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Preventive zinc supplementation for children, and the effect of additional iron: A systematic review and meta-analysis

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ABSTRACT

Objective

Zinc deficiency is widespread, and preventive supplementation may have benefits in young children. Effects for children over 5 years of age, and effects when coadministered with other micronutrients are uncertain. These are obstacles to scale-up. This review seeks to determine if preventive supplementation reduces mortality and morbidity for children ages 6 months to 12 years.

Design

Systematic review conducted with the Cochrane Developmental, Psychosocial and Learning Problems Group. Two reviewers independently assessed studies. Meta-analyses were performed for mortality, illness, and side effects.

Data sources

We searched multiple databases, including CENTRAL and Medline in January 2013. Authors were contacted for missing information.

Eligibility criteria for selecting studies

Randomised trials of preventive zinc supplementation. Hospitalised children and children with chronic diseases were excluded.

Results

Eighty randomised trials with 205401 participants were included. There was a small but non-significant effect on all-cause mortality (risk ratio 0.95 [95% CI 0.86 to 1.05]). Supplementation may reduce incidence of all-cause diarrhoea (risk ratio 0.87 [0.85 to 0.89]), but there was evidence of reporting bias. There was no evidence of an effect of incidence or prevalence of respiratory infections or malaria. There was moderate quality evidence of a very small effect on linear growth (SMD 0.09 [0.06 to 0.13]) and an increase in vomiting (RR 1.29 [1.14 to 1.46]). There was no evidence of an effect on iron status. Comparing zinc with and without iron co-supplementation and direct comparisons of zinc plus iron versus zinc administered alone favoured co-intervention for some outcomes and zinc alone for other outcomes. Effects may be larger for children over one year of age, but most differences were not significant.

Conclusions

Benefits of preventive zinc supplementation may outweigh any potential adverse effects in areas where risk of zinc deficiency is high. Further research should determine optimal intervention characteristics and delivery strategies.

STRENGTHS AND LIMITATIONS OF THIS STUDY

This large review was conducted according to best practices and includes the highest quality current evidence about the effects of zinc supplementation.

We investigated several outcomes made multiple comparisons to explore the most important main effects and interactions.

The analyses in this review could not identify the best way to deliver zinc supplements to children in need.

INTRODUCTION

Regular dietary zinc intake is required because zinc cannot be produced or stored.[1,2] In 2011, 116000 deaths in children under 5 years were attributable to zinc deficiency (1.7% of mortalities in this group).[3]

Previous reviews reach disparate conclusions about the benefits of zinc supplementation for young children,[4-12] and most have not examined evidence for children over 5 years of age. Zinc deficiency is prevalent in areas with other micronutrient deficiencies. Concerns about the administration of zinc with iron have been an obstacle to widespread delivery.[13] Understanding the effects of preventive zinc supplementation alone and with iron is crucially important to the future of global health policy.

To evaluate the effects of zinc with or without iron on illness and mortality, as well as growth, we analysed direct comparisons (i.e. zinc plus iron versus zinc alone) as well as subgroups within an overall analysis.

METHODS

Selection criteria and search strategy

Following a published protocol,[14] we conducted a systematic review of randomised clinical trials (RCTs) of orally administered zinc compared with placebo and non-zinc co-interventions received by both groups (e.g. vitamin A). We also compared zinc with and without iron co-supplementation. Participants were six months to 12 years of age. We excluded studies of food fortification and children who were acutely ill.

We searched African Index Medicus, CENTRAL, Conference Proceedings Citation Index, EMBASE, Global Health, ICTRP, IndMED, LILACS, MEDLINE, metaRegister of Controlled Trials, ProQuest Dissertations & Theses Database, and WHOLIS in December 2012 and January 2013 (Appendix 1). Reference lists from previous reviews and from included studies were examined, and trial authors were contacted for unpublished data. Two authors independently reviewed citations and extracted data, including participant demographics, details of the intervention, outcomes, and risk of bias.[15]

Data synthesis

Relative risks and 95% confidence intervals (CIs) were calculated using Mantel-Haenszel methods. Standardised mean differences (SMDs) and 95% CIs were calculated for continuous measures using Hedges *g* and combined using inverse variance methods. When studies reported data in multiple formats, we calculated the SMD and its standard error in Comprehensive Meta-Analysis (CMA) Version 2 before entering data in Review Manager (RevMan) Version 5.2. For incidence data, we combined risk ratios (events per child) and rate ratios (events per child year) because trials were relatively short and we did not anticipate interactions between the intervention and time at risk. For cluster-randomised trials, we used effects controlling for clustering, or we used a intra-cluster correlation coefficient (ICC) to estimate robust standard errors.[15] We used fixed-effect methods for all meta-analyses. Effects favour intervention when the relative risk is reduced (RR<1) or the standardised difference is positive (SMD>0).

When 10 or more studies reported an outcome, we conducted subgroup analyses to explore the effects of iron co-supplementation, national income (low-income countries compared with others), stunting, age (6-12 months, more than 12 months), dose (0-5mg, 5-10mg, etc.), duration (0-6 months, 6-12 months, more than 12 months), and formulation.

Quality of the evidence

Quality of the evidence was judged independently using GRADE.[16] The GRADE system rates evidence from each analysis (i.e., pooled data where possible) as "high", "moderate", "low" or "very low". A "high" rating suggests that evidence is unlikely to be affected by further studies; a "low" rating suggests that further research is required to confirm the direction and magnitude of the true effect. Ratings for meta-analyses of randomised controlled trials start at "high" and may be downgraded for threats to internal validity (i.e. within-study bias), inconsistency (i.e. heterogeneity in results across studies), indirectness (e.g. measures are proxies for the true outcome of interest), imprecision (e.g. few participants, wide confidence intervals), and reporting bias (i.e. publication bias and selective outcome reporting). Because GRADE considers several domains in addition to internal validity, confidence in overall effects may be "low" or "very low" even when all studies were conducted rigorously. The following sections include both significant and non-significant statistical results, and GRADE ratings in the text and tables provide further information about our confidence in these estimates.

RESULTS

Results of the search

From 6384 records, 80 studies were included (Figure 1). Seventy-five studies were published in English, two each in Spanish and Portuguese, one in Chinese. Reasons for excluding 27 studies were enumerated (Appendix 2); additionally, 11 on-going studies were identified, and 5 studies could not be obtained. Seven included studies did not contribute to any meta-analysis because they did not report sufficient data (Appendix 3).

