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

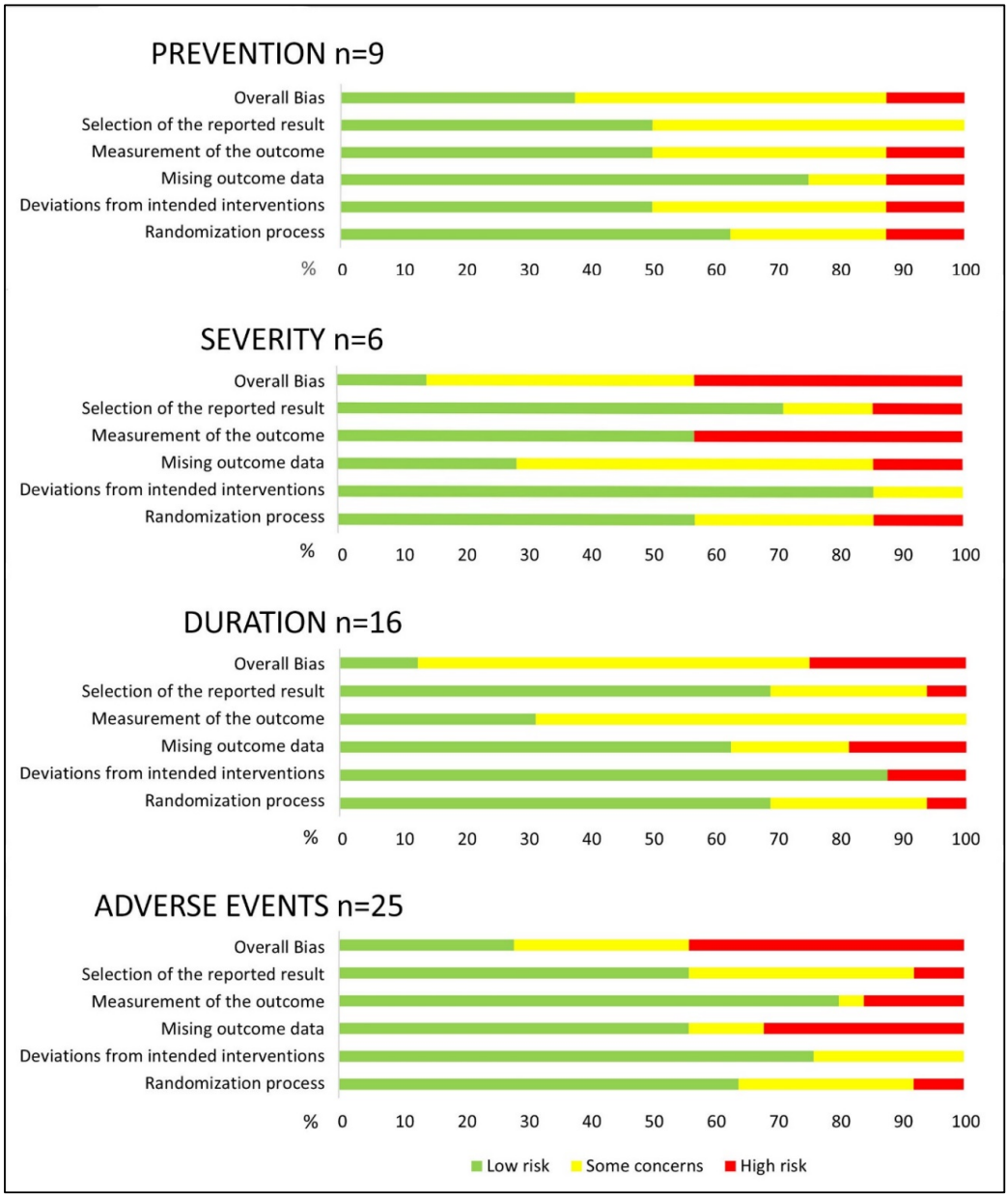

Table 3: Risk of bias for each study outcome

(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

References

1. Silk R, LeFante C. Safety of zinc gluconate glycine (Cold-Eeze) in a geriatric population: a randomized, placebo-controlled, double-blind trial. *Am J Ther* 2005;12(6):612-7. doi: 10.1097/01.mjt.0000179115.04316.18 [published Online First: 2005/11/11]
2. Al-Nakib W, Higgins PG, Barrow I, et al. Prophylaxis and treatment of rhinovirus colds with zinc gluconate lozenges. *J Antimicrob Chemother* 1987;20(6):893-901. doi: 10.1093/jac/20.6.893 [published Online First: 1987/12/01]
3. Prasad AS, Beck FW, Bao B, et al. Zinc supplementation decreases incidence of infections in the elderly: effect of zinc on generation of cytokines and oxidative stress. *Am J Clin Nutr* 2007;85(3):837-44. doi: 10.1093/ajcn/85.3.837 [published Online First: 2007/03/09]
4. Bentley DW, Bradley S, High K, et al. Practice Guideline for Evaluation of Fever and Infection in Long-Term Care Facilities. *Clinical Infectious Diseases* 2000;31(3):640-53. doi: 10.1086/314013
5. Veverka DV, Wilson C, Martinez MA, et al. Use of zinc supplements to reduce upper respiratory infections in United States Air Force Academy cadets. *Complement Ther Clin Pract* 2009;15(2):91-5. doi: 10.1016/j.ctcp.2009.02.006 [published Online First: 2009/04/04]
6. Takkouche B, Regueira-Méndez C, García-Closas R, et al. Intake of vitamin C and zinc and risk of common cold: a cohort study. *Epidemiology* 2002;13(1):38-44. doi: 10.1097/00001648-200201000-00007 [published Online First: 2002/01/24]
7. Wei J, Chen HW, You LH. [Zinc gluconate nasal spray for the prevention of upper respiratory tract infection: A randomised, double-blinded, placebo-controlled trial]. *Medical Journal of Chinese People's Liberation Army* 2009;34(7):838-40.
8. Zhang LJ, Liu GX, Zhang YX, et al. [Zinc gluconate nasal spray for the prevention of acute upper respiratory tract infection]. *Journal of Preventive Medicine Information* 2009;25(7):508-10.
9. Farr BM, Conner EM, Betts RF, et al. Two randomized controlled trials of zinc gluconate lozenge therapy of experimentally induced rhinovirus colds. *Antimicrob Agents Chemother* 1987;31(8):1183-7. doi: 10.1128/aac.31.8.1183 [published Online First: 1987/08/01]
10. Jackson G, Dowling, G., Spiesman, H.F., Boand, I.G., Arthur, V. Transmission of the common cold to volunteers under controlled conditions: I. The common cold as a clinical entity. *AMA archives of internal medicine* 1958;101(2):267-78.
11. Turner RB. Ineffectiveness of intranasal zinc gluconate for prevention of experimental rhinovirus colds. *Clin Infect Dis* 2001;33(11):1865-70. doi: 10.1086/324347 [published Online First: 2001/11/03]
12. Turner RB, Cetnarowski WE. Effect of treatment with zinc gluconate or zinc acetate on experimental and natural colds. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2000;31(5):1202-08.
13. Yao WZ, Yang W, Shen N, et al. [Zinc gluconate nasal spray versus common cold nasal spray in treating common cold: A randomised, multi-center, controlled trial]. *Chinese Journal of Clinical Pharmacology* 2005;21(2):87-90.
14. Smith AP, Tyrrell DA, Al-Nakib W, et al. Effects of zinc gluconate and nedocromil sodium on performance deficits produced by the common cold. *Journal of psychopharmacology (oxford, england)* 1991;5(3):251-54.
