [20]	US Community Single centre 2-arm RCT	Healthy adults Age 18-40 years (median age Zinc 21.2 yrs. Control 20.1 yrs.) Common cold: health practitioner diagnosed	Lozenge: 23.7mg zinc gluconate (glycine, tannic acid) 1 every 2 waking hours up to 8 daily (189.6mg) Av. daily dose: 192mg	Placebo lozenge: matched appearance, flavour, excipients 1 every 2 waking hours up to 8 daily *until asymptomatic for 48 hours or for 10 days*	1. Duration: days until asymptomatic, up to 10 days 2. Severity: 10 symptoms, 0-3 scale, self-rated daily for up to 10 days 3. AEs: PRO assessed daily for up to ten days *10 days*

		≤ 48 hours symptoms	*until asymptomatic for 48 hours or for 10 days* N=43 (35)	N=42 (28)	
Hemilä 2020 [21]	Finland Community Single centre 2-arm RCT	Healthy adults (Zinc 48 ±9 yrs. Control 46 ±10 yrs.) Common cold: self-determined *History ≥ 1 cold/winter* *Asthma n=27*	Lozenge: 13mg zinc acetate (isomaltulose, sorbitol, magnesium stearate, sucralose) up to 6 daily (78mg) *from symptom onset for 5 days* N=45 (45)	Placebo lozenge: sucrose octa-acetate matched appearance, flavour. up to 6 daily *from symptom onset for 5 days* N=42 (42)	1. Duration: days until symptom severity score 1 or 0 (12 symptoms, 0-3 scale, self-rated daily), up to 10 days or until asymptomatic)2. Fever ≥37.5°C any time during the day) (Yes / No), up to 2wks*** 3. Sickness absence from work, up to 1 month*** 4. Antibiotic, asthma medication use, up to 1 month*** 5. Complications: sinusitis, bronchitis, otitis, up to 1 month*** 6. AEs: PRO assessed daily up to 10 days *1 months*
Hirt 2000 [22]	US Community Single centre 2-arm RCT	Healthy adults Common cold: ≥ 3 of 9 symptoms for ≤ 24 hours	Nasal gel: zinc gluconate (Zicam®) 33 mM 120 µL / squirt 2 squirts 4 x day (2.1mg) *until asymptomatic or for 14 days* N=108 (108)	Placebo nasal gel: matched appearance, excipients 2 squirts 4 x day *until asymptomatic or for 14 days* N=105 (105)	1. Duration: days until asymptomatic, up to 14 days 2. Severity: 9 symptoms, 0-3 scale, self-rated daily (results not reported) 3. AEs: PRO assessed daily up to 14 days *14 days*
Mossad 1996 [23]	US Community Single centre 2-arm RCT	Healthy adults Age: 21-69 years (Zinc 37.9 ±9.2 yrs. Control 37.5 ±7.5 yrs.) Common cold: ≥ 2 of 10 symptoms for ≤ 24 hours	Lozenge: 13.3mg zinc gluconate trihydrate (glycine, amino-acetic acid). 1 every 2 waking hours, ≥4 daily (≥53.2mg) Av. daily dose: ~79.8mg, *until asymptomatic or for 18 days* N=50 (50)	Placebo lozenge: matched appearance, flavour, calcium lactate pentahydrate 1 every 2 waking hours, *until asymptomatic or for 18 days* N=50 (50)	1. Duration: days until symptom score ≤1, up to 18 days 2. Severity: 10 symptoms, 0-3 scale, self-rated daily for up to 18 days 3. Medication use: paracetamol use whilst symptomatic 4. AEs: PRO assessed daily and within one day of being asymptomatic up to 18 days *18 days*
Mossad 2003 [24]	US Community Single centre 2-arm RCT	Healthy adults Age: 21-40 years (median: Zinc 29 yrs. Control 26 yrs.) Common cold: ≤ 48 hours symptoms, physician diagnosis (Rhinovirus n=27, Parainfluenza n=1, Influenza n=2, no virus isolated n=48)	Nasal gel: zinc gluconate (Zicam®) 33 mM 120 µL / squirt 2 squirts 4 x day (2.1mg) plus paracetamol if needed for temperature control *until asymptomatic for 48 hours or for 10 days* N=40 (40)	Placebo nasal gel: matched appearance & excipients 2 squirts 4 x days plus paracetamol if needed for temperature control *until asymptomatic for 48 hours or for 10 days* N=40 (38)	1. Duration: days until asymptomatic, up to 10 days 2. Severity: 10 symptoms, self-rated 0-3[10] twice daily until symptom resolution or up to 10 days 3. Medication use: paracetamol and other cold medication use over 10 days 4. AEs: PRO assessed daily for up to 10 days and at exit interview *10 days*
Petrus 1998 [25]	US Community Single centre 2-arm RCT	Healthy adults Age: 18-54 years (Zinc 26.7 ±1.3 yrs. Control 26.2 ±1.2 yrs.) Common cold: ≥ 2 of 11	Lozenge: 9mg zinc acetate (dextralose) 1 every 1.5 waking hours for 1 day, then second hourly Av. daily dose: ~ 89.1mg	Placebo lozenge: sucrose octa-acetate matched appearance, flavour. 1 every 1.5 waking hours for 1 day, then second hourly	1. Duration: days until asymptomatic, up to 14 days 2. Severity: 11 symptoms, 0-3 scale, self-rated daily for up to 14 days 3. AEs: PRO assessed daily up to 14 days *14 days*

		symptoms, duration not reported	*until asymptomatic or for 14 days* N=52 (52)	*until asymptomatic or for 14 days* N=49 (48)	
Prasad 2000 [26]	US Community Single centre 2-arm RCT	Healthy adults Age: >18 years (Zinc 36.4 ±11.1 yrs. Control 37.8 ±10.9 yrs) Common cold: ≥ 2 of 11 symptoms for ≤ 24 hours	Lozenge: 12.8mg zinc acetate dihydrate (silica gel, dextrose, glycerol monostearate) 1 every 2-3 waking hours Av. daily dose: ~80mg *until asymptomatic or for 12 days* N=25 (25)	Placebo lozenge: sucrose octa acetate, matched for flavour, texture, appearance, excipients. 1 every 2-3 waking hours *for until asymptomatic or for 12 days* N=25 (23)	1. Duration: days until asymptomatic, up to 12 days 2. Severity: 11 symptoms, 0-3 scale, self-rated daily for up to 12 days 3.Severity: plasma cytokines day 1, and when asymptomatic or day 12 4. Serum zinc day 1 and when asymptomatic or day 12 5. AEs: PRO assessed at trial exit interview: asymptomatic or day 12 *12 days*
Prasad 2008 [27]	US Community Single centre 2-arm RCT	Healthy adults Age: >18 years (Zinc: 34.5 ±14.1 yrs. Control 35.5 ±13.4 yrs) Common cold: ≥ 2 of 10 symptoms for ≤ 24 hours	Lozenge: 13.3mg zinc acetate (sucrose, corn syrup) 1 every 2-3 waking hours Av. daily dose: ~92mg *until asymptomatic or for 8 days* N=25 (25)	Placebo lozenge: octa-acetate, matched for appearance, flavour, excipients. 1 every 2-3 waking hours, *until asymptomatic or for 8 days* N=25 (25)	1. Duration: days until symptom score ≤1, up to 8 days 2. Severity: 10 symptoms, 0-3 scale, self-rated daily for up to 8 days 3.Severity: plasma cytokines: day 1, asymptomatic or day 8 4. Serum zinc day 1, asymptomatic or day 8 5. AEs: PRO assessed at trial exit: asymptomatic or day 8 *8 days*
Smith 1989 [28]	US Community Single centre 2-arm RCT	Healthy adults Age: >18 years (Zinc 26.7 ±1.3 yrs. Control: 26.2 ±1.2 yrs.) Acute URTI: clinical diagnosis, duration not reported	Lozenge: 11.5mg zinc gluconate (mannitol, sorbitol) 4 stat, then 1 every 2 waking hours (≥ 115mg daily) *until asymptomatic or for 7 days* N=88 (53)	Placebo lozenge: unmatched 4 stat, then 1 every 2 waking hours *until asymptomatic* or *for 7 days* N=86 (57)	1. Duration: days until asymptomatic, up to 7 days 2. Severity: 11 symptoms, 0-3 scale, self-rated daily for up to 7 days 3. AEs: PRO assessed daily for up to 7 days *7 days*
Weismann 1990 [29]	Denmark Community Single centre Quasi-RCT**	Healthy adults Age: 18-65 years Common cold: ≤ 24 hours; NI case definition *History of common cold in cold season*	Lozenge: 4.5mg zinc gluconate (maltitol) 1 every 1-1.5 waking hours, up to 10 daily (45mg) *from symptom onset until asymptomatic or for 10 days* N=77 (69)	Placebo lozenge: matched appearance, excipients 1 every 1-1.5 waking hours, up to 10 daily *from symptom onset until asymptomatic or for 10 days* N=68 (61)	1. Duration: days until asymptomatic, up to 10 days 2. Severity: overall condition severity, with 11cm VAS (visual analogue scale), self-rated daily for 10 days reviewed by physician at 10 days 3. AEs: PRO assessed daily for 10 days, reviewed by physician at 10 days *10 days*

* *a priori* risks groups listed are people with low zinc status and/or increased SARS-CoV-2 morbidity risk; ** non-random allocation of participants to zinc or placebo study design confirmed by Hemilä 2011[17] who contacted the author; *** according to registered protocol NCT03309995, however, results were not reported. **AEs:** Adverse event; s**CCA:** completed cases analysed**; ±SD:** standard deviation; **Av. daily dose:** calculated from the average number of lozenges taken by participants in the zinc group as reported in the manuscript or by Hemilä 2011[17] who contacted the authors. **CDC:** Centres for Disease Control and Prevention, United States; **HRV:** human rhinovirus; **NI:** no information; **PRO:** participant/patient reported outcome; **RD:** recommended dose **RCT:** randomised controlled trial; **URTI:** upper respiratory tract infection

Table 2: Funding of studies

First author / year	Funding: study	Funding: intervention / placebo
Al Nakib 1987 [2 14]	NI: study conducted by the MRC Common Cold Unit, Salisbury, UK	Donated by RBS Pharma, Milan
Belongia 2001 [15]	CNS Inc., Minneapolis, Minnesota	
Douglas 1987 [16]	NI	Supplied by Fauldings Ltd.
Eby 1984 [18]	NI: lead author owner of George Eby Research, US	Supplied by Truett Laboratories
Eby 2006 [19]	Lead author is owner of George Eby Research, US. No outside financial support. 1 year remaining of patent right for zinc acetate lozenges.	
Farr 1987 [9]	Supported in part by Bristol Myers Products, Hillside, New Jersey, US and scholarship awarded by Milbank Memorial Fund, New York, US	
Godfrey 1992 [20]	Godfrey Science & Design, Inc., Huntingdon Valley, Pennsylvania, US. and a grant from Rorer Pharmaceutical Corp., Fort Washington, Pennsylvania, US.	
Hemilä 2020 [21]	Investigator-initiated trial NordForsk (75021) Academy of Finland (311492)	Donated by the University Pharmacy, Helsinki, Finland.
Hirt 2000 [22]	NI	NI
Mossad 1996 [23]	General Pediatrics Research Fund and Departments of infectious Diseases and General Pediatrics of the Cleveland Clinic Foundation, US. Godfrey, J.C. and N.J. gave input on study design, manuscript review.	Becton Dickinson, New Jersey, US supplied the digital thermometers. Quigley Corporation Pennsylvania, US supplied the intervention and placebo. McNeil, Pennsylvania, US supplied acetaminophen.
Mossad 2003 [24]	Gel Tech LLC, California, US. The company manufactures Zicam® Authors state the company approved the publication, yet did not participate in the study design, analysis or reporting results.	
Petrus 1998 [25]	Weider Nutrition International, Utah, US	
Prasad 2000 [26]	Grant support from George and Patsy Eby Research Foundation, US (Note: George Eby held US patent rights for the zinc acetate lozenges	
Prasad 2007 [3]	NIH grant no. 5 RO1 A150698-04 Oral glass thermometers supplied by Becton Dickinson, California, US	Supplied by Labcatal Laboratories, Paris, France
Prasad 2008 [27]	National Institutes of Health (grant 5 R01 A150698–04); partial untied support by George and Patsy Eby Research Foundation, US to Wayne State University, US.	George Eby (who also held the US patent rights for the zinc acetate lozenges)
Silk 2005 [1]	NI	NI
Smith 1989 [28]	Grant from McNeil Consumer Products Company, US.	
Turner 2000 (A) [12]	Funded by Warner Lambert Consumer Healthcare and coordinated by New Jersey Research Testing Laboratories, Inc., in Hackensack, New Jersey, US	
Turner 2000 (B) [12]	Funded by Warner Lambert Consumer Healthcare and coordinated by TKL Research, Inc., in Paramus, New Jersey, US	
Turner 2001 [11]	Gel Tech, LLC, Woodland Hills, California, US	
Veverka 2009 [5]	Air Force Office of Scientific Research	
Wei 2009 [7]	Army Medical Science and Technology Research in 'The Eleventh Five-Year Plan' Project (06G026), China	
Weismann 1990 [29]	NI	Supplied by Kirsten B. Stæhr, A/S Alfred Benzon, Helseholmen 1, DK-2650 Hvidovre.
Yao 2005 [13]	NI	NI
Zhang 2009 [8]	NI specific for funding. The study was conducted at Langfang Medical College, Hebei Province, China. Affiliation for first author was Chinese Center for Disease Control and Prevention, Chinese Field Epidemiology Training Program.	