Study characteristics

Included studies assigned 205923 eligible participants (Appendix 4). Twenty trials used factorial designs; there were 100 independent comparisons isolating zinc, and co-interventions were provided to both groups in 51 comparisons. There were 8 independent comparisons of iron with zinc versus zinc alone including 1898 eligible participants. Sample sizes ranged from 21 to 72438 eligible participants (median=200). Nine studies were cluster-randomised, including two randomising households. Three studies included 88% of participants.[17-19] Forty-six studies reported the mean baseline plasma or serum zinc concentration of their participants; the median of these mean concentrations was 72.5 μg/dL.

Thirty-two countries are represented; most studies were conducted in low- or middle-income countries: 37 in Asia, 26 in Latin America and the Caribbean, and 10 in sub-Saharan Africa. The median of mean age at baseline was 28 months, and 22 studies included children over 5 years of age. Both stunted and non-stunted children were included in 42 studies; 5 included only stunted children, 5 included only non-stunted children, and 28 did not specify if participants were stunted.

Studies provided zinc for less than 6 months (30), 6 to 12 months (33), and 12 months or more (16). Of those reporting frequency of zinc supplementation, 48 provided zinc daily and 11 provided zinc weekly. Where reported, daily dose was 0 to 5 mg (5), 5 to 10 mg (19), 10 to 15 mg (30), 15 to 20 mg (8), and 20 mg or more (12). Studies reporting the chemical compound of their zinc supplements provided zinc as sulfate (45), gluconate (12), acetate (six), and other compounds (8). Studies comparing zinc with iron versus zinc alone provided daily dose equivalents of 3 to 36 mg of iron. Outcomes were observed for about 26 weeks (median) after randomisation, with follow-up from 2 to 80 weeks.

Risk of bias

Randomisation and allocation concealment were adequate in 34 and 32 studies; 46 and 48 studies were unclear (Figure 2). For blinding of participants and personnel, 63 studies were at low risk of bias. For blinding of outcome assessment, 65 studies were at low risk of bias. For both types of blinding, 15 studies were unclear.

For all analyses, we attempted to include all randomised study participants; 47 studies were at low risk of bias for incomplete data, 31 were unclear, and 2 were at high risk. For selective reporting, 3 studies were at low risk of bias, 44 were at unclear risk, and 32 were at high risk (Appendix 5).

Bias may affect secondary outcomes in this review, but it does not appear to be important for the primary outcome. For example, mortality and other objective measures are not vulnerable to bias related to blinding, and many missing outcomes were biomarkers or growth related.

Effects of zinc supplementation

In addition to outcomes included in the Summary of Findings Table (Table 1), we analysed results for hospitalisation; prevalence of morbidities; additional measures of growth; as well as biological indicators of zinc, haemoglobin, iron, and copper status (Table 2). Subgroup analyses compare the effects of zinc supplementation with and without iron coadministration (Table 4, Appendix 6).

Fourteen studies including 138302 participants were analysed for all-cause mortality, though other studies included no deaths in either group (Figure 3), and there was high quality evidence of a small effect (risk ratio 0.95 [0.86 to 1.05]). There were similar effects for mortality due to diarrhoea (RR 0.95 [0.69 to 1.31]), mortality due to LRTI (RR 0.86 [0.64 to 1.15]), and mortality due to malaria (RR 0.90 [0.77 to 1.06]), and the evidence for these outcomes was moderate quality.

In 25 studies including 15042 participants, there was low quality evidence of a 13% reduction in incidence of all-cause diarrhoea (Figure 4; RR 0.87 [0.85 to 0.89]). Other measures of diarrhoea were consistent with no difference or with a small reduction in morbidity, including: prevalence of all-cause diarrhoea, hospitalisation due to all-cause diarrhoea, incidence of severe diarrhoea, prevalence of severe diarrhoea, incidence of persistent diarrhoea, and prevalence of persistent diarrhoea.

In twelve trials (9610 participants), there was high quality evidence of no effect on LRTI incidence (Appendix 7; RR 1.00 [0.94 to 1.07]). One trial reported no LRTI in either group.[20] Results for prevalence were consistent with no difference in respiratory morbidity.

Four trials (2407 participants) found moderate quality evidence that would be consistent with no effect or a harmful effect on malaria incidence (RR 1.04 [0.94, 1.14]). One study reported no significant effect on malaria prevalence.

Fifty studies reported height for 13669 participants (Figure 5). There was moderate quality evidence of a very small but statistically significant increase in linear growth (SMD 0.09 [0.06 to 0.13]). Results for weight, weight-to-height ratio and prevalence of stunting were consistent with no difference or a small effect on growth.

Forty-six studies reported serum zinc for 9810 participants. There was evidence of a medium effect (SMD 0.62 [0.58 to 0.67]) on zinc concentration. Results consistently favoured zinc rather than no-intervention, but they were extremely inconsistent in magnitude, possibly due to differences in participants and settings (Chi^2=582.45, df=47 (P <0.00001); I^2=91%). Eleven studies reported serum copper for 3071 participants (1% of participants in this review). There was very low quality evidence of a small reduction in copper (SMD -0.22 [-0.29 to 0.14]); as above, the results were inconsistent (Chi^2=37.47, df=10 (P <0.0002); I^2=68%). There was no evidence of an effect on haemoglobin, prevalence of anaemia, or iron status.

In five trials (35192 participants) there was high quality evidence of increased vomiting (RR 1.29 [1.14 to 1.46]). Two trials reported no adverse events in either group (i.e. supplemented or non-supplemented).[21,22] Results for study withdrawal, participants with one or more side effects, and number of vomiting episodes indicate some short-term side effects; there was no evidence of serious adverse events.

Effects of zinc plus iron compared with zinc alone

Effects on mortality were not significantly different between subgroups with and without iron (Chi^2=1.30, p=0.25); however, there was no mortality effect in groups receiving iron (RR 0.99 [0.86 to 1.15]) while the effect for groups that did not receive iron was nearly significant (RR 0.89 [0.79 to 1.00]). Effects on incidence of diarrhoea differed between groups (Figure 4; Chi^2=65.11, p<0.00001), with no benefit for the group that received iron (RR 1.00 [0.96 to 1.05]) and a significant benefit for the group that did not receive iron (RR 0.82 [0.80 to 0.84]). There were significant effects with and without iron co-supplementation on zinc status; these were greater in the studies without iron for serum zinc (Chi^2=27.07, p<0.00001) and prevalence of zinc deficiency (Chi^2=34.27, p<0.00001). There were also differences between these groups of studies for serum ferritin and serum copper; zinc had no effect in studies with iron co-intervention, but zinc without iron co-intervention reduced ferritin and copper. Overall effects on growth were small; there was a significant difference between subgroups for height but not weight, and the difference for weight-to-height ratio favoured the group that received iron (i.e. the opposite of other results). There were no significant effects in either subgroup for lower respiratory tract infections, serum haemoglobin, prevalence of anaemia, or prevalence of iron deficiency.