15. Belongia EA, Berg R, Liu K. A randomized trial of zinc nasal spray for the treatment of upper respiratory illness in adults. *The American journal of medicine* 2001;111(2):103-08.
16. Douglas RM, Miles HB, Moore BW, et al. Failure of effervescent zinc acetate lozenges to alter the course of upper respiratory tract infections in Australian adults. *Antimicrobial agents and chemotherapy* 1987;31(8):1263-65.
17. Hemilä H. Zinc lozenges may shorten the duration of colds: a systematic review. *The open respiratory medicine journal* 2011;5:51.
18. Eby GA, Davis DR, Halcomb WW. Reduction in duration of common colds by zinc gluconate lozenges in a double-blind study. *Antimicrob Agents Chemother* 1984;25(1):20-4. doi: 10.1128/aac.25.1.20 [published Online First: 1984/01/01]

19. Eby GA, Halcomb WW. Ineffectiveness of zinc gluconate nasal spray and zinc orotate lozenges in common-cold treatment: a double-blind, placebo-controlled clinical trial. *Altern Ther Health Med* 2006;12(1):34-8.
20. Godfrey JC, Conant Sloane B, Smith DS, et al. Zinc gluconate and the common cold: a controlled clinical study. *The Journal of international medical research* 1992;20(3):234-46.
21. Hemilä H, Haukka J, Alho M, et al. Zinc acetate lozenges for the treatment of the common cold: a randomised controlled trial. *BMJ open* 2020;10(1):e031662. doi: 10.1136/bmjopen-2019-031662
22. Hirt M, Nobel S, Barron E. Zinc nasal gel for the treatment of common cold symptoms: a double-blind, placebo-controlled trial. *Ear Nose Throat J* 2000;79(10):778-80, 82. [published Online First: 2000/10/31]
23. Mossad SB, Macknin ML, Medendorp SV, et al. Zinc gluconate lozenges for treating the common cold. A randomized, double-blind, placebo-controlled study. *Ann Intern Med* 1996;125(2):81-8. doi: 10.7326/0003-4819-125-2-199607150-00001 [published Online First: 1996/07/15]
24. Mossad SB. Effect of zincum gluconicum nasal gel on the duration and symptom severity of the common cold in otherwise healthy adults. *QJM : monthly journal of the Association of Physicians* 2003;96(1):35-43. doi: 10.1093/qjmed/hcg004
25. Petrus EJ, Lawson KA, Bucci LR, et al. Randomized, double-masked, placebo-controlled clinical study of the effectiveness of zinc acetate lozenges on common cold symptoms in allergy-tested subjects. *Current therapeutic research, clinical and experimental* 1998;59(9):595-607. doi: 10.1016/S0011-393X(98)85058-3
26. Prasad AS, Fitzgerald JT, Bao B, et al. Duration of symptoms and plasma cytokine levels in patients with the common cold treated with zinc acetate. A randomized, double-blind, placebo-controlled trial. *Annals of Internal Medicine* 2000;133(4):245-16.
27. Prasad AS, Beck FW, Bao B, et al. Duration and severity of symptoms and levels of plasma interleukin-1 receptor antagonist, soluble tumor necrosis factor receptor, and adhesion molecules in patients with common cold treated with zinc acetate. *J Infect Dis* 2008;197(6):795-802. doi: 10.1086/528803 [published Online First: 2008/02/19]
28. Smith DS, Helzner EC, Nuttall CE, Jr., et al. Failure of zinc gluconate in treatment of acute upper respiratory tract infections. *Antimicrobial agents and chemotherapy* 1989;33(5):646-48.
29. Weismann K, Jakobsen JP, Weismann JE, et al. Zinc gluconate lozenges for common cold. A double-blind clinical trial. *Dan Med Bull* 1990;37(3):279-81. [published Online First: 1990/06/01]
30. Sterne JA, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;366