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] *A clinically important difference is HR 1.9, that is, ≥ 20 more per 100 or NTT: 5*	⨁⨁◯◯ **LOW**	Critical

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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