Several trials compared zinc coadministered with iron versus zinc given alone (Appendix 6). One trial reported no significant difference in all-cause mortality (323 participants; RR 0.33 [0.01 to 8.39]). In five trials (1530 participants), effects on incidence of all-cause diarrhoea favoured zinc alone (RR 1.10 [1.03 to 1.18]). In one trial (399 participants), effects on prevalence of all-cause diarrhoea favoured zinc with iron, but this was not significant (RR 0.90 [0.79 to 1.06]). Five trials (1329 participants) reported no difference in height (SMD 0.06 [-0.04 to 0.16]). There was similarly low quality evidence and mixed results for other outcomes (Table 3).

Additional subgroup analyses

Studies in high-income countries did not evaluate most outcomes, so we were unable to explore differences in effect by national income. Effects on weight and weight–to-height ratio were not statistically different, and there was no evidence of consistent differences in biological outcomes (Appendix 6).

Most studies included both stunted and non-stunted children, and it was not possible to compare effects between studies for most outcomes. Differences between groups were not significant for growth, but these would be consistent with larger effects in studies of stunted children.

Age was not significantly associated with effects on mortality or incidence diarrhoea, but results would be consistent with greater benefits in children over 1 year of age (Figure 3). Effects on weight were greatest in studies of older children, and there was a similar pattern for height, though the largest study of children over 5 years of age included only 804 participants. The effect of supplementation on zinc deficiency was greater in studies of older children, as was the negative effect on copper. There was no evidence of consistent differences in other biological outcomes.

Dose was not significantly associated with effects on mortality, incidence of LRTI, haemoglobin, or weight-to-height ratio. The pattern of results was inconsistent for incidence and prevalence of diarrhoea, height, weight, and plasma ferritin (Appendix 6). Subgroups were significantly different for serum zinc, prevalence of zinc deficiency, prevalence of iron deficiency, and plasma copper; only these results are consistent with a dose-response relationship.

Duration of supplementation was not significantly associated with effects on mortality, incidence of diarrhoea, incidence of LRTI, or weight-to-height ratio, or prevalence of iron deficiency (Appendix 6). There was a significant difference for prevalence of diarrhoea, but the magnitude of this difference may not be important. Studies of longer supplementation were associated with greater effects on height; the pattern of results was not consistent for weight. By contrast, the largest benefits for biological markers (serum zinc and prevalence of zinc deficiency) were reported in the shortest studies.

Formulation was associated with differences among subgroups, though few studies included capsules or powder. Comparing solution and tablets, differences were not significant for mortality, incidence and prevalence of diarrhoea, incidence of LRTI, blood haemoglobin, prevalence of anaemia, or prevalence of iron deficiency. There were significant differences in the effects of serum ferritin and serum copper, but only three studies of each outcome used tablets, and they were highly heterogeneous. Effects on height, weight, and serum zinc were greater in studies using solution compared with tablet, but all effects were small (Appendix 6).

Reporting bias

For outcomes included in the Summary of Findings Table with 10 or more studies, we also conducted a trim-and-fill analysis to investigate reporting bias (Appendix 8).[23] There was some evidence of small study bias—studies were trimmed for all-cause mortality (1 trimmed) and incidence of all-cause diarrhoea (13 trimmed; Figure 6). None were trimmed for incidence of LRTI, nor were any trimmed for height. The adjusted effect for mortality was not importantly different from the observed effect, but the observed effect for diarrhoea (RR 0.87 [0.85 to 0.89]) was larger than the adjusted value (RR 0.95 [0.93 to 0.97]).

DISCUSSION

Consistent with previous reviews, this review finds high quality evidence from several large, well-conducted trials.[5,7,10] We believe that these results suggest zinc supplementation is probably associated with a small reduction in all-cause mortality for children at risk of deficiency. In interpreting these results, we considered that the results of this meta-analysis are drawn from 13 trials including almost 140,000 participants. The results of those studies are statistically consistent, the overall confidence intervals are relatively small, and the balance of probability favours zinc supplementation rather than placebo. Small reductions in cause-specific mortality were consistent with effects on illness and cause-specific mortality, and the results were biologically plausible. Benefits in any specific are may be related to level of deficiency; countries with very high levels of deficiency could expect the largest reductions in mortality as a result of supplementation.[24] This review also suggests that benefits may not be restricted to young children; there is some evidence of benefits on secondary outcomes in trials including children over 5 years of age, but there is a lack of evidence about effects on mortality in this group.

Results for secondary outcomes suggest modest benefits. Main results for diarrhoea morbidity were consistent with previous reviews,[4,5,7,10] but an asymmetrical funnel plot was indicative of small-study bias. After adjustment, the effect for diarrhoea was halved, and the reduced estimate was consistent with other critical outcomes in this review. Previous reviews have also suggested beneficial effects on respiratory infections[4,5,9-12] and malaria,[10] which this review does not confirm. Previous reviews have reported variable effects on growth;[5,6,8] this review suggests that preventive zinc supplementation alone is unlikely to have large effects on linear growth and morbidity. Supplementation is associated with increased risk of vomiting, but there is no evidence of lasting adverse effects.

Critical outcomes included data for 2407 to 138302 participants, so further placebo-controlled trials of preventive zinc supplementation for young children may not be necessary. However, subgroup analyses did not identify an optimal supplementation strategy (i.e. dose, formulation, and frequency), and large trials comparing active interventions could inform clinical guidelines. Subgroup analyses identify some sources of observed heterogeneity; however, subgroups that were statistically different included a large amount of residual heterogeneity, which is reflected in our judgements about the quality of the evidence (Table 1). Analyses of group-level data are of limited value for identifying moderators, particularly in analyses dominated by a few large studies. Further analyses of individual patient data would be more conclusive.

Effects on biological indicators were inconsistent across studies, but large effects on these measures were not always reflected in clinical outcomes. Supplementation may increase serum zinc, but the magnitude of the effect appears to differ across populations and interventions. Effects on other micronutrients, including iron and copper, are uncertain. Researchers have suggested that iron supplementation may interfere with the absorption of zinc and, conversely, that zinc may interfere with iron and copper absorption;[25,26] however, the relationships between these biomarkers and clinical outcomes (i.e. mortality and morbidities) have not been established.

