## Appendix 5 (as supplied by the authors): Grade evidence profile

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of Bias | Inconsistency | Indirectness | Imprecision | Other | Zinc | Placebo | Relative (95% CI) | Absolute | | |
| **Duration of Cold Symptoms (Better indicated by lower values)** | | | | | | | | | | | | |
| 8 | randomized trials | no serious risk of bias[1] | serious[2] | no serious indirectness | no serious imprecision[3] | none | 468 | 466 | - | MD 1.65 lower (2.5 to 0.81 lower) | ⊕⊕⊕O MODERATE | IMPORTANT |
| **Severity of Symptoms (Better indicated by lower values)** | | | | | | | | | | | | |
| 4 | randomized trials | no serious risk of bias | serious[4] | no serious indirectness | serious[5] | none | 207 | 205 | - | SMD 0.27 lower (0.58 lower to 0.05 higher) | ⊕⊕OO LOW | IMPORTANT |
| **Number Symptomatic after 3 Days Treatment** | | | | | | | | | | | | |
| 8 | randomized trials | serious[6] | serious[7] | no serious indirectness | no serious imprecision | none | 572/766 (74.7%) | 417/486 (85.8%) | RR 0.92 (0.83 to 1.02) | 69 fewer per 1000 (from 146 fewer to 17 more) | ⊕⊕OO LOW | IMPORTANT |
| **Number Symptomatic after 7 Days Treatment** | | | | | | | | | | | | |
| 9 | randomized trials | serious[8] | serious[9] | no serious indirectness | no serious imprecision | none | 239/801 (29.8%) | 247/524 (47.1%) | RR 0.63 (0.44 to 0.9) | 174 fewer per 1000 (from 47 fewer to 264 fewer) | ⊕⊕OO LOW | IMPORTANT |
| **Any Adverse Event** | | | | | | | | | | | | |
| 9 | randomized | no serious | no serious | no serious | serious[11] | none | 342/879 | 234/608 | RR 1.24 (1.05 to | 92 more per 1000 (from 19 more to 177 | ⊕⊕⊕O | IMPORTANT |

Appendix to: Science M, Johnstone J, Roth DE et al. Zinc for the treatment of the common cold: a systematic review and meta-analysis of randomized controlled trials. *CMAJ* 2012. DOI:10.1503/cmaj111990.

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | trials | risk of bias[10] | inconsistency | indirectness | | | (38.9%) | (38.5%) | 1.46) | more) | MODERATE | |
| **Adverse Events Leading to Discontinuation** | | | | | | | | | | | | |
| 2 | randomized trials | serious[12] | no serious inconsistency | no serious indirectness | serious[13] | none | 5/111 (4.5%) | 0/119 (0%) | RR 11 (0.62 to 193.8) | - | ⊕⊕OO LOW | IMPORTANT |
| **Side Effects: Bad Taste** | | | | | | | | | | | | |
| 8 | randomized trials | no serious risk of bias[14] | no serious inconsistency | no serious indirectness | serious[15] | none | 166/481 (34.5%) | 98/480 (20.4%) | RR 1.65 (1.27 to 2.16) | 133 more per 1000 (from 55 more to 237 more) | ⊕⊕⊕O MODERATE | IMPORTANT |
| **Side Effects: Nausea** | | | | | | | | | | | | |
| 9 | randomized trials | no serious risk of bias[16] | no serious inconsistency | no serious indirectness | serious[17] | none | 85/493 (17.2%) | 49/480 (10.2%) | RR 1.64 (1.19 to 2.27) | 65 more per 1000 (from 19 more to 130 more) | ⊕⊕⊕O MODERATE | IMPORTANT |
| **Side Effects: Abdominal Pain** | | | | | | | | | | | | |
| 7 | randomized trials | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[18] | none | 51/440 (11.6%) | 41/436 (9.4%) | RR 1.19 (0.83 to 1.72) | 18 more per 1000 (from 16 fewer to 68 more) | ⊕⊕⊕O MODERATE | IMPORTANT |
| **Side Effects: Diarrhea** | | | | | | | | | | | | |
| 7 | randomized trials | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[19] | none | 24/420 (5.7%) | 12/411 (2.9%) | RR 1.88 (0.95 to 3.72) | 26 more per 1000 (from 1 fewer to 79 more) | ⊕⊕⊕O MODERATE | IMPORTANT |
| **Side Effects: Constipation** | | | | | | | | | | | | |
| 7 | randomized trials | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[20] | none | 18/440 (4.1%) | 10/436 (2.3%) | RR 1.42 (0.64 to | 10 more per 1000 (from 8 fewer to 49 | ⊕⊕⊕O MODERATE | IMPORTANT |