NI: no information

Figure 1: Risk of bias for each outcome category

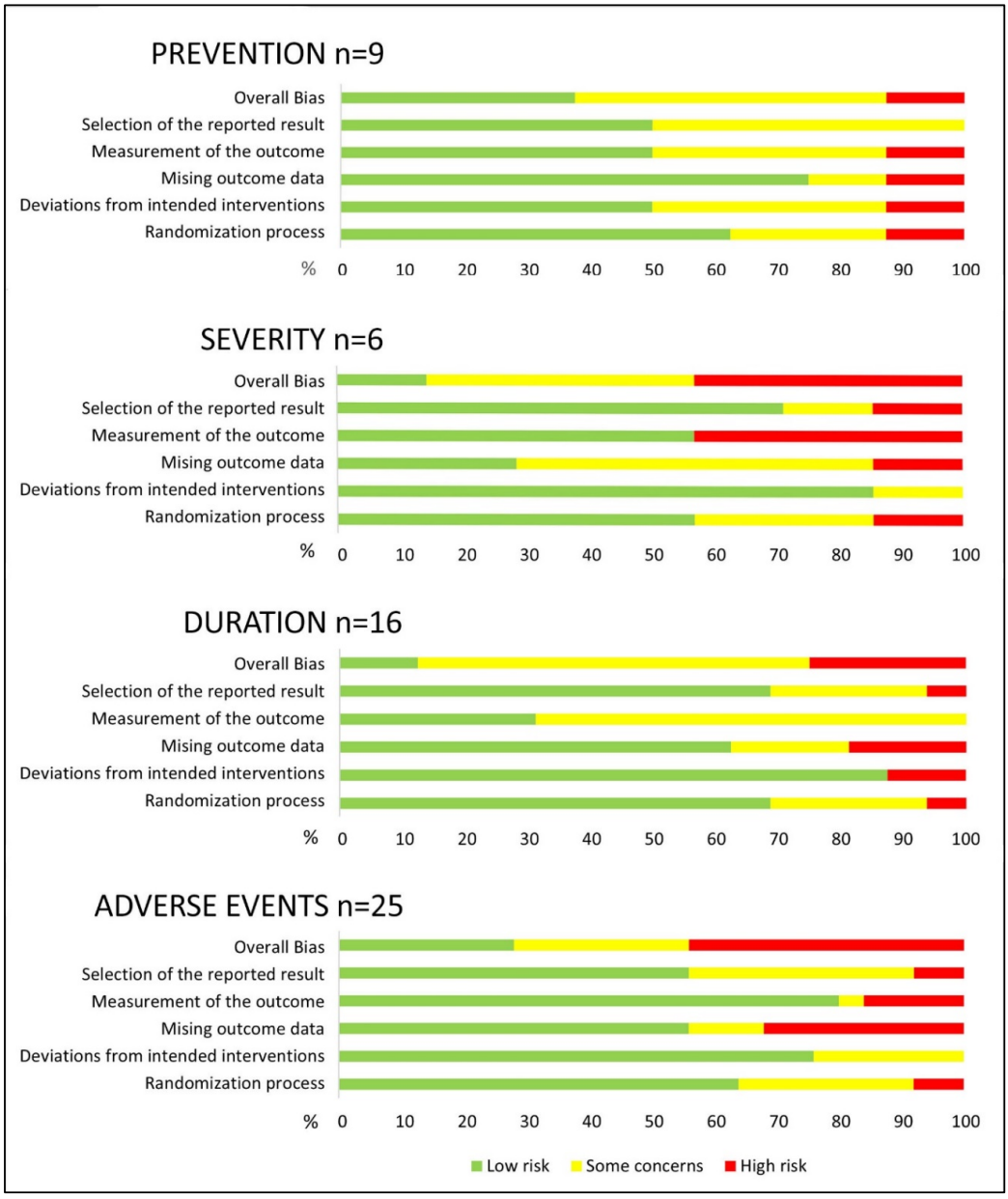

Table 3: Risk of bias for each study outcome

(see footnote for details of prespecified additional considerations and parameters used for RoB 2.0 assessment[30])**Study**	**Intervention**	**Control**	**1) Randomization process**	**2) Deviations from intended interventions**	**3) Missing outcome data**	**4) Measurement of the outcome**	**5) Selection of the reported result**	**OVERALL RISK OF BIAS**	**Comments**
AlNakib 1984 (A)[2]	Sublingual lozenge / placebo	Prevention	Low	Low	Low	Low	Low	**Low**	
AlNakib 1984 (B)[2]	Sublingual lozenge / placebo	Prevention	Low	Low	Low	Low	Low	**Low**	
AlNakib 1984 (C)[2]	Sublingual lozenge / placebo	Adverse events	Low	Low	Low	Low	**High**	**High**	5) Non-specific results were narrated only, no numerical data reported
Belongia 2001[15]	Nasal spray / placebo	Adverse events	Low	Low	Low	Low	Low	**Low**	
Belongia 2001[15]	Nasal gel / placebo	Duration	Low	Low	Low	Low	Low	**Low**	
Belongia 2001[15]	Nasal gel / placebo	Severity	Low	Low	**Some**	Low	Low	**Some**	3) Low participant MOD (1/161), however, MOD for daily multiple severity PROM not reported
Douglas 1987[16]	Sublingual lozenge / placebo	Adverse events	Low	**Some**	**High**	**High**	Low	**High**	2) mITT analysis for AE outcome; 15/55 assigned more than once so risk of residual effects, and then may self-prescribe if they think they received placebo. 3) High MOD: 8 participant MOD > 5 events. 4) Recall bias: AE assessed at 2 wks
Douglas 1987[16]	Sublingual lozenge / placebo	Duration	Low	**High**	**Some**	**Some**	Low	**High**	2) Per-protocol analysis, 10% excluded from analysis for non-adherence. 3) Mod-low drop out; NI about MOD from symptom questionnaire. 4) Blinding OK; Higher AE in zinc group may unmask blinding, unlikely to bias subjective reporting of duration.

Eby 1984[18]	Sublingual lozenge / placebo	Adverse events	**High**	Low	**High**	Low	**High**	**High**	1) NI allocation concealment, enrolment on site, >10% more allocated to zinc group and higher symptom severity at baseline in placebo group. Correlation analysis for severity - no impact on duration, only partially reported. 3) High MOD ~34 participant MOD = 33 events; 5) Post hoc changes declared, yet still only reported some of the results in detail
Eby 1984[18]	Sublingual lozenge / placebo	Duration	**High**	Low	**High**	**Some**	**High**	**High**	1) NI allocation concealment, enrolment on site, >10% more allocated to zinc group and higher symptom severity at baseline in placebo group; correlation analysis for severity only partially reported no impact on duration. 3) High MOD ~50% MOD. 4) Higher AE in zinc group may unmask blinding, subjective outcome, possible unmasking unlikely to overly bias ascertainment of symptom duration. 5) Post hoc changes declared, yet still only reported some of the results in detail
Eby 1984[18]	Sublingual lozenge / placebo	Severity	**High**	Low	**High**	**High**	**High**	**High**	1) NI allocation concealment, enrolment on site, >10% more allocated to zinc group and higher symptom severity at baseline in placebo group. 3) High MOD ~50% MOD. 4) Higher AE in zinc group may unmask blinding, likely to bias subjective reporting of symptom severity. 5) Post hoc changes declared, yet still only reported some of the results in detail
Eby 2006[19]	Sublingual lozenge / placebo & nasal spray	Adverse events	**Some**	Low	**High**	Low	**Some**	**High**	1) NI about randomization schedule, allocation internal by one physician; no significant baseline differences. 3) High 30% MOD, AE for some dropouts included, however, MOD still greater than no. events. 5) no protocol.
Eby 2006[19]	Sublingual lozenge & nasal spray / placebo	Duration	**Some**	Low	**High**	**Some**	**Some**	**High**	1) NI about randomization schedule, allocation internal by one physician; no significant baseline differences. 3) High 50% MOD. 4) Blinding OK, Higher AE in zinc group may unmask blinding, unlikely to bias subjective reporting of duration. 5) no protocol
Farr 1987 (A)[9]	Sublingual lozenge / placebo	Adverse events	Low	Low	Low	Low	Low	**Low**	
Farr 1987 (A)[9]	Sublingual lozenge / placebo	Prevention	Low	Low	Low	Low	Low	**Low**	
Farr 1987 (A)[9]	Sublingual lozenge / placebo	Severity	Low	Low	Low	Low	Low	**Low**	
Farr 1987 (B)[9]	Sublingual lozenge / placebo	Adverse events	Low	Low	Low	Low	Low	**Low**	
Farr 1987 (B)[9]	Sublingual lozenge / placebo	Prevention	Low	Low	Low	Low	Low	**Low**	
Godfrey 1992[20]	Sublingual lozenge / placebo	Adverse events	Low	Low	**Some**	Low	Low	**Some**	3) low-moderate MOD, 9 participant MOD, 34 events, however, unclear if 1 participant who dropped out due to nausea was included.

Godfrey 1992[20]	Sublingual lozenge / placebo	Duration	Low	Low	**Some**	**Some**	Low	**Some**	3) Moderate participant MOD, similar between groups. 4) Blinding OK. Higher AE in zinc group may unmask blinding, unlikely to bias subjective reporting of duration.
Hemilla 2020[21]	Sublingual lozenge / placebo	Adverse events	Low	Low	Low	Low	Low	**Low**	
Hemilla 2020[21]	Sublingual lozenge / placebo	Duration	Low	Low	Low	**Some**	Low	**Some**	4) Blinding OK. Higher AE in zinc group may unmask blinding, however, sensitivity analysis no significant difference to result.
Hirt 2000[22]	Nasal gel / placebo	Adverse events	**Some**	Low	Low	Low	Low	**Some**	1) NI randomisation, concealment, and baseline differences.
Hirt 2000[22]	Nasal gel / placebo	Duration	**Some**	Low	Low	Low	Low	**Some**	1) NI randomisation, concealment, and baseline differences.
Mossad 1996[23]	Sublingual lozenge / placebo	Adverse events	Low	Low	Low	Low	Low	**Low**	
Mossad 1996[23]	Sublingual lozenge / placebo	Duration	Low	Low	Low	**Some**	Low	**Some**	4) Blinding OK. Sensitivity analyses of non-adherence (High AE) - no change to results
Mossad 2003[24]	Nasal gel / placebo	Adverse events	Low	Low	Low	Low	**Some**	**Some**	5) No protocol reported
Mossad 2003[24]	Nasal gel / placebo	Duration	Low	Low	Low	Low	**Some**	**Some**	5) No protocol reported
Petrus 1998[25]	Sublingual lozenge / placebo	Duration	**Some**	Low	Low	**Some**	Low	**Some**	1) NI randomisation and concealment details. No baseline differences between groups. 4) Adequacy of blinding not assessed. Higher AE in zinc group may unmask blinding, unlikely to bias subjective reporting of duration.
Petrus 1998[25]	Sublingual lozenge / placebo	Severity	**Some**	Low	**Some**	**High**	Low	**High**	1) NI randomisation and concealment details. No baseline differences between groups. 3) Low participant MOD, however, NI MOD for daily symptom severity PROM 4) Adequacy of blinding not assessed. Higher AE in zinc group may unmask blinding, likely to bias subjective reporting of symptom severity.
Prasad 2000[26]	Sublingual lozenge / placebo	Adverse events	Low	Low	Low	**High**	Low	**High**	4) Recall bias AEs only assessed at end of study
Prasad 2000[26]	Sublingual lozenge / placebo	Duration	Low	Low	Low	Low	Low	**Low**	
Prasad 2000[26]	Sublingual lozenge / placebo	Severity	Low	Low	**Some**	Low	Low	**Some**	3) NI MOD from multiple daily symptoms PROM

Prasad 2007[3]	Oral capsule / placebo	Adverse events	**Some**	Low	Low	Low	**Some**	**Some**	1) Random assignment in blocks of 2. Allocation concealed in sealed envelopes. NI about onsite or remotely administered allocation. 5) No reported protocol
Prasad 2007[3]	Oral capsule / placebo	Prevention	**Some**	Low	Low	Low	**Some**	**Some**	1) Random assignment in blocks of 2. Allocation concealed in sealed envelopes. NI about onsite or remotely administered allocation. 5) No reported protocol
Prasad 2008[27]	Sublingual lozenge / placebo	Adverse events	Low	Low	Low	**High**	**Some**	**High**	4) Recall bias AEs only assessed at end of study. 5) No protocol reported
Prasad 2008[27]	Sublingual lozenge / placebo	Duration	Low	Low	Low	Low	**Some**	**Some**	5) No protocol reported
Prasad 2008[27]	Sublingual lozenge / placebo	Severity	Low	Low	**Some**	Low	**Some**	**Some**	3) NI MOD from multiple daily symptoms PROM. 5) No protocol reported
Silk 2005[1]	Sublingual lozenge / placebo	Adverse events	Some	Low	**High**	**Some**	**Some**	**High**	3) High MOD - 9 lost f/u, 11 events. 4) Recall bias for PROM only asked weekly, however, low risk of bias for clinical examinations and laboratory tests. 5) No protocol reported
Smith 1989[28]	Sublingual lozenge / placebo	Adverse events	Low	Low	**High**	Low	Low	**High**	2) mITT analysis for AE outcome 3) High MOD - 68 participant MOD, 34 events.
Smith 1989[28]	Sublingual lozenge / placebo	Duration	Low	**High**	**High**	**Some**	Low	**High**	2) Per-protocol analysis, 38% excluded from analysis for non-adherence. 3) High MOD 39% 4) Blinding OK; Higher AE in zinc group may unmask blinding, unlikely to bias subjective reporting of duration.
Turner 2000 (A)[12]	Sublingual lozenge / matched active control	Adverse events	Low	Low	Low	Low	Low	**Low**	
Turner 2000 (A)[12]	Sublingual lozenge / matched active control	Duration	Low	Low	Low	**Some**	Low	**Some**	4) Blinding OK. Higher AE in zinc group may unmask blinding, unlikely to bias subjective reporting of duration.
Turner 2000 (B)[12]	Sublingual lozenge / matched active control	Adverse events	Low	Low	Low	Low	Low	**Low**	
Turner 2000 (B)[12]	Sublingual lozenge / matched active control	Duration	Low	Low	Low	**Some**	Low	**Some**	4) Blinding OK. Higher AE in zinc group may unmask blinding, unlikely to bias subjective reporting of duration.
Turner 2001[11]	Nasal gel / placebo	Adverse events	**Some**	**Some**	Low	Low	Low	**Some**	1) NI randomisation process or allocation concealment, no baseline differences. 2) per protocol analysis, however, only 1 participant excluded