Subgroup analyses comparing zinc with and without iron did not resolve uncertainty about the effect of co-supplementation. Only four studies with iron co-supplementation reported mortality outcomes, and evidence of outcome reporting bias for diarrhoea incidence leads to cautious interpretation of differences in this outcome. There was no evidence that larger doses or increased duration were associated with increased iron deficiency, but these comparisons are observational and could be affected by uncontrolled covariates.

Direct comparisons within trials provide the only experimental evidence about the effects of co-supplementation with iron. For rare events like mortality, effects of zinc and iron can only be detected in large studies, so studies of interaction effects will need to be very large to detect real differences. Future studies are needed to identify main effects and to explore how administration (i.e. separate or combined) affects uptake and costs.

Dietary intake and supplementation have reduced micronutrient deficiencies in Asia, but micronutrient deficiencies remain common.[3,27] The prevalence of micronutrient deficiencies is declining in Africa, but the absolute number of deficient children is increasing.[3] This review suggests that the overall benefits of preventive zinc supplementation outweigh potential harms in areas with a high risk of zinc deficiency. Further research is needed to determine if these benefits extend to children over 5 years of age. Current estimates suggest that delivering 10 evidence-based nutrition-specific interventions, including preventive zinc supplements, could reduce global mortality in children under 5 years of age by 15%.[28] To that end, research is needed to identify the most effective strategies for delivering zinc supplements to populations in need.[29]

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Contributors

All authors contributed to the background. EMW and JJ were responsible for the methods. JJ executed the first literature search, and EMW and AI executed the update. JJ, EMW, AI, and EC reviewed citations for inclusion. JJ, EMW, AI, SD, XHC, and AJ extracted data. JJ and EMW entered outcome data into RevMan and analysed the data. EMW, JJ, and AI wrote the results and discussion. EMW and AI drafted the summary of findings table, which was agreed on by all authors. ZB contributed to the writing and interpretation of findings. EMW is the guarantor.

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Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years. ZAB is an author of some of the included trials. ZAB and AI have published previous reviews about zinc.

Ethical approval

Not required.

Data sharing

Data are provided in the appendices and available from the authors upon request.

APPENDICIES

Appendix 1: Electronic searches
Appendix 2: Excluded studies
Appendix 3: On-going studies
Appendix 4: Included studies
Appendix 5: Risk of bias
Appendix 6: Subgroup analyses
Appendix 7: Additional forest plots
Appendix 8: Tests for reporting bias