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| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | 3.12) | more) | | |

[1] No serious design limitations: Blinding was adequate in all trials. Two trials had unclear allocation concealment (Kurugol 2006, Petrus 1998). One trial (Petrus 1998) did not describe random sequence generation and two trials had unclear selective reporting bias (Godfrey 1992, Petrus 1998). Godfrey 1992 had incomplete outcome data. Other bias was unclear in three trials (Godfrey 1992, Mossad 1996 and Petrus 1998). Sensitivity analysis excluding these trials did not change the results so the evidence was not downgraded.
[2] Serious Inconsistency: There was very high statistical heterogeneity. $I^2$ statistic = 95% ($p < 0.00001$). Age, ionic zinc dose, zinc formulation partially accounted for between-study variation.
[3] No serious imprecision: Cumulative sample size was appropriate. The optimal information size to detect a 1-day difference in duration of symptoms (alpha 0.05, 90% power) assuming a mean of 7 days (standard deviation 3 days) was 190 subjects per arm. The 95% CI (2.50, 0.81) crossed the minimally important difference of 1 day. However, the CI was narrow and did not include 'no treatment effect'.
[4] Serious Inconsistency: There was high statistical heterogeneity ($I^2 = 55\%$, $p=0.09$).
[5] Serious Imprecision: Total sample size 412. The optimal information size to detect a 1 point score difference in severity of symptoms ($\alpha = 0.05$, 80% power) assuming a mean score 3 (standard deviation 4) was 252 subjects per arm.
[6] Serious design limitations: Five of the eight trials had serious design limitations (Eby 1984, Smith 1989, Turner 2000a, Turner 2000b, Weismann 1990). All five trials had incomplete outcome data, unclear allocation concealment and did not report the method of randomization. The remaining three trials had no significant limitations.
[7] Serious Inconsistency: There was high statistical heterogeneity ($I^2 = 80\%$, $p < 0.00001$) that was not explained by subgroup analyses.
[8] Serious design limitations: Six of the nine trials had significant design limitations (Eby 1984, Godfrey 1992, Smith 1989, Turner 2000a, Turner 2000b, Weismann 1990). All six trials had incomplete outcome data. Allocation concealment and method of randomization were unclear in all but one of the six (Godfrey 1992). Other bias was present in Eby 1984.
[9] Serious Inconsistency: There was high statistical heterogeneity ($I^2 = 78\%$, $p< 0.0001$).
[10] No serious limitations: Five of the nine trials had serious design problems (Eby 1984, Godfrey 1992, Turner 2000a, Turner 2000b, Weismann 1990). These trials all had incomplete outcome data reporting. All had unclear allocation concealment and did not report the randomization method (except Godfrey 1992). Sensitivity analysis excluding these trials did not change the results so the evidence was not downgraded.
[11] Serious Imprecision: Estimated range of adverse events from 19 more to 177 more per 1000.
[12] Serious design limitations: One of the two studies (Weismann 1990) had serious design limitations. This trial had incomplete outcome data and was high risk for selective reporting. It also had unclear allocation concealment and did not report the method of randomization.
[13] Serious imprecision: Only two trials and one trial had no outcomes to report in either group (Weismann 1990). This resulted in a very large confidence interval and small sample size.
[14] No serious design limitations: Two of the eight trials had serious design limitations (Eby 1984, Weismann 1990). Sensitivity analysis excluding these trials did not change the results so the evidence was not downgraded.
[15] Serious Imprecision: Estimated range of bad taste events from 55 to 237 more per 1000.
[16] No serious design limitations: Three of the nine trials had significant design concerns (Eby 1984, Farr 1987b, Smith 1989). All three had complete outcome data and unclear allocation concealment. The method of randomization was not reported in two trials (Eby 1984, Smith 1989). The remaining 6 trials had low risk of bias. Sensitivity analysis excluding the trials with high risk of bias did not change the results so the evidence was not downgraded.
[17] Serious Imprecision: Estimated range of nausea events from 19 more to 130 more per 1000.
[18] Serious Imprecision: Low number of events (102) and 95% confidence interval crosses no treatment effect (1.0) and the threshold for appreciable harm (1.25).
[19] Serious Imprecision: Low number of events (36) and 95% confidence interval crosses no treatment effect (1.0) and the threshold for appreciable harm (1.25).
[20] Serious Imprecision: Low number of events (28) and 95% confidence interval crosses no treatment effect (1.0) and threshold for appreciable harm (1.25).

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