Turner 2001[11]	Nasal gel / placebo	Prevention	**Some**	**Some**	Low	**Some**	Low	**Some**	1) NI randomisation process or allocation concealment, no baseline differences. 2) per protocol analysis, however, only 1 participant excluded. 4) Blinding OK. Higher AE in zinc group may unmask blinding, unlikely to bias ascertainment of any symptoms
Turner 2001[11]	Nasal gel / placebo	Severity	**Some**	**Some**	Low	**High**	Low	**High**	1) NI randomisation process or allocation concealment, no baseline differences. 2) per protocol analysis, however, only 1 participant excluded 4) Blinding OK. Higher AE in zinc group may unmask blinding, could still bias subjective symptoms severity reporting.
Ververka 2009[5]	Oral capsule / placebo	Adverse events	**High**	**Some**	**High**	**High**	**Some**	**High**	1) Quasi-randomised: last number of each cadet's social security number may reveal allocation to participants. 2) placebo group may self-prescribe OTC, serum zinc increased equally in both placebo and zinc groups suggesting possible non-protocol contamination, however, less likely to bias AE outcome 3) High MOD - 10 participant MOD, 9 events. 4) Except for 10 participants who dropped out, ascertainment of AE required participant to book consultation with physician 5) No protocol reported
Ververka 2009[5]	Oral capsule / placebo	Prevention	**High**	**High**	**High**	**High**	**Some**	**High**	1) Quasi-randomised: last number of each cadet's social security number may reveal allocation to participants. 2) placebo group may self-prescribe OTC, serum zinc increased equally in both placebo and zinc groups suggesting possible non-protocol contamination 3) High MOD - 10 participant MOD, 9 events. 4) Ascertainment of RTI required participant to book consultation with physician 5) No protocol reported
Wei 2009[7]	Nasal spray / placebo	Adverse events	Low	**Some**	**High**	Low	**Some**	**High**	2) per protocol analysis, no. excluded for non-adherence not reported. 3) High MOD: 128 participant MOD, 47 events, equal proportion groups. 5) No protocol reported
Wei 2009[7]	Nasal spray / placebo	Prevention	Low	**Some**	**Some**	**Some**	**Some**	**Some**	2) per protocol analysis, no. excluded for non-adherence not reported. 3) Moderate MOD, 128 participant MOD, 255 events, equal proportion groups. 4) Adequacy of blinding not assessed. Higher AE in zinc group may unmask blinding, unlikely to bias subjective reporting of symptoms and ascertainment of infection. 5) No protocol reported
Weismann 1990[29]	Sublingual lozenge / placebo	Adverse events	**Some**	Low	**Some**	Low	Low	**Some**	1) NI Randomisation and concealment. Interventions prepared externally so probably concealed and randomized; however, physicians were directly recruiting via their clinics. 3) Moderate MOD: 14 participant MOD, 36 events. Equal proportion groups.
Weismann 1990[29]	Sublingual lozenge / placebo	Duration	**Some**	Low	**Some**	**Some**	**Some**	**Some**	1) NI Randomisation and concealment. Interventions prepared externally so probably concealed and randomized; however, physicians were directly recruiting via their clinics. 3) Moderate-high 10% participant MOD, balanced groups. 4) Adequacy of blinding not assessed. Higher AE in zinc group could unmask blinding, unlikely to bias subjective reporting of duration. 5) Survival curve is presented in Fig 1. Inferential tests are not reported; however, the negative findings are narrated in detail, including "stressing that zinc did not shorten the duration of the disease."
Yao 2005[13]	Nasal spray / active control unmatched	Adverse events	**Some**	**Some**	**High**	Low	**Some**	**High**	1) NI about allocation concealment. 2) per protocol analysis, however, only 1/151 participants excluded non-adherence. 3) High MOD: 8 participant MOD, 8 events. 5) No protocol reported
Zhang 2009[8]	Nasal spray / placebo	Adverse events	Low	**Some**	**Some**	Low	**Some**	**Some**	2) per protocol analysis, NI no. excluded for non-adherence, however, overall MOD is low. 3) Moderate MOD: 55 participant MOD, 105 events, balanced between groups 5) No protocol reported
Zhang 2009[8]	Nasal spray / placebo	Prevention	Low	**Some**	Low	**Some**	**Some**	**Some**	2) per protocol analysis, NI no. excluded for non-adherence, however, overall MOD is low. 4) Adequacy of blinding not assessed. Higher AE in zinc group may unmask blinding, unlikely to bias subjective reporting of infection. 5) No protocol reported

AE: adverse events; **MOD:** missing outcome data; **mITT:** modified intention to treat analysis; **Additional prespecified considerations and parameters used for the RoB 2.0 assessment.**[30] **1. Randomisation process:** *Q 1.2. Allocation concealment:* (PN) block sizes of 2, 4, 6, or 8 and not remotely allocated; (PN) allocation on-site and no information about allocation concealment; (PN) allocated according to a number pre-known to investigators/participants (e.g. Military ID number, DoB, enrolment date). *Q 1.3 Imbalances suggest a problem*: (PY) Higher number of participants in the intervention arm (n>10%) and/or significant prognostic baseline characteristics favour the intervention (e.g. age, symptom severity at enrolment, history recurrent RTI, asthma, allergies, smoking) **2. Deviations from intended interventions:** *Q 2.1 Aware of allocation*: (PY) blinded, however, possible to guess (e.g. unmatched placebo/comparator OR difference in AEs for zinc sublingual/nasal – nose/mouth/taste symptoms, sublingual/oral zinc – nausea/GI symptoms) and adequacy of blinding was not assessed. Q *2.2 Deviations from assignment not consistent with protocol:* Short-term non-serious RTI (PN) acute treatment, short-term prevention, as unlikely that participant would self-prescribe OTC zinc; Long-term non-serious RTI (PY) if contamination not assessed, or zinc levels not monitored as more incentive to self-prescribe OTC zinc; COVID-19 (PY or NI) higher risk of deviations from intended interventions due to seriousness of infection. If community setting: participant can easily access zinc or other OTC, and the fear of deterioration is a strong incentive to self-prescribe. If hospital setting: practitioners may prescribe pharmaceuticals not consistent with trial protocol. (PN) only if contamination/deviations reported and are low. *Q 2.6 Appropriate analysis:* (Y) intention-to-treat (ITT) or modified intention-to-treat (mITT) analysis. *Q 2.7 Impact of inappropriate analysis:* (Y, PY) if >5-10% participants inappropriately analysed/excluded especially if imbalanced, or rare outcome. **3. Missing outcome data (MOD)** Two types of MOD were considered. 1) MISSING PARTICIPANT DATA (MPD): for rare events: low MOD must have zero MPD; for common events/ dichotomous/ categorical outcomes: low MOD no. events substantially higher than MPD, moderate MOD no. events at least double MPD, high MOD no. events almost equal to or less than MPD; for continuous outcomes: low MOD < 5% MPD, moderate MOD ≤10% MPD, high MOD >10% MPD. 2) MISSING DATA POINTS (MDP): if not reported and no sensitivity analysis for imputed data, assume low MOD for i) single question, ii) multiple questions asked only once, iii) multiple questions asked over multiple time-points when the response is recoded into binary outcome (e.g. symptomatic recovery, any adverse event, incidence), iv) daily symptom severity questions were collected by an investigator and the participant was on site in a dedicated trial setting (e.g. motel, research unit), or v) participants with incomplete data excluded from analysis (this is already accounted for in participant MOD). **4. Measurement of the outcome** *Q 4.1 Inappropriate measurement:* (PN) if symptom severity questionnaire unreferenced but description matches the validated assessment tool. *Q 4.3 Assessor aware*: see Q 2.1 re: adequacy of blinding for different zinc/control interventions. For participant reported adverse events (AEs) (N) if either adequacy of blinding was assessed and preserved, or the placebo intervention was matched. *Q 4.5 Likely to influence measurement: Subjective* clinical assessment (PN) double-blind study design (as unmasking of participants unlikely to bias), Participant reported outcomes (PRO) & partially matched control (PN) no difference in AEs; or higher AEs in zinc group, however, blinding tested and intact; (PN) sensitivity analysis. **5. Selection of the reported result:** *Q 5.1 Analysis according to protocol:* (Y) published pre-2002 and sufficient details reported in methods

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Appendix 4: Meta-analysis and other calculations

CONTENTS

FIGURES

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1 FURTHER DETAILS OF METHODS

The protocol was first registered on PROSPERO CRD42020182044.[1] Following feedback from our content experts who at that stage were blinded to the search results, amendments were made pre-data extraction and a revised protocol was submitted for publication (Supplementary file: protocols).[2] This included expanding the inclusion criteria from only including RTIs that can be caused by a coronavirus to RTIs caused by any virus (e.g. rhinovirus inoculation), tightening the exclusion criteria to exclude respiratory illnesses not predominantly caused by viral infections (e.g. pneumonia in adults) unless a viral infection is confirmed, and finalising the measures of effect to be extracted for the *a priori* outcomes. For pragmatic reasons, the *post hoc* decision was made to only extract data for adult populations.

RevMan 5.4,[3] R software,[4 5] Microsoft Excel, and GRADEpro GDT[6] were used for the statistical analyses. Irrespective of statistical heterogeneity, due to considerable clinical and methodological heterogeneity random effects models were used for all meta-analyses.

The effect measures for dichotomous outcomes were risk ratios, calculated using the Mantel-Haenszel method. Events measured over different timeframes were calculated and reported as the incidence rate per person-months (Table 6.6), from which incidence rate ratios (IRR) and rate differences (RD) were estimated using an inverse variance method. Studies reporting separate counts for different types of viral RTIs (e.g. common cold, bronchitis, flu-like illness) were combined to calculate the total number of RTIs. In one RCT there were no moderate RTI events in the zinc arm.[7] In another RCT there were no adverse events (AEs) in the zinc arm.[8] In both instances, it was not a rare event, the study arm sizes were balanced, there was only one zero cell in the meta-analysis, and meta-analysis heterogeneity was acceptable. Therefore, as per Cochrane guidance, 0.5 was recorded to facilitate analysis.[9]

For continuous data, either the weighted or standardised mean differences were calculated using the generic inverse variance method. Day-3 mean symptom severity scores were transformed to a modified Jackson common cold scale (Table 6.2).[10] For the secondary outcome, mean days duration, data was not imputed and instead extracted from published systematic reviews who had performed the calculations or contacted the authors (Table 6.5).[11-13] For the 4-arm RCT (Table 4.2), as per the preferred approach recommended in the Cochrane Handbook,[9] the three zinc arms were combined and the SD was calculated with RevMan. To allow comparisons of zinc doses and salts, the number of participants in the placebo arms were divided into thirds. A sensitivity analyses compared the two approaches (Table 4.2, Analysis 4.2.7). Rapid review constraints included not imputing missing data for any secondary outcome such as mean days duration, and not

contacting the authors. Instead, additional information from previous systematic reviews was extracted (Table 6.5).[11-13]

For time-to-event data, hazard ratios (HR) were calculated using an O-E variance method. Data extracted from survival curves with WebPlotDigitizer Version 4.2[14] (Table 6.5) was imputed for the first seven days using the direct method 10 in the 'HR calculations spreadsheet' published by Tierney et al.[15] The other option was the direct method 11. that used less of the data that was extracted. Sensitivity analysis confirmed the effect estimate was relatively stable and that method 10 was the more conservative approach (Table 4.1, Analysis 4.1.8). For the two 4-arm RCTs (Table 4.2), the three zinc arms were combined. It was not possible to accurately divide the daily survival counts for the placebo groups into thirds. This unaddressed correlation was ignored to allow comparisons of zinc doses and salts and a sensitivity analysis compared the two approaches (Table 4.2, Analyses 4.2.4 and 4.2.5.). The sensitivity analysis found an insignificant conflation from the unaddressed correlation arising from the unit-of-analysis error (Table 4.2, Analysis 4.2.7).

When data from at least 10 studies were pooled, publication bias was assessed with visual inspection of contour-enhanced funnel plots (Figures 1, 2, and 3) and statistically analysed using Egger's regression for continuous outcomes and the Harbord score for dichotomous outcomes.[16] Due to ongoing methodological uncertainties no statistical test was used for hazard ratio outcomes.[16 17]

A priori subgroup analyses were conducted for different ages groups, RTI causes and severity, and zinc administration routes, salts, and doses. Zinc doses were converted to milligrams (mg) of elemental zinc per day (Table 6.1). *A priori* subgroup analyses compared ages groups, RTI causes and severity, and zinc administration routes, salts, and doses. *Post hoc* subgroup analyses compared days symptomatic prior to study enrolment and study definitions of symptomatic recovery. To investigate potential dose effects of oral or sublingual zinc, the chi² test comparing three categories (<50mg daily, 50-200mg daily, >200mg daily) was used for dichotomous and time-to-event data. The categories were selected *post hoc* based on a no observed adverse effect level (NOAEL) of 50mg and a higher risk of more severe adverse effects, such as vomiting, with doses above 225mg.[18]

A priori sensitivity analyses investigated the point estimate and 95% CI changes when study outcomes with a higher RoB and statistical outliers were removed. *Post hoc* sensitivity analyses investigated the analytical decision zero with 0.5 for person-time rates (Analyses 2.1.7., 2.1.8., 5.2.6., 5.2.7.), the impact of reclassifying the control lozenge containing an unspecified amount of quinine as a placebo control (Analysis 4.1.9.) and combining the three zinc arms and dividing the placebo arms of the two 4-arm RCTs (Analysis 4.2.7).

Statistical heterogeneity was assessed using the Cochrane Q test and I^2 statistic that were interpreted according to guidelines from the Cochrane Handbook (0–40%: might not be important; 30–60%: may represent moderate heterogeneity; 50–90%: may represent substantial heterogeneity; 75–100%: considerable heterogeneity).[9] When statistical heterogeneity was identified, we explored possible explanations with subgroup and sensitivity analyses.

For symptom severity on day-3 for mild RTIs, the MID for mean difference was *post hoc* set at 1 point on a standardized scale (Analysis 6.3).[19 20] For the purpose of estimating an absolute effect from zinc use, the probability of remaining symptomatic on day-7 was set *post hoc* at 33% for the placebo and active controls.[21]

2 META-ANALYSIS RESULTS: PREVENTION

2.1 Pre-exposure prevention (1 – 12 months) of community acquired respiratory tract infections (RTIs): Zinc vs. placebo

Outcome	Studies	Participants (person months)	Statistical Method	Effect estimate [95% CI]	P value	I^2
2.1.1 Risk of any respiratory tract infection (RTI) per person-months						
Incidence RTIs [7 8 22 23]	4	2804 (3565)	IRR (IV, R)	**0.68 [0.58, 0.80]**	**<0.001**	0%
			IRD (IV, R)	**-0.05 [-0.08, -0.01]**	**0.01**	**63%***
2.1.2 Risk of a mild symptoms only (e.g. common cold) per person-months						
Incidence mild RTIs [7 22 23]	3	2767 (3306)	IRR (IV, R)	**0.72 [0.61, 0.85]**	**<0.001**	0%
			IRD (IV, R)	**-0.05 [-0.07, -0.02]**	**0.02**	7%
2.1.3 Risk of a moderately severe symptoms (e.g. flu-like illness) per person-months						
Incidence moderate RTIs [7 22 23]	3	2767 (3306)	IRR (IV, R)	**0.13 [0.04, 0.38]**	**<0.001**	0%
			IRD (IV, R)	**-0.01 [-0.02, -0.01]**	**<0.001**	0%
2.1.4 Risk of RTIs in low & high-risk age groups per person-months						
Incidence RTIs young adults [8 22 23]	3	2755 (2977)	IRR (IV, R)	**0.70 [0.59, 0.82]**	**<0.001**	0%
Incidence RTIs older adults [7]	1	49 (588)	IRR (IV, R)	**0.38 [0.16, 0.91]**	**0.03**	n/a
Test for subgroup differences: $Chi^2 = 1.91$, df = 1 (P = 0.17), $I^2 = 47.6\%$						
Incidence RTIs young adults [8 22 23]	3	2755 (2977)	IRD (IV, R)	-0.05 [-0.11, 0.00]	0.07	**79%***
Incidence RTIs older adults [7]	1	49 (588)	IRD (IV, R)	**-0.04 [-0.07, -0.01]**	**0.02**	n/a
Test for subgroup differences: $Chi^2 = 0.20$, df = 1 (P = 0.65), $I^2 = 0\%$						
2.1.5 Risk of RTIs according to zinc administration route and daily dose per person-months						
Incidence RTIs 45 mg oral [7]	1	49 (588)	IRR (IV, R)	**0.38 [0.16, 0.91]**	**0.03**	n/a
Incidence RTIs 15 mg oral [8]	1	30 (259)	IRR (IV, R)	1.06 [0.29, 3.96]	0.09	n/a
Incidence RTIs 1.2 mg topical nasal spray [22 23]	2	2718 (2718)	IRR (IV, R)	**0.69 [0.59, 0.81]**	**<0.001**	0%
Test for subgroup differences: $Chi^2 = 2.30$, df = 2 (P = 0.32), $I^2 = 13.0\%$						