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TABLES AND FIGURES

Figure 1: PRISMA flowchart

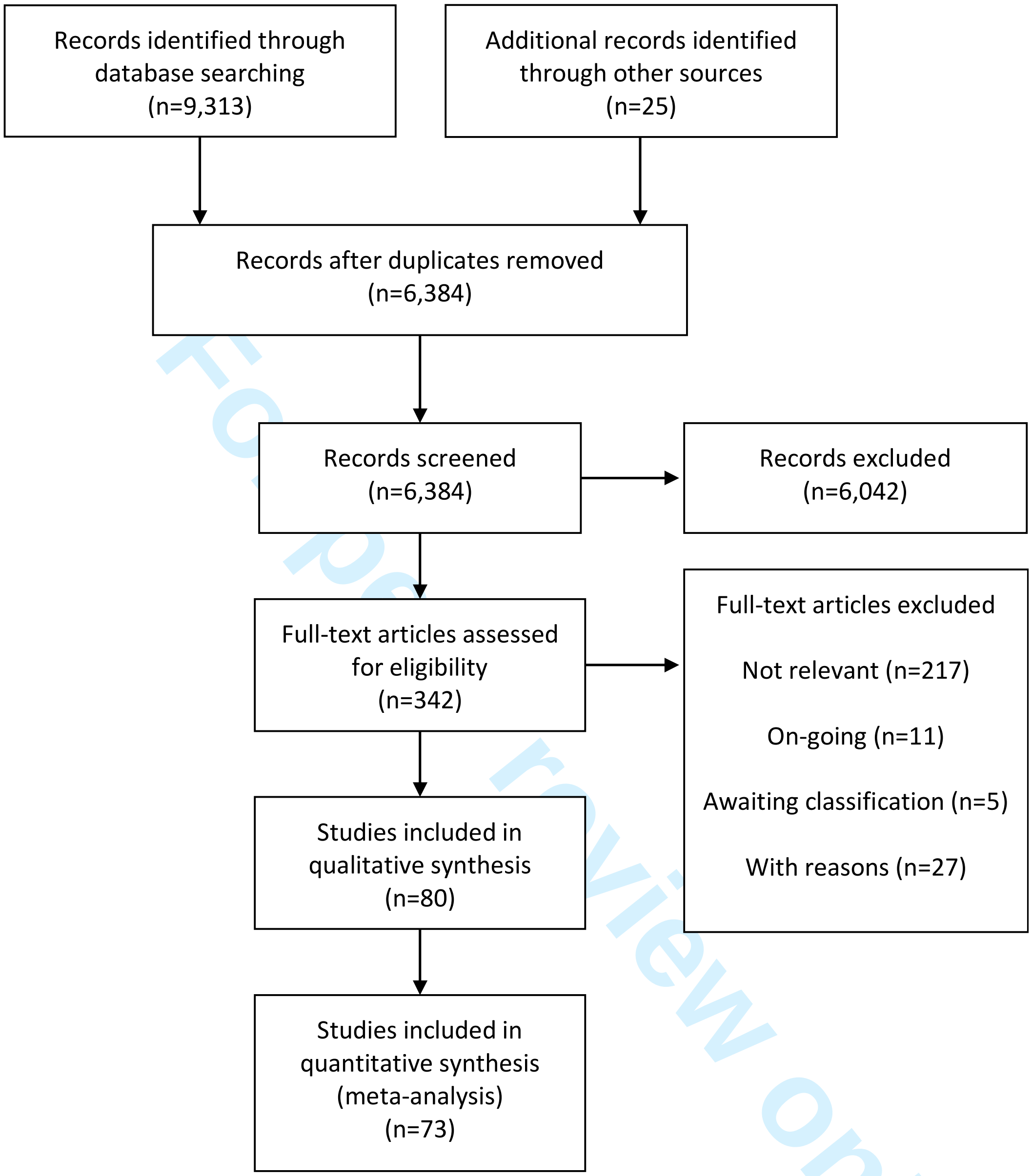

Figure 2: Risk of bias summary

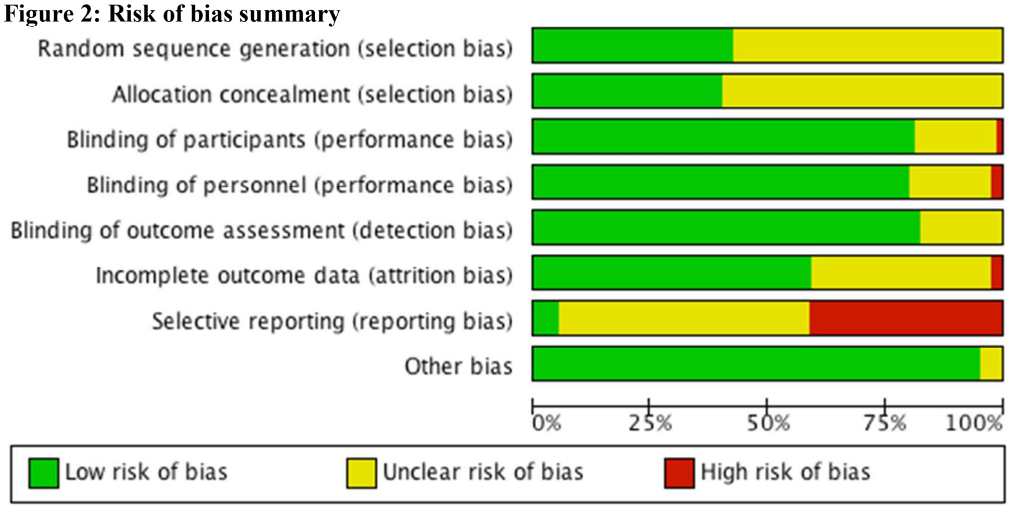

Figure 3: All-cause mortality by age

Study or Subgroup	log[Risk Ratio]	SE	Zinc Total	No Zinc Total	Weight	Risk Ratio IV, Fixed, 95% CI
3.1.1 6 months to < 1 year						
Baqui 2003	1.07361099	1.62916074	161	157	0.1%	2.93 [0.12, 71.29]
Chang 2010	−1.59447504	1.54597037	198	201	0.1%	0.20 [0.01, 4.20]
Lind 2003	1.60943791	1.54541389	170	170	0.1%	5.00 [0.24, 103.38]
Chhagan 2009	0.02643326	0.99114872	112	115	0.2%	1.03 [0.15, 7.16]
Tielsch 2006 (2)	0.01267064	0.31113591	1017	966	2.4%	1.01 [0.55, 1.86]
Sazawal 2006	0.05826891	0.10048763	13294	13318	23.0%	1.06 [0.87, 1.29]
Subtotal (95% CI)			**14952**	**14927**	**25.9%**	**1.06 [0.88, 1.27]**
Heterogeneity: $Chi^2 = 2.56$, df = 5 (P = 0.77); $I^2 = 0\%$						
Test for overall effect: Z = 0.60 (P = 0.55)						
3.1.2 1 to < 5 years						
Larson 2010	1.10424611	1.6295395	176	177	0.1%	3.02 [0.12, 73.56]
Penny 2004	−1.58534036	1.54139551	81	83	0.1%	0.20 [0.01, 4.20]
Bhandari 2002	−1.93942189	1.51132135	1228	1236	0.1%	0.14 [0.01, 2.78]
Veenemans 2011 (2)	−0.6670019	1.2193957	151	155	0.2%	0.51 [0.05, 5.60]
Shankar 2000	1.11321109	1.14836145	136	138	0.2%	3.04 [0.32, 28.90]
Muller 2001	−0.86670956	0.52677681	341	344	0.8%	0.42 [0.15, 1.18]
Tielsch 2006	−0.22948879	0.12870764	8731	8484	14.0%	0.79 [0.62, 1.02]
Sazawal 2006 (2)	−0.03756725	0.11932628	8120	7950	16.3%	0.96 [0.76, 1.22]
Bhandari 2007	0.04493755	0.11212408	36293	36145	18.4%	1.05 [0.84, 1.30]
Sazawal 2006	−0.19845094	0.09838509	7980	7954	24.0%	0.82 [0.68, 0.99]
Subtotal (95% CI)			**63237**	**62666**	**74.1%**	**0.89 [0.80, 0.99]**
Heterogeneity: $Chi^2 = 10.28$, df = 9 (P = 0.33); $I^2 = 12\%$						
Test for overall effect: Z = 2.08 (P = 0.04)						
Total (95% CI)			**78189**	**77593**	**100.0%**	**0.93 [0.85, 1.02]**
Heterogeneity: $Chi^2 = 15.32$, df = 15 (P = 0.43); $I^2 = 2\%$						
Test for overall effect: Z = 1.49 (P = 0.14)						
Test for subgroup differences: $Chi^2 = 2.48$, df = 1 (P = 0.11), $I^2 = 59.8\%$						

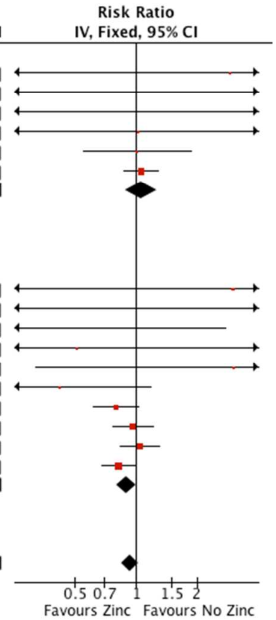

Figure 4: Incidence of all cause diarrhoea with and without iron co-supplementation