2.1.6 Sensitivity analysis: risk of bias						
Incidence RTIs: some concerns RoB [7 22 23]	3	2767(3306)	IRR (IV, R)	**0.68 [0.56, 0.81]**	**<0.001**	0%
Incidence mild RTIs	*Not relevant: the three studies do not have high risk of bias*					
Incidence moderate RTIs	*and all three studies have some concerns*					
Incidence RTIs older adults	*Not relevant: only one study with some concerns*					
Incidence young adults: some concerns RoB [22 23]	2	2718 (2718)	IRR (IV, R)	**0.69 [0.59, 0.81]**	**<0.001**	0%

RTI: Respiratory tract infection, **HRV:** Human rhinovirus, **CI:** Confidence interval, **IRR:** Incidence rate ratio, **IRD:** Incidence rate difference, **IV:** Inverse variance method, **R:** Random effects model, **I^2:** % variation due to heterogeneity, *I^2 P value ≤ 0.05, **I^2 P value ≤ 0.01, ***I^2 P value ≤ 0.001

2.2 Prevention of RTIs caused by human rhinovirus (HRV) inoculation: short-term (2 – 36 hours) Zinc vs. placebo

Outcome	Studies	Participants	Statistical Method	Effect estimate [95% CI]	P value	I^2
2.2.1 Risk of clinical cold per person PrEP or PEP						
Incidence clinical cold [24-26]	4	221	RR (M-H, R)	0.96 [0.77, 1.21]	0.75	0%
2.2.2 Risk of laboratory confirmed HRV infection per person PrEP or PEP						
Incidence infection [24-26]	4	221	RR (M-H, R)	1.00 [0.91, 1.10]	0.93	0%
2.2.3 Risk of clinical cold per person PrEP						
Incidence clinical cold [24 26]	2	148	RR (M-H, R)	1.05 [0.69, 1.60]	0.82	0%
2.2.4 Risk of laboratory confirmed HRV infection per person PEP						
Incidence infection [24 26]	2	148	RR (M-H, R)	1.00 [0.85, 1.17]	1.00	10%
2.2.5 Risk of clinical cold per person PEP						
Incidence clinical cold [25]	2	73	RR (M-H, R)	0.92 [0.66, 1.29]	0.64	34%
2.2.6 Risk of laboratory confirmed HRV infection per person PrEP						
Incidence infection [25]	2	73	RR (M-H, R)	1.01 [0.89, 1.14]	0.90	0%
2.2.7 Sensitivity analysis: risk of bias						
Not relevant, the study outcomes do not have high risk of bias						

HRV: Human rhinovirus, **PrEP:** Pre-exposure prophylaxis, PEP**:** Post-exposure prophylaxis, **CI:** Confidence interval, **RR:** Risk ratio, **M-H:** Mantel-Haenszel method, **R:** Random effects model, **I^2:** % variation due to heterogeneity, *I^2 P value ≤ 0.05, **I^2 P value ≤ 0.001

3 META-ANALYSIS RESULTS: TREATMENT OF SYMPTOM SEVERITY

3.1 Symptom severity of mild to moderate RTI: Zinc vs. placebo

Outcome	Studies	Participants	Statistical Method	Effect estimate [95% CI]	P value	I^2
3.1.1 Symptom severity at the peak of infection: composite score on day 3 of common colds						
Mean day 3 score [26-30]	5	392	MD (IV, R)	**-1.20 [-1.74, -0.67]**	**<0.001**	0%
3.1.2 Symptom severity per day: average daily composite score						
Mean av. daily score [25 26 31]	3	195	SMD (IV, R)	-0.15 [-0.43, 0.13]	0.31	0%

3.1.3 Symptom severity at the peak of infection (day 3) according to type of infection						
Mean day 3 score community acquired [27-30]	4	323	MD (IV, R)	**-1.36 [-2.14, -0.58]**	**0.001**	0%
Mean day 3 score HRV inoculation [26]	1	69	MD (IV, R)	**-1.05 [-1.80, -0.30]**	**0.006**	n/a
Test for subgroup differences: Chi² = 0.33, df = 1 (P = 0.57), I² = 0%						
Mean av. daily score community acquired [31]	1	101	SMD (IV, R)	-0.31 [-0.71, 0.08]	0.12	n/a
Mean av. daily score HRV inoculation [25 26]	2	94	SMD (IV, R)	0.03 [-0.38, 0.44]	0.88	0%
Test for subgroup differences: Chi² = 1.43, df = 1 (P = 0.23), I² = 29.9%						
3.1.4 Symptom severity according to administration route						
Mean day 3 score sublingual lozenge [27-29]	3	163	MD (IV, R)	**-1.66 [-2.65, -0.66]**	**0.001**	0%
Mean day 3 score topical nasal [26 30]	2	229	MD (IV, R)	**-1.01 [-1.65, -0.37]**	**0.002**	0%
Test for subgroup differences: Chi² = 1.14, df = 1 (P = 0.3), I² = 12.2%						
Mean av. daily score sublingual lozenge [25 31]	2	126	SMD (IV, R)	-0.12 [-0.66, 0.42]	0.65	42%
Mean av. daily score topical nasal [26]	1	69	SMD (IV, R)	-0.06 [-0.53, 0.42]	0.81	n/a
Test for subgroup differences: Chi² = 0.03, df = 1 (P = 0.86), I² = 0%						
3.1.5 Sensitivity analyses: risk of bias						
Mean day 3 score: some concerns RoB [28-30]	3	258	MD (IV, R)	**-1.19 [-2.05, -0.33]**	**0.007**	0%
Mean av. daily score: some concerns RoB [25]	1	25	SMD (IV, R)	0.27 [-0.51, 1.06]	0.50	n/a

RTI: Respiratory tract infection, **HRV:** Human rhinovirus, **CI:** Confidence interval, **av.:** average, **MD:** Mean difference, **SMD:** Standardised mean difference **IV:** Inverse variance method, **R:** Random effects model, **I²:** % variation due to heterogeneity, *I^2 P value ≤ 0.05, **I^2 P value ≤ 0.01, ***I^2 P value ≤ 0.001

4 META-ANALYSIS RESULTS: DURATION OF SYMPTOMS

4.1 Duration of symptoms from community acquired RTIs: Zinc vs. placebo

Outcome	Studies	Participants	Statistical Method	Effect estimate [95% CI]	P value	I^2
4.1.1 Likelihood on any given day of symptomatic recovery from mild RTIs (up to 7 days)						
Symptomatic risk [a 27 29 30 32-38]	10	1023	HR (IV, R)	**1.83 [1.07, 3.13]**	**0.03**	**82%*** **
			Absolute effect [b]	**0.19 [0.02,0.38]**		
4.1.2 Mean duration (days) of symptoms from community acquired mild RTIs						
Mean duration (days) [27-31 34-40]	12	1180	MD (IV, R)	**-2.05 [-3.50, -0.59]**	**0.006**	**97%*** **

4.1.3 Duration according to administration route						
Symptomatic risk [a] sublingual lozenge [27 29 32 33 36-38]	7	572	HR (IV, R)	1.43 [0.85, 2.40]	0.18	**69%****
Symptomatic risk [a] topical nasal [30 34 35]	3	451	HR (IV, R)	3.38 [0.79, 14.45]	0.10	**93%*****
Test for subgroup differences: $Chi^2 = 1.20$, df = 1 (P = 0.27), $I^2 = 17.0\%$						
Mean duration (days) sublingual lozenge [27-29 31 36-40]	9	729	MD (IV, R)	**-1.84 [-3.08, -0.59]**	**0.004**	**90%****
Mean duration (days) topical nasal [30 34 35]	3	451	MD (IV, R)	-2.88 [-6.61, 0.85]	0.13	**97%*****
Test for subgroup differences: $Chi^2 = 0.27$, df = 1 (P = 0.60), $I^2 = 0\%$						
4.1.4 Duration according to zinc lozenge dose						
Symptomatic risk [a] < 50mg daily [38]	1	130	HR (IV, R)	0.83 [0.44, 1.55]	0.55	n/a
Symptomatic risk [a] 50 – 200mg daily [29 33 36 37]	4	334	HR (IV, R)	1.58 [0.71, 3.53]	0.26	**80%****
Symptomatic risk [a] > 200mg daily [27 32]	2	98	HR (IV, R)	1.74 [0.78, 3.84]	0.17	21%
Test for subgroup differences: $Chi^2 = 2.64$, df = 2 (P = 0.27), $I^2 = 24.3\%$						
Mean duration (days) < 50mg daily [38]	1	130	MD (IV, R)	0.18 [-0.17, 0.52]	0.31	n/a
Mean duration (days) 50 – 200mg daily [28 29 31 36 37 39]	6	471	MD (IV, R)	**-0.92 [-1.66, -0.18]**	**0.01**	**93%****
Mean duration (days) > 200mg daily [27 40]	2	128	MD (IV, R)	**-0.85[-1.65, -0.08]**	**0.03**	**77%****
Test for subgroup differences: **$Chi^2 = 10.85$, df = 2 (P = 0.004), $I^2 = 81.6\%$**						
4.1.5 Duration according to zinc salt						
Symptomatic risk [a] zinc acetate [29 33]	2	135	HR (IV, R)	1.73 [0.23, 13.05]	0.56	**92%*****
Symptomatic risk [a] zinc gluconate [27 33-38]	7	782	HR (IV, R)	1.86 [0.92, 3.75]	0.08	**86%*****
Symptomatic risk [a] zinc orotate & gluconate [32]	1	33	HR (IV, R)	1.02 [0.31, 3.37]	0.97	n/a
Symptomatic risk [a] zinc sulfate [30]	1	160	HR (IV, R)	1.16 [0.68, 1.97]	0.58	n/a
Test for subgroup differences: $Chi^2 = 1.39$, df = 3 (P = 0.71), $I^2 = 0\%$						
Mean duration (days) zinc acetate [28 29 31 39]	4	262	MD (IV, R)	**-2.44 [-3.77, -1.11]**	**<0.001**	**77%****
Mean duration (days) zinc gluconate [27 34-38 40]	7	758	MD (IV, R)	**-2.45 [-4.68, -0.22]**	**0.03**	**98%*****
Mean duration (days) zinc sulfate [30]	1	160	MD (IV, R)	-0.22 [-1.07, 0.63]	0.61	n/a

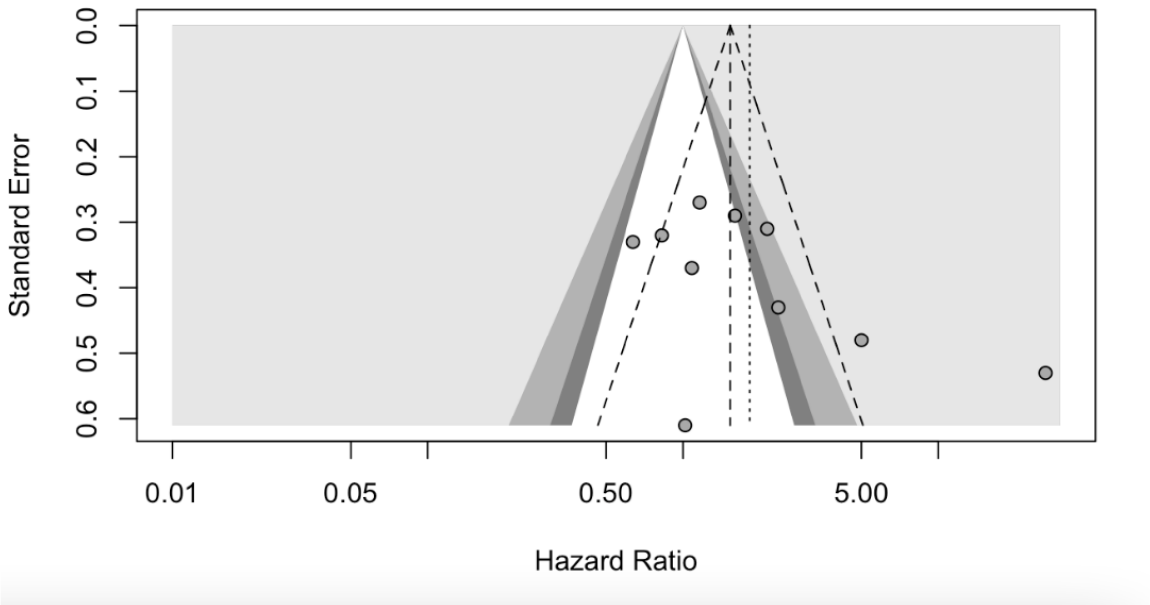
Test for subgroup differences: **Chi² = 9.41, df = 2 (P = 0.009), I² = 78.7%**						
4.1.6 Duration according to days symptomatic prior to study enrolment – *post hoc*						
Symptomatic risk: [a] ≤ 3 days symptomatic when started [27 32]	2	98	HR (IV, R)	1.74 [0.78, 3.84]	0.26	21%
Symptomatic risk: [a] ≤ 2 days symptomatic when started [30]	1	160	HR (IV, R)	1.16 [0.68, 1.97]	0.58	n/a
Symptomatic risk: [a] ≤ 1 day symptomatic when started [29 33-36 38]	6	655	HR (IV, R)	2.33 [0.97, 5.55]	0.06	**89%*** **
Symptomatic risk: [a] timing unknown [37]	1	110	HR (IV, R)	1.08 [0.52, 2.24]	0.83	n/a
Test for subgroup differences: Chi² = 2.54, df = 3 (P = 0.47), I² = 0%						
Mean duration ≤ 3 days symptomatic when started [27]	1	65	MD (IV, R)	**-3.62 [-5.07, -2.17]**	**<0.001**	**n/a**
Mean duration ≤ 2 days symptomatic when started [30 35 39 40]	4	364	MD (IV, R)	-0.79 [-1.99, 0.41]	0.20	**81%****
Mean duration ≤ 1 day symptomatic when started [28 29 34 36 38]	5	540	MD (IV, R)	**-3.39 [-6.02, -0.76]**	**0.01**	**98%*** **
Mean duration timing started unknown [31 37]	2	211	MD (IV, R)	-0.98 [-2.40, 0.44]	0.18	63%
Test for subgroup differences: **Chi² = 11.48, df = 3 (P = 0.009), I² = 73.9%**						
4.1.7 Duration according to definition of recovery – *post hoc*						
Symptomatic risk: [a] recovery is asymptomatic [27 32 34 35 37 38]	6	629	HR (IV, R)	2.04 [0.88, 4.73]	0.10	**86%*** **
Symptomatic risk: [a] recovery is 48 hrs asymptomatic [30]	1	160	HR (IV, R)	1.16 [0.68, 1.97]	0.58	n/a
Symptomatic risk: [a] recovery is symptom score ≤ 1 [29 36]	2	147	HR (IV, R)	**3.02 [1.33, 6.85]**	**0.008**	55%
Symptomatic risk: [a] recovery is self-determined [33]	1	87	HR (IV, R)	0.64 [0.33, 1.22]	0.17	n/a
Test for subgroup differences: **Chi² = 10.00, df = 3 (P = 0.02), I² = 70.0%**						
Mean duration recovery is asymptomatic [27 29 31 34 35 37 38 40]	8	808	MD (IV, R)	**-2.33 [-4.28, -0.38]**	**0.01**	**97%*** **
Mean duration recovery 48 hrs asymptomatic [30]	1	160	MD (IV, R)	-0.22 [-1.07, 0.63]	0.61	n/a
Mean duration recovery symptom score ≤ 1 [28 36 39]	3	212	MD (IV, R)	-2.25 [-4.63, 0.13]	0.06	81%**
Test for subgroup differences: Chi² = 5.55, df = 2 (P = 0.06), I² = 64.0%						
4.1.8 Sensitivity analysis: Tierney et al. method 11 to estimate hazard ratio [a]						
Symptomatic risk [27 29 30 32-38]	10	1023	HR (IV, R)	**1.99 [1.06, 3.73]**	**0.03**	**93%*** **
4.1.9 Sensitivity analyses: addition of Turner 2000[19] with an active control (3 zinc arms combined)						
Symptomatic risk [a 19 27 29 30 32-38]	12	1570	HR (IV, R)	**1.61 [1.07, 2.43]**	**0.02**	**80%*** **
Mean days duration [c 19 27-31 34-40]	13	1459	MD (IV, R)	**-1.89 [-3.29, -0.50]**	**0.008**	**97%*** **

4.1.10 Sensitivity analyses: risk of bias						
Symptomatic risk:[a] low RoB [29 30]	2	208	HR (IV, R)	2.28 [0.55, 9.52]	0.26	**86%****
Symptomatic risk:[a] some concerns or low RoB[29 30 33-36 38]	6	815	HR (IV, R)	**2.06 [1.01, 4.22]**	**0.05**	**87%*****
Mean duration: low RoB [28-30]	2	108	MD (IV, R)	-1.90 [-5.21, 1.41]	0.26	**96%*****
Mean duration: some concerns or low RoB [28-30 34-36 39 40]	9	942	MD (IV, R)	**-2.44 [-4.12, -0.76]**	**0.004**	**98%*****
4.1.11 Sensitivity analyses: removal of statistical outliers						
Symptomatic risk (publication bias) [a 27 29 30 32 33 35-38]	9	810	HR (IV, R)	1.39 [0.96, 2.02]	0.08	**60%****
Symptomatic risk (heterogeneity) [a 27 30 32 35-38]	7	675	HR (IV, R)	**1.37 [1.03, 1.81]**	**0.03**	19%
Mean days duration (heterogeneity) [27-31 35-38 40]	10	904	MD (IV, R)	**-1.86 [-2.74, -0.98]**	**<0.001**	**90%*****

RTI: Respiratory tract infection, **CI:** Confidence interval, **HR:** Hazard ratio, **MD:** Mean difference, **IV:** Inverse variance method, **R:** Random effects model, **I^2:** % variation due to heterogeneity, *I^2 P value ≤ 0.05, **I^2 P value ≤ 0.01, ***I^2 P value ≤ 0.001
[a] Tierney method 10 was selected in preference to method 11 based on greater precision and HR favouring the null hypothesis[15]
[b] Absolute effect calculated in GRADEpro GDT[6] probability of remaining symptomatic on day-7 was set *post hoc* at 33%.[21]
[c] The means and SD for the three zinc arms were combined in RevMan 5.4

4.1.12 Assessment of publication bias

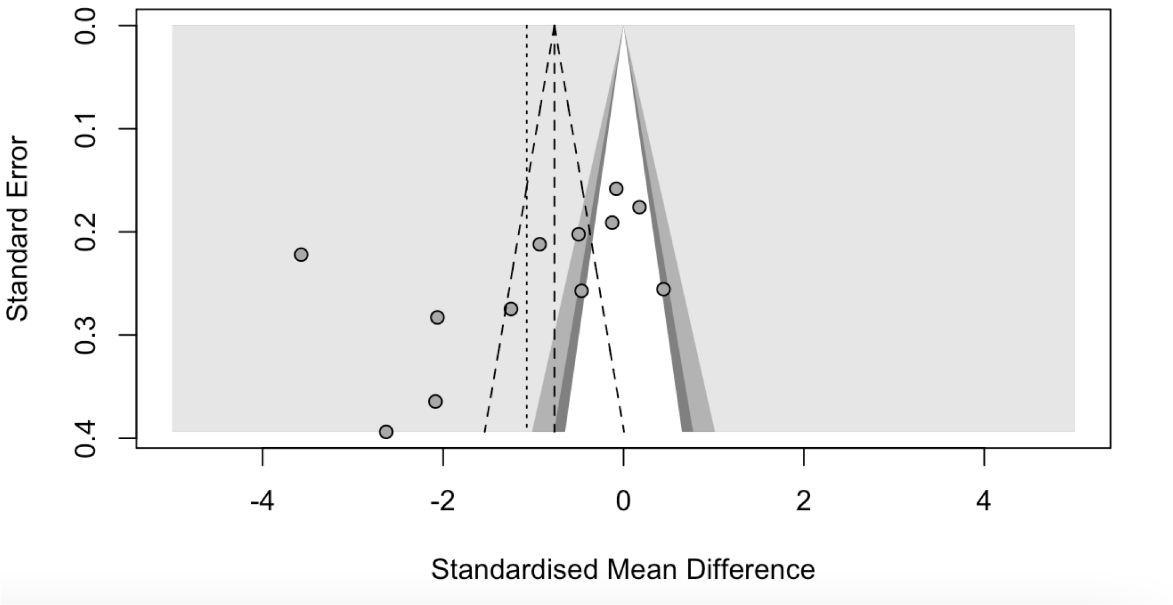
Figure 1. Funnel plot: Zinc vs. placebo on duration of community acquired RTIs, likelihood of symptomatic recovery



Visual inspection of the funnel plot is suggestive of asymmetry. However, the outlying study with the largest effect size, also had the largest sample size (n=213).[34] Heterogeneity can exacerbate funnel plot asymmetry.[16] Removal of this outlier substantially reduced this asymmetry and reduced statistical

heterogeneity from I^2=82% to 60% (Table 4.1.11. symptomatic risk, publication bias). Overall, small study bias is not strongly suspected.

Figure 2. Funnel plot: Zinc vs. placebo on duration of community acquired RTIs, mean number of days symptomatic



Visual inspection of the funnel plot shows asymmetry that is suggestive of small study bias. However, Egger's regression was not significant (p = 0.54). Overall, small study bias is not strongly suspected.

4.2 Duration of symptoms from community acquired and HRV inoculated RTI: Zinc vs. active control

Outcome	Studies	Participants	Statistical Method	Effect estimate [95% CI]	P value	I^2
4.2.1 Likelihood of recovery from mild RTIs on any given day for up to 7 days						
Asymptomatic risk [a 19]	2	547	HR (IV, R)	1.06 [0.79, 1.41]	0.71	0%
			Absolute Risk [d]	0.02 [-0.03, 0.07]		
4.2.2 Mean duration of symptoms (days) from community acquired mild RTI						
Mean duration (days) [19]	1	279	MD (IV, R)	-0.16 [-1.22, 0.90]	0.80	n/a
4.2.3 Duration according to type of infection						
Asymptomatic risk community acquired [19]	1	275	HR (IV, R)	1.03 [0.64, 1.65]	0.90	n/a
Asymptomatic risk HRV inoculation [19]	1	272	HR (IV, R)	1.07 [0.74, 1.56]	0.71	n/a
Test for subgroup differences: Chi^2 = 0.02, df = 1 (P = 0.90), I^2 = 0%						
4.2.4 Duration according to zinc dose						
Asymptomatic risk < 50mg daily [19]	2 [c]	276 [c]	HR (IV, R)	0.93 [0.69, 1.25]	0.62	0%

Asymptomatic risk 50 – 200mg daily [19]	4 [c]	551 [c]	HR (IV, R)	1.14 [0.93, 1.41]	0.25	0%
Test for subgroup differences: Chi² = 1.30, df = 1 (P = 0.25), I² = 22.9%						
Mean duration (days) < 50mg daily [19]	1	97	MD (IV, R)	0.35 [-1.49, 2.19]	0.71	n/a
Mean duration (days) 50 – 200mg daily [19]	2	182	MD (IV, R)	-0.41 [-1.70, 0.89]	0.54	0%
Test for subgroup differences: Chi² = 0.44, df = 1 (P = 0.51), I² = 0%						
4.2.5 Duration according to zinc salt						
Asymptomatic risk zinc acetate [19]	4 [c]	552 [c]	HR (IV, R)	1.00 [0.81, 1.24]	0.96	0%
Asymptomatic risk zinc gluconate [19]	2 [c]	275 [c]	HR (IV, R)	1.19 [0.90, 1.59]	0.22	0%
Test for subgroup differences: Chi² = 0.91, df = 1 (P = 0.34), I² = 0%						
Mean duration (days) zinc acetate [19]	2	282	MD (IV, R)	0.11 [-1.20, 1.42]	0.71	0%
Mean duration (days) zinc gluconate [19]	1	139	MD (IV, R)	-0.66 [-2.46, 1.14]	0.47	n/a
Test for subgroup differences: Chi² = 0. 46, df = 1 (P = 0.50), I² = 0%						
4.2.6 Sensitivity analysis: Tierney et al. method 11 to estimate hazard ratio [a]						
Symptomatic risk [19]	2	547	HR (IV, R)	1.10 [0.89, 1.38]	0.38	0%
4.2.7 Sensitivity analysis: no. participants in placebo group divided into 3-arms						
Mean duration (days) [19]	3	279	MD (IV, R)	-0.18 [-0.93, 0.56]	0.63	0%
4.2.8 Sensitivity analysis: unit of analysis error ignored						
Asymptomatic risk [a 19]	6 [c]	827 [c]	HR (IV, R)	1.07 [0.90, 1.27]	0.45	0%
Mean duration (days) [19]	3	421	MD (IV, R)	-0.18 [-0.93, 0.56]	0.63	0%
4.2.9 Sensitivity analysis: risk of bias						
Not relevant, the study outcomes do not have high risk of bias, all studies and study arms have some concerns						

RTI: Respiratory tract infection, **HRV:** Human rhinovirus, **CI:** Confidence interval, **HR:** Hazard ratio, **MD:** Mean difference, **IV:** Inverse variance method, **R:** Random effects model, **I²:** % variation due to heterogeneity, *I^2 P value ≤ 0.05, **I^2 P value ≤ 0.01, ***I^2 P value ≤ 0.001 [a] Tierney method 10 was selected in preference to method 11 based on greater precision and HR favoured the null hypothesis; [b] The means and SD for the three zinc arms were combined in RevMan 5.4; [c] NOTE: unit of analysis error as events in placebo arms are counted three times, however, sensitivity analysis (4.2.7) suggests only small, insignificant conflation from unaddressed correlation. [d] Absolute effect calculated in GRADEpro GDT[6] probability of remaining symptomatic on day-7 was set *post hoc* at 33%.[21]

5 META-ANALYSIS RESULTS: ADVERSE EVENTS

5.1 Tolerance and safety studies: Zinc lozenges vs. placebo

Outcome	Studies	Participants	Statistical Method	Effect estimate [95% CI]	P value	I^2
5.1.1 Risk of any adverse events (AE) per asymptomatic participant						
Incidence of AE [41]	1	66	RR	1.33 [0.32, 5.50]	0.69	n/a

RTI: Respiratory tract infection, **CI:** Confidence interval, **RR:** Risk ratio, **I^2:** % variation due to heterogeneity, *I^2 P value ≤ 0.05, **I^2 P value ≤ 0.01, ***I^2 P value ≤ 0.001

5.2 Adverse Effects for prevention of RTI: Zinc vs. placebo

Outcome	Studies	Participants (person-months)	Statistical Method	Effect estimate [95% CI]	P value	I^2
5.2.1 Risk of any adverse events (AE) per person-month						
Incidence of any AE [8 22 23]	3	2758 (2,998)	IRR (IV, R)	1.63 [0.81, 3.31]	0. 17	**62%**
			IRD (IV, R)	0.02 [-0.02, 0.05]	0.44	**85%*** **
5.2.2 Risk of nausea or stomach-ache from 15mg zinc daily in oral capsules						
Incidence of nausea or stomach-ache [8]	1	40 (280)	IRR	0.17 [0.01, 3.51]	0.25	n/a
5.2.3 Risk of nasal irritation/soreness from nasal gels/sprays						
Incidence of nasal irritation/soreness [22 23]	2	2718 (2718)	IRR (IV, R)	1.80 [0.92, 3.53]	0.09	**74%***
5.2.4 Risk of copper deficiency in adults 55-87 years from 45mg zinc daily for 12-months						
Serum copper µg/dL [7]	1	49 (98)	MD	-4.70 [-38.15, 28.75]	0.78	n/a
5.2.5 Sensitivity analysis: risk of bias						
Incidence of any AE [22 23]	2	2918 (2718)	IRR (IV, R)	1.80 [0.92, 3.53]	0.09	**74%***
5.2.6 Sensitivity analysis: RCT with zero events in zinc arm excluded						
Incidence of any AE [22 23]	2	2718 (2718)	IRR (IV, R)	1.80 [0.92, 3.53]	0.09	**74%***
5.2.7 Sensitivity analysis: RCT with zero events in zinc arm replaced with 1 event						
Incidence of any AE [8 22 23]	3	2758 (2,998)	IRR (IV, R)	**1.81 [1.08, 3.01]**	**0.02**	**45%**

RTI: Respiratory tract infection, **AE:** Adverse effects, **CI:** Confidence interval, **IRR:** Incidence rate ratio, **RD:** Incidence rate difference, **MD:** Mean difference, **IV:** Inverse variance method, **R:** Random effects model, **I^2:** % variation due to heterogeneity, *I^2 P value ≤ 0.05, **I^2 P value ≤ 0.01, ***I^2 P value ≤ 0.001, **µg/dL:** micrograms per decilitre of blood

5.3 Adverse events for treatment of RTI: Zinc vs. placebo

Outcome	Studies	Participants	Statistical Method	Effect estimate [95% CI]	P value	I^2
5.3.1 Risk of any adverse events (AE)						
Incidence of any AE [25-27 30 32-36 38 40]	11	1102	RR (M-H, R)	**1.41 [1.17, 1.69]**	**<0.001**	36%