Study or Subgroup	log[Risk Ratio]	SE	Zinc Total	No Zinc Total	Weight	Risk Ratio IV, Fixed, 95% CI
3.9.1 Iron co-intervention						
Meeks Gardner 2005	−4.48367263	1.42163731	55	59	0.0%	0.01 [0.00, 0.18]
Cole 2012	−0.26503449	0.37388896	75	68	0.1%	0.77 [0.37, 1.60]
Alarcon 2004	−0.33963305	0.30181636	112	111	0.1%	0.71 [0.39, 1.29]
Rosado 1997 (2)	−0.52044108	0.18680745	55	54	0.4%	0.59 [0.41, 0.86]
Veenemans 2011 (2)	−0.27010424	0.17803183	151	155	0.4%	0.76 [0.54, 1.08]
Lind 2003 (2)	−0.07145896	0.09311961	170	170	1.4%	0.93 [0.78, 1.12]
Chang 2010 (2)	−0.25350318	0.0794688	400	201	2.0%	0.78 [0.66, 0.91]
Richard 2006 (2)	0.03619935	0.06581383	210	208	2.9%	1.04 [0.91, 1.18]
Baqui 2003 (2)	0.08849308	0.05540904	162	165	4.0%	1.09 [0.98, 1.22]
Soofi 2013	0.03774033	0.02689562	853	865	17.1%	1.04 [0.99, 1.09]
Subtotal (95% CI)			**2243**	**2056**	**28.4%**	**1.00 [0.96, 1.05]**
Heterogeneity: $Chi^2 = 37.33$, df = 9 (P < 0.0001); $I^2 = 76\%$						
Test for overall effect: Z = 0.20 (P = 0.84)						
3.9.2 No iron co-intervention						
Chang 2010 (2)	−0.27537422	0.36843806	201	201	0.1%	0.76 [0.37, 1.56]
Chang 2010	−0.58978851	0.33149677	198	201	0.1%	0.55 [0.29, 1.06]
Han 2002	−0.75662302	0.28075433	33	22	0.2%	0.47 [0.27, 0.81]
Han 2002 (2)	−0.17923468	0.27919905	24	26	0.2%	0.84 [0.48, 1.44]
Meeks Gardner 1998	0.00421645	0.25610818	31	30	0.2%	1.00 [0.61, 1.66]
Umeta 2000	−0.78170058	0.23234928	100	100	0.2%	0.46 [0.29, 0.72]
Gupta 2003	−0.89381788	0.22473329	186	94	0.2%	0.41 [0.26, 0.64]
Rosado 1997	−0.40188729	0.20280294	54	56	0.3%	0.67 [0.45, 1.00]
Veenemans 2011	−0.22342699	0.19743482	153	153	0.3%	0.80 [0.54, 1.18]
Penny 2004	−0.11778304	0.10486269	80	79	1.1%	0.89 [0.72, 1.09]
Ruel 1997	−0.25131443	0.10417938	55	53	1.1%	0.78 [0.63, 0.95]
Gupta 2007	−0.14660347	0.097381	854	858	1.3%	0.86 [0.71, 1.05]
Wuehler 2008	−0.30010459	0.09601332	353	116	1.3%	0.74 [0.61, 0.89]
Lind 2003	0.06899287	0.09065627	170	170	1.5%	1.07 [0.90, 1.28]
Larson 2010	−0.23381808	0.08123116	176	177	1.9%	0.79 [0.68, 0.93]
Muller 2001	−0.14077255	0.07595902	342	344	2.1%	0.87 [0.75, 1.01]
Chhagan 2009	−0.04913269	0.07335707	104	105	2.3%	0.95 [0.82, 1.10]
Richard 2006	−0.28106642	0.07078211	209	215	2.5%	0.75 [0.66, 0.87]
Long 2006	0.12218449	0.07061765	181	183	2.5%	1.13 [0.98, 1.30]
Long 2006 (2)	−0.26514098	0.06888881	192	180	2.6%	0.77 [0.67, 0.88]
Rahman 2001 (2)	−0.05001042	0.06042171	175	160	3.4%	0.95 [0.84, 1.07]
Rahman 2001	−0.13353139	0.0579042	170	161	3.7%	0.88 [0.78, 0.98]
Baqui 2003	−0.02439145	0.05739701	161	157	3.8%	0.98 [0.87, 1.09]
Sazawal 1996	−0.08461665	0.04515217	286	293	6.1%	0.92 [0.84, 1.00]
Malik 2013	−0.48917615	0.02918358	134	124	14.5%	0.61 [0.58, 0.65]
Bhandari 2002	−0.10583655	0.02613411	1228	1236	18.1%	0.90 [0.85, 0.95]
Subtotal (95% CI)			**5850**	**5494**	**71.6%**	**0.82 [0.80, 0.84]**
Heterogeneity: $Chi^2 = 196.27$, df = 25 (P < 0.00001); $I^2 = 87\%$						
Test for overall effect: Z = 14.83 (P < 0.00001)						
Total (95% CI)			**8093**	**7550**	**100.0%**	**0.87 [0.85, 0.89]**
Heterogeneity: $Chi^2 = 298.70$, df = 35 (P < 0.00001); $I^2 = 88\%$						
Test for overall effect: Z = 12.45 (P < 0.00001)						
Test for subgroup differences: $Chi^2 = 65.11$, df = 1 (P < 0.00001), $I^2 = 98.5\%$						