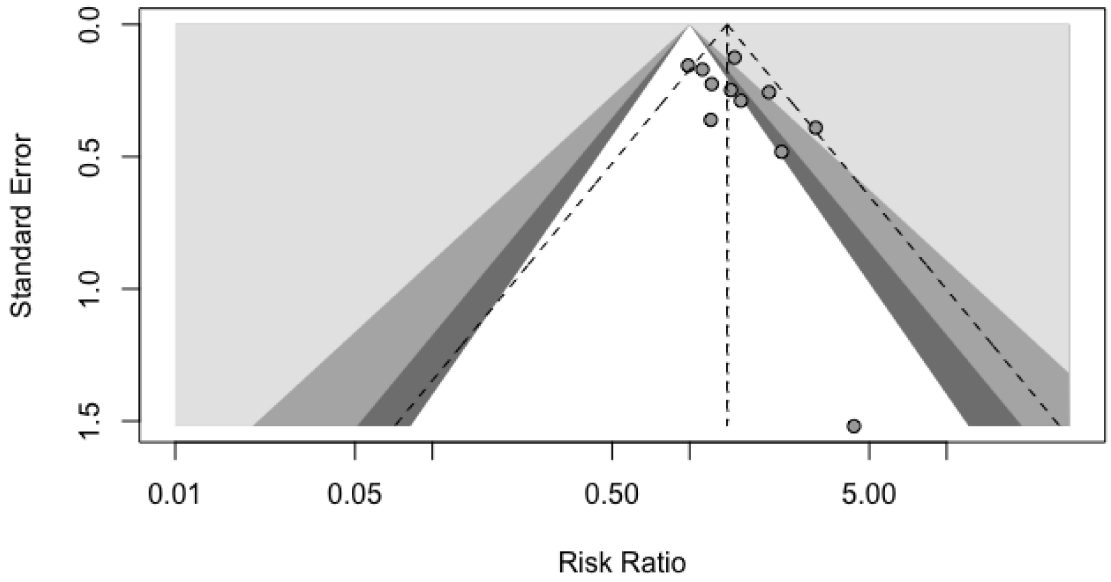
			RD (M-H, R)	**0.14 [0.09, 0.20]**	**<0.001**	**49%***
5.3.2 Risk of nausea or stomach-ache						
Incidence of nausea or stomach-ache [25 27-29 32-37 39 40]	12	1015	RR (M-H, R)	**1.46 [1.03, 2.06]**	**0.04**	9%
5.3.3 Risk of mouth irritation or soreness from sublingual lozenges						
Incidence of mouth irritation or soreness [25 27-29 32 37 40]	7	505	RR (M-H, R)	**1.55 [1.05, 2.29]**	**0.03**	1%
5.3.4 Risk of taste aversion from sublingual lozenges						
Incidence of taste aversion [27-29 32 36-39]	9	719	RR (M-H, R)	**2.11 [1.47, 3.04]**	**<0.001**	24%
5.3.5 Risk of nasal irritation from nasal gels/sprays						
Incidence of nasal irritation [26 30 35]	3	328	RR (M-H, R)	1.22 [0.72, 2.05]	0.45	0%
5.3.6 Risk of any AE according to administration route						
Sublingual lozenges [25 27 33 36 38 40]	6	514	RR (M-H, R)	**1.64 [1.36, 1.99]**	**<0.001**	3%
Nasal spray/gel [26 30 34 35]	4	541	RR (M-H, R)	1.12 [0.92, 1.36]	0.28	1%
Lozenge & nasal spray [32]	1	47	RR (M-H, R)	1.21 [0.60, 2.46]	0.60	n/a
Test for subgroup differences: **Chi² = 7.66, df = 2 (P = 0.02), I² = 73.9%**						
5.3.7 Risk of nausea or stomach-ache according to administration route						
Sublingual lozenges [25 28 29 33 35 36 39 40 42]	11	830	RR (M-H, R)	**1.48 [1.00, 2.18]**	**0.05**	16%
Topical nasal gel/spray [30 34]	2	372	RR (M-H, R)	1.44 [0.24, 8.72]	0.69	0%
Lozenge & nasal spray [32]	1	47	RR (M-H, R)	1.72 [0.59, 5.02]	0.32	n/a
Test for subgroup differences: Chi² = 0.07, df = 2 (P = 0.97), I² = 0%						
5.3.8 Risk of any AE according to daily zinc dose						
Zinc <50 mg/day [26 30 34 35 38]	5	671	RR (M-H, R)	1.17 [0.96, 1.43]	0.1	9%
Zinc 50-200 mg/day [25 33 36 40]	4	303	RR (M-H, R)	**1.57 [1.29, 1.92]**	**<0.001**	0%
Zinc >200 mg/day [27 32]	2	128	RR (M-H, R)	1.91 [0.75, 4.91]	0.2	69%
Test for subgroup differences: Chi² = 4.69, df = 2 (P = 0.10), I² = 57.4%						
5.3.9 Risk of nausea or stomach-ache according to daily zinc dose						
Zinc <50 mg/day [30 34]	2	372	RR (M-H, R)	1.44 [0.24, 8.72]	0.69	0%
Zinc 50-200 mg/day [25 29 33 36 37 39 40]	9	671	RR (M-H, R)	1.41 [0.96, 2.06]	0.08	13%
Zinc >200 mg/day [27 32]	2	136	RR (M-H, R)	3.48 [0.42, 28.58]	0.25	55%
Test for subgroup differences: Chi² = 0.69, df = 2 (P = 0.71), I² = 0%						
5.3.10 Risk of mouth irritation/soreness from sublingual lozenges according to daily zinc dose						
Zinc 50-200mg/day [25 28 29 37 40]	5	379	RR (M-H, R)	**1.51 [1.01, 2.27]**	**0.05**	6%
Zinc >200mg/day [27 32]	2	128	RR (M-H, R)	3.02 [0.35, 25.79]	0.31	52%
Test for subgroup differences: Chi² = 0.39, df = 1 (P = 0.53), I² = 0%						
5.3.11 Risk of taste aversion from sublingual lozenges according to daily zinc dose						
Zinc < 50mg/day [38]	1	130	RR (M-H, R)	7.90 [0.42, 150.01]	0.17	n/a
Zinc 50-200mg/day [25 28 29 36 37 39]	6	461	RR (M-H, R)	**2.13 [1.34, 3.40]**	**0.001**	47%

Zinc >200mg/day [27 32]	2	128	RR (M-H, R)	2.12 [0.81, 5.55]	0.13	0%
Test for subgroup differences: $Chi^2 = 0.75$, df = 2, (P = 0.69), $I^2 = 0\%$						
5.3.12 Risk of any AE according to zinc salt						
Zinc acetate [33]	1	88	RR (M-H, R)	**2.04 [1.23, 3.37]**	**0.006**	n/a
Zinc gluconate [25-27 34-36 38 40]	8	808	RR (M-H, R)	**1.45 [1.21, 1.74]**	**<0.001**	16%
Zinc orotate & gluconate [32]	1	49	RR (M-H, R)	1.32 [0.64, 2.71]	0.45	n/a
Zinc sulfate [30]	1	159	RR (M-H, R)	0.99 [0.73, 1.34]	0.93	n/a
Test for subgroup differences: $Chi^2 = 7.11$, df = 3 (P = 0.07), $I^2 = 57.8\%$						
5.3.13 Risk of nausea or stomach-ache according to zinc salt						
Zinc acetate [28 29 33 39]	4	249	RR (M-H, R)	1.53 [0.47, 4.95]	0.48	34%
Zinc gluconate [25 27 34 36 37 40]	7	716	RR (M-H, R)	**1.47 [1.02, 2.10]**	**0.04**	0%
Zinc orotate & gluconate [32]	1	55	RR (M-H, R)	14.48 [0.87, 241.82]	0.06	n/a
Zinc sulfate [30]	1	179	RR (M-H, R)	1.93 [0.18, 20.81]	0.59	n/a
Test for subgroup differences: $Chi^2 = 2.54$, df = 3 (P = 0.47), $I^2 = 0\%$						
5.3.14 Risk of mouth irritation or soreness from sublingual lozenges according to zinc salt						
Zinc acetate [28 29]	2	98	RR (M-H, R)	1.56 [0.42, 5.77]	0.51	28%
Zinc gluconate [25 27 37 40]	4	360	RR (M-H, R)	1.62 [0.88, 2.97]	0.12	38%
Zinc orotate & gluconate [32]	1	47	RR (M-H, R)	1.47 [0.40, 5.44[	0.57	n/a
Test for subgroup differences: $Chi^2 = 0.02$, df = 2 (P = 0.99), $I^2 = 0\%$						
5.3.15 Risk of taste aversion from sublingual lozenges according to zinc salt						
Zinc acetate [28 29 39]	3	156	RR (M-H, R)	1.79 [0.81, 3.94]	0.15	58%
Zinc gluconate [25 27 36-38]	5	516	RR (M-H, R)	**2.76 [1.88, 4.07]**	**<0.001**	0%
Zinc orotate & gluconate [32]	1	47	RR (M-H, R)	1.76 [0.50, 6.22]	0.38	n/a
Test for subgroup differences: $Chi^2 = 1.24$, df = 2 (P = 0.54), $I^2 = 0\%$						
5.3.16 Sensitivity analysis: risk of bias						
Incidence of any AE: some or low RoB [25 26 30 33-36 40]	10	974	RR (M-H, R)	**1.35 [1.14, 1.60]**	**<0.001**	26%
Incidence of any AE: low RoB only [25 30 33 36]	4	389	RR (M-H, R)	**1.41 [0.99, 2.02]**	**0.05**	62%
Incidence of nausea or stomach-ache: some or low RoB[25 33 34 36 40]	6	549	RR (M-H, R)	1.22 [0.82, 1.83]	0.33	0%
Incidence of mouth irritation or soreness: some or low RoB[25 40]	2	105	RR (M-H, R)	1.24 [0.74, 2.08]	0. 35	0%
Incidence of taste aversion: some or low RoB[25 38 40]	3	261	RR (M-H, R)	**2.70 [1.77, 4.12]**	**<0.001**	0%
Incidence of nasal irritation	*Not relevant, the study outcomes do not have high risk of bias, all studies have some concerns*					

RTI: Respiratory tract infection, **AE:** Adverse effects, **CI:** Confidence interval, **RR:** Risk ratio, **MD:** Mean difference, **IV:** Inverse variance method, **R:** Random effects model, **I^2:** % variation due to heterogeneity, *I^2 P value ≤ 0.05, **I^2 P value ≤ 0.01, ***I^2 P value ≤ 0.001, µg/dL: micrograms per decilitre of blood

5.3.17 Assessment of publication bias

Figure 3. Funnel plot: Any adverse events for treatment of RTI: Zinc vs. placebo



Visual inspection of the funnel plot showed some asymmetry. However, the asymmetry is in favour of lower risk for placebo controls, which is the opposite of what is expected if there was publication bias, and the Harbord score was not significant (p = 0.073). Overall, small study bias is not strongly suspected.

5.4 Adverse effects for treatment of RTI: Zinc vs. active controls

Outcome	Studies	Participants	Statistical Method	Effect estimate [95% CI]	P value	I^2
5.4.1 Risk of any adverse effects (AE)						
Incidence of any AE [19 43]		703	RR (M-H, R)	1.12 [0.76, 1.65]	0.57	0%
		703	RD (M-H, R)	0.02 [-0.03, 0.07]	0.40	0%
5.4.2 Risk of nasal burning from nasal gels/sprays containing zinc vs. naphazoline						
Incidence of nasal burning [43]	1	151	RR (M-H, R)	0.34 [0.01 to 8.16]	0.50	n/a
5.4.3 Risk of taste aversion from sublingual lozenges containing zinc vs. quinine						
Incidence of taste aversion [19]	1	279	RR (M-H, R)	0.94 [0.31, 2.85]	0.91	n/a
5.4.4 Sensitivity analysis: risk of bias						
Incidence of taste aversion: low RoB [19]	2		RR (M-H, R)	1.17 [0.71, 1.92]	0.35	26%

RTI: Respiratory tract infection, **AE:** Adverse effects, **GI:** Gastrointestinal, **CI:** Confidence interval, **RR:** Risk ratio, **IV:** Inverse variance model **M-H:** Mantel-Haenszel method, **R:** Random effects model, **I^2:** % variation due to heterogeneity, *I^2 P value ≤ 0.05, **I^2 P value ≤ 0.01, ***I^2 P value ≤ 0.001

6 OTHER CALCULATIONS

6.1 Daily dose estimates for Zinc Gluconate Nasal Sprays

Molecular Weight Zinc Gluconate: 455.7 g/mol [44]

Turner 2001 [26]
Preparation: Zicam (No manufacturer cited – currently produced by Matrixx Initiatives, Inc Bridgewater, NJ)
Formula: 33 m*M* zinc gluconate
Zinc Gluconate in Formula = (455.7 x 33)/1000g = 15.04g mixed into emulsion per litre of solution
Zinc Gluconate per Dose: Single nasal spray of 120 µL per nostril (ie two sprays per dose)
1 spray = 15.04g x (120µL/1000mL) = 15.04g x (0.12mL/1000mL)
= 15.04g x 0.00012 = 0.001805g = 1.8mg zinc gluconate
2 sprays per dose = 3.6mg zinc gluconate
Zinc as a percentage of zinc gluconate = 14.35% elemental Zinc by weight
Zinc per Nasal Spray:
1 spray = 1.8mg zinc gluconate = 0.26mg elemental zinc per spray
2 sprays = 0.52mg elemental zinc in a dose
Five doses per day = 2.6mg elemental zinc daily dose

Wei 2009 [22] **and Zhang 2009** [23]
Preparation: Shandong Tianshun Pharmaceutical Ltd.
Zinc Gluconate per Dose: This manufacture only has two specifications of zinc nasal spray:

- 15g: 0.3g (Each bottle contains 140 sprays, and each spray contains 2.0mg of zinc gluconate nasal spray)
- 10g: 0.2g (Each bottle contains 90 sprays, and each spray contains 2.0mg of zinc gluconate nasal spray)

Zinc as a percentage of zinc gluconate = 14.35% elemental Zinc by weight
Zinc per Nasal Spray:
1 spray = 2.0mg zinc gluconate = 0.287mg elemental zinc per spray
2 sprays = 0.57mg elemental zinc in a dose
Two doses per day = 1.15mg elemental zinc daily dose

6.2 Day-3 symptom severity score transformations

	Zinc mean	Zinc SD	Placebo mean	Placebo SD	No. items (score)	Score Range (Range ratio)
*Belongia 2001 [30]	4.5	4.1	5.4	4.0	8 (0 to 3)	24 (n/a)
Eby 1984 [27]	2.79	3.65	5.5	5.40	10 (0 to 3)	30 (0.80)
Prasad 2000 [29]	5.3	4.35	7.2	3.31	11 (0 to 4)	33 (0.73)
Prasad 2008 [28]	5.2	4.55	7.1	3.3	10 (0 to 3)	30 (0.80)
Turner 2001 [26]	2.1	0.51	3.5	3.04	8 (0 to 4)	32 (0.75)
TRANSFORMED **						
Eby 1984 [27]	2.23	2.92	4.40	4.32		
Prasad 2000 [29]	3.85	3.16	5.24	2.41		
Prasad 2008 [28]	4.16	3.64	5.68	2.64		
Turner 2001 [26]	1.58	0.38	2.63	2.28		

SD: Standard deviation; *Reference scale: Jackson cold scale, modified; **Transformation according to Thorlund et al. [10]

6.3 Day-3 symptom severity score minimally important difference

The minimally important difference (MID) in symptom severity for mild RTIs on day-3 was set at 1 point. This was the half-way mark between two proposed MIDs. Turner et al.[19] proposed a 10% improvement for mild RTIs. Based on the pooled mean scores for the control arms on day-3, a MID would be 0.5 points. Norman et al.[20] proposed that for populations with at least moderately impaired quality of life scores, the MID is approximately half the pooled standard deviation (SD) from the control arms, which for day-3 symptom severity would be 1.5 points.