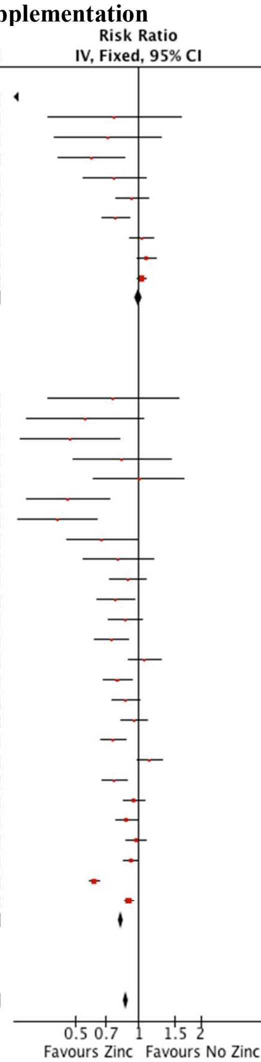

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Figure 5: Height

Study or Subgroup	Std. Mean Difference	SE	No Zinc Total	Zinc Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Sayeg Porto 2000	0.46637519	0.45563575	9	9	0.1%	0.47 [−0.43, 1.36]
Nakamura 1993	0.96009475	0.44484717	11	10	0.2%	0.96 [0.09, 1.83]
Smith 1999	0.725292	0.43412761	11	10	0.2%	0.73 [−0.13, 1.58]
Ince 1995	0.45028253	0.40793136	9	16	0.2%	0.45 [−0.35, 1.25]
Garcia 1998	0.10584806	0.34006946	17	16	0.3%	0.11 [−0.56, 0.77]
Castillo-Duran 1994	0.35835025	0.313	21	19	0.3%	0.36 [−0.26, 0.97]
Walravens 1983	0.3564118	0.31249613	20	20	0.3%	0.36 [−0.26, 0.97]
Dehbozorgi 2007	−1.97349853	0.31209312	30	30	0.3%	−1.97 [−2.59, −1.36]
Clark 1999	−0.49205024	0.295419	21	25	0.3%	−0.49 [−1.07, 0.09]
Sempertegui 1996	−0.13048108	0.28450141	25	23	0.4%	−0.13 [−0.69, 0.43]
Walravens 1989	0.2375538	0.27941182	25	25	0.4%	0.24 [−0.31, 0.79]
Han 2002	0.97763178	0.26685037	28	34	0.4%	0.98 [0.45, 1.50]
Meeks Gardner 1998	0.11783456	0.26252076	26	31	0.4%	0.12 [−0.40, 0.63]
Han 2002 (2)	−0.03791509	0.26134196	29	28	0.4%	−0.04 [−0.55, 0.47]
Silva 2006	−0.04607318	0.25926942	30	28	0.5%	−0.05 [−0.55, 0.46]
Gibson 1989	0.07592408	0.25493989	30	30	0.5%	0.08 [−0.42, 0.58]
Hambidge 1978	0.31355858	0.24369413	31	36	0.5%	0.31 [−0.16, 0.79]
Hettiarachchi 2008 (2)	0.13930582	0.23580261	30	113	0.5%	0.14 [−0.32, 0.60]
Tupe 2009	0.05864615	0.22908102	40	43	0.6%	0.06 [−0.39, 0.51]
Mozaffari-Khosravi 2009	0.88453187	0.22577077	45	40	0.6%	0.88 [0.44, 1.33]
Sazawal 2006	−0.30537883	0.22312277	58	44	0.6%	−0.31 [−0.74, 0.13]
Hettiarachchi 2008	0.43865049	0.21702312	40	99	0.6%	0.44 [0.01, 0.86]
Sazawal 2006 (2)	−0.07944316	0.21183638	54	56	0.7%	−0.08 [−0.49, 0.34]
Ruel 1997	0.05883983	0.21022626	44	45	0.7%	0.06 [−0.35, 0.47]
Rosado 1997	0.07813202	0.20362659	47	48	0.7%	0.08 [−0.32, 0.48]
Ruz 1997	0.25866462	0.20129773	49	49	0.7%	0.26 [−0.14, 0.65]
Fonseca 2002	−0.16854426	0.19990018	48	51	0.8%	−0.17 [−0.56, 0.22]
Rosado 1997 (2)	0.11812477	0.19963612	50	49	0.8%	0.12 [−0.27, 0.51]
Kikafunda 1998	−0.02125815	0.18705861	54	59	0.9%	−0.02 [−0.39, 0.35]
Meeks Gardner 2005	−0.23589118	0.18682894	59	55	0.9%	−0.24 [−0.60, 0.13]
Hong 1982	1.09400346	0.18644996	67	64	0.9%	1.09 [0.73, 1.46]
Ninh 1996	0.34634509	0.16590035	73	73	1.1%	0.35 [0.02, 0.67]
Penny 2004	0.13724615	0.16491512	75	71	1.1%	0.14 [−0.19, 0.46]
Cavan 1993	−0.19093721	0.15976556	80	76	1.2%	−0.19 [−0.50, 0.12]
Brown 2007	0.02831727	0.15073647	92	83	1.3%	0.03 [−0.27, 0.32]
Chen 2012	0.15227332	0.1483077	93	88	1.4%	0.15 [−0.14, 0.44]
Umeta 2000	0.33222629	0.14785133	92	92	1.4%	0.33 [0.04, 0.62]
Akramuzzaman 1994	0	0.14216714	104	93	1.5%	0.00 [−0.28, 0.28]
Shankar 2000	0.07055089	0.13696712	109	103	1.6%	0.07 [−0.20, 0.34]
Alarcon 2004	0.17562403	0.13685249	104	109	1.6%	0.18 [−0.09, 0.44]
Gracia 2005	−0.01896341	0.13144479	115	115	1.8%	−0.02 [−0.28, 0.24]
Friis 1997	0.03899074	0.12009587	135	141	2.1%	0.04 [−0.20, 0.27]
Baqui 2003	−0.03690719	0.11899992	140	141	2.1%	−0.04 [−0.27, 0.20]
Baqui 2003 (2)	−0.03759149	0.11833	150	135	2.2%	−0.04 [−0.27, 0.19]
Long 2006	0.1584015	0.11813857	142	144	2.2%	0.16 [−0.07, 0.39]
Long 2006 (2)	−0.10160093	0.11663237	144	149	2.2%	−0.10 [−0.33, 0.13]
Wuehler 2008	−0.03193409	0.11140371	108	313	2.4%	−0.03 [−0.25, 0.19]
Lind 2003 (2)	−0.26456209	0.11134035	163	161	2.4%	−0.26 [−0.48, −0.05]
Rahman 2001	−0.00867309	0.11069586	160	165	2.5%	−0.01 [−0.23, 0.21]
Rahman 2001 (2)	−0.20323135	0.11056287	157	171	2.5%	−0.20 [−0.42, 0.01]
Lind 2003	0.04482357	0.11052917	164	162	2.5%	0.04 [−0.17, 0.26]
Richard 2006 (2)	0.01147736	0.10286111	182	195	2.9%	0.01 [−0.19, 0.21]
Richard 2006	0.12404623	0.10262789	189	190	2.9%	0.12 [−0.08, 0.33]
Mazariegos 2010	−0.04454505	0.10189635	196	188	2.9%	−0.04 [−0.24, 0.16]
Muller 2001	0.09988615	0.07775177	329	332	5.0%	0.10 [−0.05, 0.25]
Ebrahimi 2006	1.2611452	0.07721922	418	386	5.1%	1.26 [1.11, 1.41]
DiGirolamo 2010	−0.09680936	0.07476273	355	360	5.4%	−0.10 [−0.24, 0.05]
Bhandari 2007	0.14273438	0.0697166	427	448	6.2%	0.14 [0.01, 0.28]
Bhandari 2002	−0.04596797	0.04238854	1133	1093	16.9%	−0.05 [−0.13, 0.04]
Total (95% CI)			**6687**	**6982**	**100.0%**	**0.09 [0.06, 0.13]**

Heterogeneity: $Chi^2 = 407.92$, df = 58 ($P < 0.00001$); $I^2 = 86\%$

Test for overall effect: Z = 5.31 ($P < 0.00001$)

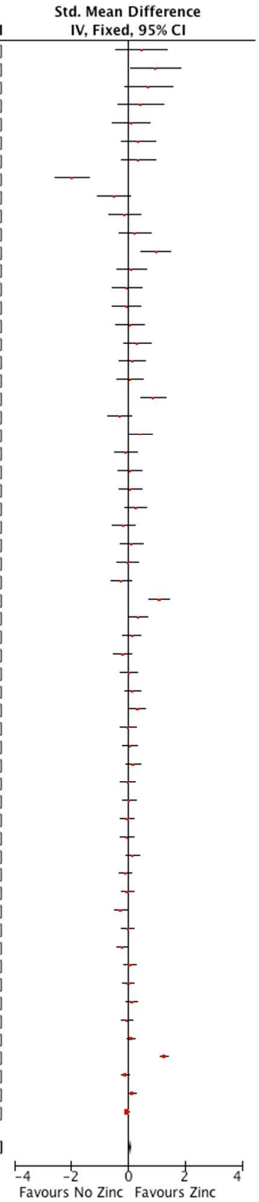


Figure 6: Incidence of diarrhoea funnel plot (trim-and-fill analysis)