Lower MID calculation: 10% improvement in the average mean placebo score[19]
Lower MID = (4.0 + 4.4 + 5.2 + 5.7 + 2.6)/5 x 10% = 0.47

Upper MID calculation: half the pooled standard deviation of zinc and placebo means[20]
Upper MID = √(2922.68/315) = 1.52

$$Pooled\ SD = \sqrt{\frac{(n_1 - 1) \times {SD_1}^2 + (n_2 - 1) \times {SD_2}^2}{n_1 + n_2 - 2}}$$

6.4 Survival curve data extraction for days symptomatic

	Eby 1984 Fig.1 [27]				Mossad 1996 Fig 1. [36]			
Day	Zinc %	no.	Control %	no.	Zinc %	no.	Control %	no.
0	100	37	100	28	100	49	100	50
1	78.4	29	100	28	91.8	45	100	50
2	62.2	23	92.9	26	81.6	40	92	46
3	54.1	20	82.1	23	69.4	34	86	43
4	35.1	13	78.6	22	53.1	26	76	38
5	29.7	11	71.4	20	44.9	22	72	36
6	18.9	7	67.9	19	32.7	16	62	31
7	13.5	5	53.6	15	18.4	9	56	28
	Eby 2006 Fig 1. [32]				Mossad 2003 Fig.2 [35]			
Day	Zinc %	no.	Control %	no.	Zinc %	no.	Control %	no.
0	100	16	100	17	100	40	100	38
1	87.5	14	100	17	92.5	37	97.4	37
2	81.3	13	94.1	16	82.5	33	94.7	36
3	68.8	11	76.5	13	67.5	27	86.8	33
4	56.3	9	76.5	13	50	20	71.1	27
5	43.8	7	64.7	11	35	14	52.6	20
6	43.8	7	58.8	10	20	8	39.5	15
7	37.5	6	47.1	8	15	6	26.3	11
	Hemilla 2020 [33]				Prasad 2000 Fig 1. [29]			
Day	Zinc %	no.	Control %	no.	Zinc %	no.	Control %	no.
0	100	45	100	42	100	25	100	23
1	100	45	100	42	100	25	100	23
2	88.9	40	90.5	38	92	23	100	23
3	80.0	36	76.2	32	64	16	100	23
4	68.9	31	64.3	27	48	12	100	23
5	60.0	27	42.9	18	28	7	91.3	21
6	57.8	26	26.2	11	12	3	82.6	19
7	37.8	17	26.2	11	0.01	0	65.2	15

	Hirt 2000 1 Fig.1 [34]				Smith 1989 Fig 1. [37]			
Day	Zinc %	no.	Control %	no.	Zinc %	no.	Control %	no.
0	100	108	100	105	100	57	100	53
1	100	108	100	105	100	57	98.1	52
2	48.1	52	100	105	100	57	96.2	51
3	30.5	33	98.1	103	96.4	55	92.5	49
4	18.5	2	98.1	103	86	49	79.2	42
5	0.01	0	95.2	100	77.2	44	67.8	36
6	0.001	0	90.5	95	57.9	33	62.3	33
7	0.0001	0	66.6	70	42.1	24	54.7	29
	Turner 2000 (A-1) Fig.1A [19]				Turner 2000 (B-1) Fig.1B [19]			
Day	Zinc %	no.	Control %	no.	Zinc %	no.	Control %	no.
0	100	69	100	67	100	68	100	71
1	79.7	55	86.6	58	98.5	67	98.6	70
2	59.4	41	73.1	49	89.7	61	94.4	67
3	36.2	25	53.7	36	80.8	55	81.7	58
4	21.7	15	28.4	19	72.1	49	67.6	48
5	18.8	13	23.8	16	57.3	39	56.3	40
6	14.5	10	22.4	15	44.1	30	43.7	31
7	13	9	21	14	36.7	25	38	27
	Turner 2000 (A-2) Fig.1A [19]				Turner 2000 (B-2) Fig.1B [19]			
Day	Zinc %	no.	Control %	no.	Zinc %	no.	Control %	no.
0	100	66	100	67	100	72	100	71
1	92.4	61	86.6	58	98.6	71	98.6	70
2	77.3	51	73.1	49	93.1	67	94.4	67
3	54.5	36	53.7	36	86.1	62	81.7	58
4	36.3	24	28.4	19	72.2	52	67.6	48
5	28.7	19	23.8	16	58.3	42	56.3	40
6	19.7	13	22.4	15	48.6	35	43.7	31
7	16.6	11	21	14	36.1	26	38	27
	Turner 2000 (A-3) Fig.1A [19]				Turner 2000 (B-3) Fig.1B [19]			
Day	Zinc %	no.	Control %	no.	Zinc %	no.	Control %	no.
0	100	70	100	67	100	68	100	71
1	81.4	57	86.6	58	100	68	98.6	70
2	65.7	46	73.1	49	92.6	63	94.4	67
3	50	35	53.7	36	83.8	57	81.7	58
4	38.6	27	28.4	19	67.6	46	67.6	48
5	25.7	18	23.8	16	51.5	35	56.3	40
6	18.6	13	22.4	15	38.2	26	43.7	31
7	12.8	9	21	14	28	19	38	27
	Turner 2000 (3-arms combined) Fig.1A [19]				Turner 2000 (3-arms combined) Fig.1B [19]			
Day	Zinc %	no.	Control %	no.	Zinc %	no.	Control %	no.
0	100	205	100	67	100	208	100	71
1	84.4	173	86.6	58	99.0	206	98.6	70
2	67.3	138	73.1	49	91.8	191	94.4	67
3	46.8	96	53.7	36	83.7	174	81.7	58
4	32.2	66	28.4	19	70.7	147	67.6	48
5	24.4	50	23.8	16	55.8	116	56.3	40
6	17.6	36	22.4	15	43.8	91	43.7	31
7	14.1	29	21	14	33.7	70	38	27

	Weismann 1990 Fig 1. [38]				
Day	Zinc %	no.	Control %	no.	
0	100	69	100	61	
1	98.5	68	100	61	
2	97.1	67	98.3	60	
3	92.8	64	93.4	57	
4	81.2	56	83.6	51	
5	65.2	45	68.9	42	
6	60.9	42	47.5	29	
7	49.3	34	31	19	

6.5 Mean days symptomatic, data extraction

	Zinc mean	SD	Control mean	SD	Data source
Belongia 2001 [30]	7.5	2.93	7.72	2.52	D'Cruze 2009 [13]
Douglas 1987 [39]	12.1	9.8	7.7	9.8	Hemilä 2011 [12]
Eby 1984 [27]	3.92	2.61	7.54	3.18	Hemilä 2011 [12]
Godfrey 1992 [40]	4.86	2.7	6.13	2.7	Hemilä 2017 [11]
Hirt 2000 [34]	2.3	0.9	9	2.5	Hirt 2000 [34]
Mossad 1996 [36]	5.2	2.83	9.2	5.32	Hemilä 2017 [11]
Mossad 2003 [35]	4.3	0.75	6	0.88	D'Cruze 2009 [13]
Petrus 1998 [31]	5.3	52	5.3	48	Petrus 1998 [31]
Prasad 2000 [29]	4.5	1.6	8.1	1.8	Prasad 2000 [29]
Prasad 2008 [28]	4	1.04	7.12	1.26	Prasad 2008 [28]
Smith 1989 [37]	7.23	2.29	7.57	3.01	Hemilä 2017 [11]
Turner 2000 (B-1) [19]	6.89	3.35	7.55	3.95	Hemilä 2011 [12]
Turner 2000 (B-2) [19]	7.9	4.25	7.55	3.96	Hemilä 2011 [12]
Turner 2000 (B-3) [19]	7.41	3.88	7.55	3.94	Hemilä 2011 [12]
Weismann 1990 [38]	7.16	2.62	6.72	2.29	Hemilä 2011 [12]

This was a secondary outcome

6.6 Incidence per-person month, data extraction & calculations

	Zinc events	Zinc total	Control events	Control total	Time months	Zinc Ee/Te	Control Ee/Te	IRR IRD	ln(IRR) ln(IRC)	SE ln(IRR) SE (IRD)
All RTIs										
Prasad 2007 [7]	7	24	19	25	12	0.024	0.063	0.384 -0.039	-0.958	0.442 0.017
Veverka 2009 [8]	5	20	4	17	7	0.036	0.034	1.063 0.002	0.061	0.671 0.023
Wei 2009 [22]	105	386	141	387	1	0.272	0.364	0.747 -0.092	-0.292	0.129 0.041
Zhang 2009 [23]	139	978	210	967	1	0.142	0.217	0.654 -0.075	-0.424	0.109 0.019
Mild RTIs										
Prasad 2007 [7]	7	24	16	25	12	0.024	0.053	0.456 -0.029	-0.786	0.453 0.016

Wei 2009 [22]	104	386	133	387	1	0.269	0.344	0.784 -0.074	-0.243	0.131 0.040
Zhang 2009 [23]	137	978	193	967	1	0.140	0.200	0.702 -0.060	-0.354	0.112 0.019
Moderate RTIs										
Prasad 2007 [7]	0.5	24	3	25	12	0.002	0.010	0.174 -0.008	-1.751	1.528 0.006
Wei 2009 [22]	1	386	8	387	1	0.003	0.021	0.125 -0.018	-2.077	1.061 0.008
Zhang 2009	2	978	17	967	1	0.002	0.018	0.116 -0.016	-2.151	0.748 0.005
Non-serious AEs										
Veverka 2009 [8]	0.5	20	2	20	7	0.004	0.014	0.250 -0.011	-1.386	1.581 0.011
Wei 2009 [22]	26	386	21	387	1	0.067	0.054	1.241 0.013	0.216	0.293 0.018
Zhang 2009 [23]	75	978	30	967	1	0.077	0.031	2.472 0.046	0.905	0.216 0.011

IRR: incidence rate ratio; **IRD:** incidence rate difference

$$SE(\log(IRR)) = \sqrt{\left(\frac{1}{a}\right) + \left(\frac{1}{b}\right)} \qquad SE(Rate\ Difference) = \sqrt{\frac{a}{(t_1)^2} + \frac{c}{(t_0)^2}}$$

6.1 Contour enhanced funnel plots: R code

6.1.1 Mean duration of symptoms (days) from community acquired mild RTI

Study	tx.n	tx.mean	tx.SD	con.n	con.mean	con.SD
Belongia 2001	81	7.5	2.93	79	7.72	2.52
Douglas 1987	33	12.1	9.8	30	7.7	9.8
Eby 1984	37	3.92	2.61	28	7.54	3.18
Godfrey 1992	35	4.86	2.7	28	6.13	2.7
Hirt 2000	108	2.3	0.9	105	9	2.5
Mossad 1996	49	5.2	2.83	50	9.2	5.32
Mossad 2003	40	4.3	0.75	38	6	0.88
Petrus 1998	52	5.3	2.9	49	7.1	4.2
Prasad 2000	25	4.5	1.6	23	8.1	1.8
Prasad 2008	25	4	1	25	7.1	1.3

Smith 1989	53	7.23	2.29	57	7.57	3.01
Weismann 1990	69	7.16	2.62	61	6.72	2.29

R code

```
> library(readxl)
> zinc_duration2 <- read_excel("Downloads/zinc_duration2.xlsx")
> View(zinc_duration2)
> zinc_duration=data.frame(zinc_duration2)
> zinc_meta=metacont(zinc_duration[,2], zinc_duration[,3],  zinc_duration[,4], zinc_duration[,5],
zinc_duration[,6], zinc_duration[,7], sm=SMD )
```

6.1.2 Adverse events for treatment of RTI: Zinc vs. placebo

study	events.int	n.int	events.con	n.con
Belongia 2001	41	81	40	78
Eby 1984	27	48	6	33
Eby 2006	11	25	8	22
Farr 1987 (B)	2	23	0	20
Godfrey 1992	20	35	15	38
Hemilä 2020	29	46	13	42
Hirt 2000	45	108	39	105
Mossad 1996	44	49	30	50
Mossad 2003	12	40	5	38
Turner 2001	21	41	21	50
Weismann 1990	21	61	15	69

R code

```
> Library(meta)
> library(readxl)
> Zinc_AE2 <- read_excel("Downloads/Zinc_AE2.xlsx")
> View(Zinc_AE2)
> zinc_AE=data.frame(Zinc_AE2)
> Zinc_meta_AE=metabin(zinc_AE[,2],zinc_AE[,3], zinc_AE[,4], zinc_AE[,5])
> cc <- funnel(Zinc_meta_AE, xlim=c(0.01,30),
          level = 0.95, contour = c(0.9, 0.95, 0.99))$col.contour
```

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Appendix 5: Summary of findings table

CONTENTS

SUMMARY OF FINDINGS

Included studies	Certainty assessment	Participants	Effect (95% confidence interval)	Certainty	Importance
1. All-cause mortality of adults with acute viral respiratory tract infections (RTIs): zinc vs. any type of intervention					
			No information	?	Critical
2. Clinical outcomes of adults with severe or critical acute viral RTIs: zinc vs. any type of intervention					
			No information	?	Critical
3. Quality of life outcomes of adults with acute viral RTIs: zinc vs. any type of intervention					
			No information	?	Critical
4. Risk of serious adverse events from zinc use for preventing or treating acute viral RTIs **Condition:** symptoms consistent with a mild to moderate acute viral RTIs that were community acquired or from human rhinovirus inoculation, no SARS-CoV-2 infections **Settings/Participants:** adults of all ages living in community settings in USA, China, UK, Scandinavia, or Australia **Zinc interventions:** oral capsules 15mg to 45mg elemental zinc daily, sublingual lozenges 45mg to 300mg elemental zinc daily and/or low dose topical nasal sprays or gels					
Randomised controlled trials (n=4) [1-4]	Risk of bias; Inconsistency between studies; Indirectness of evidence; Imprecision of effect; Publication bias or other considerations		No serious adverse events were reported by 2,804 adults who used up to 45mg zinc daily **for prevention of** viral RTIs over 1,792 person-months or a placebo over 1,773 person-months (range 1 to 12 months zinc/control use per person)	⊕⊕○○ LOW	Critical
Randomised controlled trials (n=16) [5-20]	Risk of bias; Inconsistency between studies; Indirectness of evidence; Imprecision of effect; Publication bias or other considerations		No serious adverse events were reported by 1141 participants who used up to 300mg zinc daily **to treat or prevent viral** RTIs or 851 participants who used a placebo or active control (range 1 to 14 days zinc/control use per person)	⊕⊕○○ LOW	Critical

5. Prevention of symptoms consistent with a community acquired viral RTIs: zinc vs. placebo

Condition: symptoms consistent with acute viral RTIs that were community acquired, no SARS-CoV-2 infections
Settings/Participants: college students (China), males at an army boot camp (China), air force cadets (USA), community day centre for older adults (USA)
Zinc interventions: oral capsules 15mg to 45mg daily, or low dose topical nasal sprays

Randomised controlled trials (n=4) [1-4]	Risk of bias	Inconsistency between studies	Indirectness of evidence	Imprecision of effect	Publication bias or other considerations	1492 adults over 1792 person-months	1499 adults over 1773 person-months	32% lower risk of mild to moderate RTI **Rate ratio 0.68** (0.58 to 0.80)	**5 fewer mild to moderate RTIs per 100 adults who use zinc for 1 month** (from 8 to 1 fewer) [c] **NTT: 20** (13 to 100)	⊕⊕⊕○ **MODERATE**	Critical
Randomised controlled trials (n=3) [2-4]	Risk of bias	Inconsistency between studies	Indirectness of evidence	Imprecision of effect	Publication bias or other considerations	1472 adults over 1,652 person-months	1479 adults over 1,654 person-months	87% lower risk of moderately severe RTI **Rate ratio 0.13** (0.04 to 0.38)	**1 fewer moderate RTI per 100 adults who use zinc for 1 month** (from 2 to 1 fewer) [c] **NTT: 100** (50 to 100)	⊕⊕⊕○ **MODERATE**	Important
								28% lower risk of mild severity RTI **Rate ratio 0.72** (0.61 to 0.85)	**5 fewer mild RTIs per 100 adults who use zinc for 1 month** (from 7 to 2 fewer) [c] **NNT: 20** (14 to 50)	⊕⊕⊕○ **MODERATE**	Important

6. Risk of non-serious adverse events when preventing acute viral RTIs: zinc vs. placebo

Condition: symptoms consistent with a mild to moderate acute viral RTIs that were community acquired or from human rhinovirus inoculation, no SARS-CoV-2 infections
Settings/Participants: college students (China), males at an army boot camp (China), air force cadets (USA)
Zinc interventions: oral capsules 15mg to 45mg daily, or low dose topical nasal sprays

Randomised controlled trials (n=3) [1-3]	Risk of bias	Inconsistency between studies	Indirectness of evidence	Imprecision of effect	Publication bias or other considerations	1467 adults over 1504 person-months	1474 adults over 1494 person-months	1.6 times higher risk of non-serious adverse effects **Rate ratio 1.63** (0.81 to 3.31)	**2 more non-serious adverse effects per 100 persons who use zinc for 1 month** (from 2 fewer to 5 more) [c]	⊕⊕○○ **LOW**	Critical

7. Symptom severity of mild to moderate acute viral RTIs: zinc vs. placebo

Condition: symptoms of a community acquired common cold or a clinical cold following human rhinovirus inoculation, no SARS-CoV-2 infections
Settings/Participants: healthy adults, living in community settings in the USA
Zinc interventions: sublingual lozenges 45mg to 276mg elemental zinc daily, or low dose topical nasal gel or spray

Randomised controlled trials (n=5) [9 14-16 18]	Risk of bias	Inconsistency between studies	Indirectness of evidence	Imprecision of effect	Publication bias or other considerations	200 adult participants	192 adult participants	**Day-3 symptom severity scores were reduced by an average of 1.2 points** (from 1.7 lower to 0.7 lower) *A clinically important difference for mild illness is 1 point lower*	⊕⊕○○ **LOW**	Critical
Randomised controlled trials (n=3) [6 18 21]	Risk of bias	Inconsistency between studies	Indirectness of evidence	Imprecision of effect	Publication bias or other considerations	97 adult participants	98 adult participants	**Average daily symptom severity scores were reduced by a standardised mean difference of 0.2** (from 0.4 lower to 0.1 higher) *A clinically important difference is 0.5 lower*	⊕⊕○○ **LOW**	Critical

8. Duration of illness from mild to moderate acute viral RTIs: zinc vs. placebo

Condition: symptoms of a community acquired common cold, no SARS-CoV-2 infections
Settings/Participants: adults living in community settings in USA, Scandinavia, or Australia
Zinc interventions: sublingual lozenges 45mg to 300mg elemental zinc daily, or low dose topical nasal gel or spray

Randomised controlled trials (n=10) [7-9 11-15 19 22]	Risk of bias	Inconsistency between studies	Indirectness of evidence	Imprecision of effect	Publication bias or other considerations	413 adult participants	414 adult participants	45% more likely to recover first with zinc use **Hazard ratio 1.83** (1.07 to 3.13)	**19 more per 100 who did not use zinc were symptomatic for up to 7 days** (from 2 more to 38 more) [k] **NNT: 5** (from 3 to 50)	⊕⊕○○ **LOW**	Critical
								A clinically important difference is HR 1.9, [a] *that is, ≥ 20 more per 100 or NTT: 5*			

Randomised controlled trials (n=12) 8-17 21 22	Risk of bias	Inconsistency between studies	Indirectness of evidence	Imprecision of effect	Publication bias or other considerations	607 adult participants	573 adult participants	**Duration of symptoms were reduced by an average of 2 days** (from 3.5 days shorter to 0.6 days shorter) *A clinically important difference for mild illness is at least 1 day shorter duration*		⊕○○○ **VERY LOW**	Important

9. Risk of non-serious adverse events from short-term use when treating acute viral RTIs: zinc vs. placebo

Condition: symptoms of a community acquired common cold or a clinical cold following human rhinovirus inoculation, no SARS-CoV-2 infections
Settings/Participants: adults living in community settings in USA or Scandinavia
Zinc interventions: sublingual lozenges 45mg to 300mg elemental zinc daily, or low dose topical nasal gel or spray

Randomised controlled trials (n=11) 6-14 18 19	Risk of bias	Inconsistency between studies	Indirectness of evidence	Imprecision of effect	Publication bias or other considerations	273/557 (49.0%) adult participants with adverse events	192/545 (35.2%) adult participants with adverse events	29% higher risk of non-serious adverse events **Risk ratio 1.41** (1.17 to 1.69)	**14 more non-serious adverse events per 100 adults** (from 9 more to 20 more) **NTT: 7** (5 to 11)	⊕⊕⊕○ **MODERATE**	Important

10. Duration of illness from mild to moderate acute viral RTIs: zinc vs. an active control

Condition: symptoms of a community acquired common cold or a clinical cold following human rhinovirus inoculation, no SARS-CoV-2 infections **Settings/Participants:** healthy adults, age 18-65 years living in community settings in the US
Zinc interventions: zinc gluconate or acetate sublingual lozenges 30mg to 80mg elemental zinc daily
Active controls: sublingual lozenge with quinine

Randomised controlled trials (n=2 x 4-arm) [5]	Risk of bias	Inconsistency between studies	Indirectness of evidence [h]	Imprecision of effect	Publication bias or other considerations	413 adult participants	138 adult participants	1.1 times more likely to recover first with zinc use **Hazard ratio 1.06** (0.79 to 1.41)	**2 more per 100 who <u>do not use zinc</u> are symptomatic on day-7** (from 3 fewer to 7 more) [j]	⊕⊕○○ **LOW**	Critical
								A clinically important difference is HR 1.9, that is, ≥ 20 more per 100 or NTT: 5			

Randomised controlled trials (n=1 x 4-arm) [5]	Risk of bias	Inconsistency between studies	Indirectness of evidence	Imprecision of effect	Publication bias or other considerations	208 adult participants	71 adult participants	**Duration of symptoms were reduced by an average of 4 hours** (from 22 hours shorter to 14 hours longer) *A clinically important difference for mild illness is at least 24 hours shorter duration*	⊕⊕○○ **LOW**	Important

11. Risk of non-serious adverse events from use when treating acute viral RTIs: zinc vs. active controls

Condition: symptoms of a community acquired common cold or a clinical cold following human rhinovirus inoculation, no SARS-CoV-2 infections
Settings/Participants: healthy adults, age 18-65 years living in community settings in the US
Zinc interventions: zinc gluconate or acetate sublingual lozenges 30mg to 80mg elemental zinc daily
Active controls: sublingual lozenge with quinine, or topical nasal spray with naphazoline hydrochloride

Randomised controlled trials (n=3: 1 x 2-arm 2 x 4-arm) [5 20]	Risk of bias	Inconsistency between studies	Indirectness of evidence	Imprecision of effect	Publication bias or other considerations	89/489 (18.2%) adult participants with adverse events	28/214 (15.5%) adult participants with adverse events	16% higher risk of non-serious adverse events **Risk ratio 1.12** (0.76 to 1.65)	**2 more non-serious events effects per 100 adults** (from 3 fewer to 7 more)	⊕⊕○○ **LOW**	Important

NNT: numbers needed to treat; **HR-QoL:** Health related quality of life

LEGEND	**Assessment of certainty**		**Certainty of the evidence**			
	+ 1 point	Rated up by 1 point e.g. dose response, large effect	⊕⊕⊕⊕ HIGH	High certainty of benefit or no harm	⊕⊕⊕⊕ HIGH	High certainty of harm or no benefit
	neutral	Not serious Not rated down	⊕⊕⊕○ MODERATE	Moderate certainty of benefit or no harm	⊕⊕⊕○ MODERATE	Moderate certainty of harm or no benefit
	- 1 point	Serious Rated down by 1 point	⊕⊕○○ LOW	Low certainty of benefit or no harm	⊕⊕○○ LOW	Low certainty of harm or no benefit
	- 2 points	Very serious Rated down by 2 points	⊕○○○ VERY LOW	Very low certainty of benefit or harm	?	No information

FOOTNOTES FOR GRADE-CERTAINTY/QUALITY ASSESSMENTS

4. **Risk of serious adverse events from zinc for preventing or treating acute viral RTIs:** RoB serious: 6 RCTs low RoB,[5-9] 8 RCTs some concerns RoB,[3 4 10-13 18] 8 RCTs high RoB[1 2 14-17 19 20]; Imprecision serious: OIS is not me for rare AEs or for mean difference in serum copper; Publication bias not serious: the 2 RCTs[2] that did not report AEs were not industry funded, so publication bias not strongly suspected.

5. **Prevention of symptoms consistent with a community acquired viral RTIs from zinc vs. placebo:** RoB serious: when 1 RCT high RoB [1] removed, effect estimates are stable with 3 RCTs some concerns[2-4] IRR 0.68 [95% CI 0.56 to 0.81] p < 0.001; Publication bias not serious: n/a <10 RCTs
6. **Risk of non-serious adverse events from zinc vs. placebo for prevention:** RoB serious: when 2 RCTs[1 2] high RoB removed, effect estimate stable 1 RCT[3] some concerns RoB IRR 1.18 [95% CI 0.67 to 2.07] p = 0.09. Inconsistency not serious: I^2 = 62% p < 0.05, however, all 95% CI overlap, and removal of statistical outlier[3] effect estimate stable with remaining RCTs[1 2] IRR 1.18 [95% CI 0.67 to 2.07] p = 0.09 I^2 = 0%; Imprecision serious: control event rate 0.35 and OIS is met, however, 95% CI does not exclude important benefit and risk. Publication bias not serious: <10 RCTs
7. **Day-3 symptom severity score from zinc vs. placebo:** RoB serious: when 2 RCTs[14 18] high RoB removed, effect estimate with 3 RCTs[9 15 16] some concerns RoB MD -1.19 [95% CI -2.05 to -0.33] p = 0.007. Imprecision serious: OIS is not met, and 95% CI excludes no effect. Publication bias not serious: <10 RCTs
7. **Average daily symptom severity score from zinc vs. placebo:** RoB serious: when 2 RCTs[18 21] high RoB removed, effect estimate with 1 RCT[6] some concerns RoB SMD 0.27 [95% CI -0.51 to 1.06] p = 0.50. Imprecision serious: OIS is not met, and 95% CI excludes no effect. Publication bias not serious: <10 RCTs
8. **Risk of remaining symptomatic from placebo vs. zinc:** RoB serious: when 3 RCTs high RoB[14 19 22] removed, effect estimate with 2 RCTs low RoB[9 15] and 5 RCTs some concerns[7 8 11-13] HR 2.44 [95% CI 1.08 to 5.50] p = 0.03. Inconsistency serious: substantial statistical heterogeneity I^2 = 82% p < 0.001, however, 95% CI mostly overlap, subgroup analysis suggests clinical and methodological diversity, and removal of 3 statistical outliers[7 12 15] effect estimate with remaining 7 RCTs[8 9 11 13 14 19 22] HR 1.37 [95% CI 1.03 to 1.81] p = 0.03 I^2 = 19%. Publication bias not serious: Visual inspection of the funnel plot is suggestive of asymmetry. However, the outlying study with the largest effect size, also had the largest sample size (n=213).[12] Heterogeneity can exacerbate funnel plot asymmetry.[23] Removal of this outlier[12] reduced asymmetry and statistical heterogeneity, effect estimate with remaining 9 RCTs [7-9 11 13-15 19 22] HR 1.39 [95% CI 0.96 to 2.02] p = 0.08, I^2 = 60% p < 0.01. Overall, small study bias is not strongly suspected.
8. **Mean days duration of symptoms from zinc vs. placebo:** RoB serious: when 3 RCTs high RoB[14 19] removed, effect estimate 2 RCTs low RoB[9 15 17] and 7 RCTs some concerns[8 10-13 16 21] MD -2.44 [95% CI -4.12 to -0.76] p = 0.004. Inconsistency very serious: considerable statistical heterogeneity I^2 = 97% (p < 0.001), all clinical & methodological subgroups have substantial heterogeneity I^2 > 60% and sensitivity analysis with removal of statistical outliers only reduces I^2 < 60% if more than half the studies are removed, point estimates vary widely across studies with clinically important positive and negative effects, and 95% CI show minimal overlap that possibly reflects the use of means (SD) instead of median duration when analysing studies with non-parametric distributions. Publication bias not serious: Visual inspection of the funnel plot shows asymmetry that is suggestive of small study bias. However, Egger's regression was not significant (p = 0.54). Overall, small study bias is not strongly suspected.
9. **Risk of non-serious adverse events from zinc vs. placebo for treatment:** RoB serious: when 2 RCTs high RoB[14 19] removed, effect estimate with 5 RCTs some concerns[10-13 18] and 4 RCTs low RoB[6-9] RR 1.35 [95% CI 1.14 to 1.60] p < 0.001. Publication bias not serious: Visual inspection of the funnel plot showed some asymmetry. However, the asymmetry is in favour of lower risk for placebo controls. This is the opposite of what is expected when there is publication bias from small studies in favour of lower risk for zinc. The Harbord score was not significant (p = 0.073). Overall, does not meet criteria for "strongly suspected" for small study bias.
10. **Risk of remaining symptomatic from active control vs. zinc:** RoB serious: all RCTs had some concerns with RoB; Imprecision serious: OIS is not met, 95% CI includes no effect. Publication bias not serious: <10 RCTs
10. **Mean days duration of symptoms from zinc vs. active control:** RoB serious: all RCTs had some concerns with RoB; Imprecision serious: OIS is not met, 95% CI includes no effect. Publication bias not serious: <10 RCTs
11. **Risk of non-serious adverse events from zinc vs. active control for treatment:** RoB not serious: when 1 RCT high RoB[20] removed, effect estimate with 2 RCTs low RoB[5] RR 1.17 [95% CI 0.71 to 1.92] p = 0.35 Imprecision very serious: OIS is not met, 95% CI includes important risk for active control (RR <0.75, RD 0.03) and important risk for zinc (RR>1.25, RD 0.07)

AEs: adverse events; **RoB:** risk of bias; **OIS:** optimum information size; **IRR:** Incidence rate ratio; **RR:** Risk ratio; **RD:** Risk difference; **MD:** Mean difference; **SMD:** Standardised mean difference

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