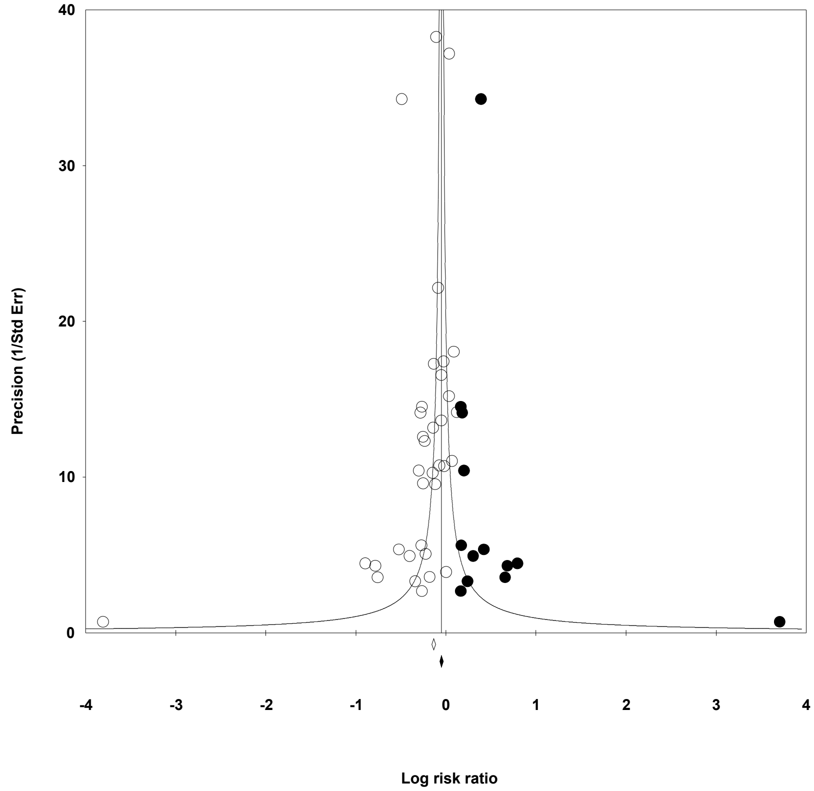


Table 1: Summary of findings

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Control	Corresponding risk Zinc			
All-cause mortality Follow-up: 17 to 72 weeks	Low 2,400 per 1,000,000 High 34,900 per 1,000,000	 2,280 per 1,000,000 (2,064 to 2,520) 33,155 per 1,000,000 (30,014 to 36,645)	RR 0.95 (0.86 to 1.05)	138,302 (13 studies)	⊕⊕⊕⊕ high
Mortality due to all-cause diarrhoea Follow-up: 52 to 69 weeks	Low 800 per 1,000,000 High 3,000 per 1,000,000	 760 per 1,000,000 (552 to 1,048) 2,850 per 1,000,000 (2,070 to 3,930)	RR .95 (0.69 to 1.31)	132,321 (4 studies)	⊕⊕⊕⊝ moderate[1]
Mortality due to LRTI Follow-up: 52 to 69 weeks	Low 1,200 per 1,000,000 High 3,000 per 1,000,000	 1,032 per 1,000,000 (768 to 1,380) 2,580 per 1,000,000 (1,920 to 3,450)	RR 0.86 (0.64 to 1.15)	132,063 (3 studies)	⊕⊕⊕⊝ moderate[1]
Mortality due to malaria Follow-up: 46 to 69 weeks	Low 7,400 per 1,000,000 High 14,200 per 1,000,000	 6,660 per 1,000,000 (5,698 to 7,844) 12,780 per 1,000,000 (10,934 to 15,052)	RR 0.90 (0.77 to 1.06)	42,818 (2 study)	⊕⊕⊕⊝ moderate[1]
Incidence of all-cause diarrhoea Follow-up: 12 to 72 weeks	Low 20,000 per 1,000,000 High 1,770,000 per 1,000,000	 17,400 per 1,000,000 (17,000 to 17,800) 1,539,900 per 1,000,000 (1,504,500 to 1,575,300)	RR 0.87 (0.85 to 0.89)	15,042 (35 studies)	⊕⊕⊝⊝ low[2,3]
Incidence of LRTI Follow-up: 12 to 52 weeks	Low 30,000 per 1,000,000 High 370,000 per 1,000,000	 30,000 per 1,000,000 (28,200 to 32,100) 370,000 per 1,000,000 (347,800 to 395,900)	RR 1.00 (0.94 to 1.07)	9,610 (12 studies)	⊕⊕⊕⊕ high
Incidence of malaria Follow-up: 24 to 47 weeks	Low 140,000 per 1,000,000 High 2,950,000 per 1,000,000	 147,000 per 1,000,000 (133,000 to 161,000) 3,097,500 per 1,000,000 (2,802,500 to 3,392,500)	RR 1.05 (0.95 to 1.15)	2,407 (4 studies)	⊕⊕⊕⊝ moderate[4]
Height Follow-up: 10 to 60 weeks	The mean height in the control groups was -1 HAZ	The mean height in the intervention groups was 0.1 HAZ better (0 to 0.2 better)	SMD 0.09 (0.06 to 0.13)	13,669 (51 studies)	⊕⊕⊕⊝ moderate[5]
Participants with 1 vomiting episode Follow-up: 24 to 52 weeks	Low 17,500 per 1,000,000 High 300,600 per 1,000,000	 22,575 per 1,000,000 (19,950 to 25,550) 387,774 per 1,000,000 (342,684 to 438,876)	RR 1.29 (1.14 to 1.46)	35,192 (4 studies)	⊕⊕⊕⊕ high

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval; RR: Risk ratio; SMD: Standardised Mean Difference

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Footnotes
[1] Few deaths observed overall.
[2] I^2=88%
[3] Trim and fill analysis suggests the effect may be overestimated due to publication bias.
[4] I^2=44%
[5] I^2=86%

Table 2: Zinc compared with no zinc (all outcomes)

Outcomes	Trials	People	ES (95% CI), fixed effects	Heterogeneity I^2; Chi^2 (p value)
ZINC VERSUS NO ZINC				
Mortality				
All-cause	13 (16%)	138302 (67%)	Risk=0.95 (0.86 to 1.05)	0%; 10.57 (p=0.65)
Due to diarrhoea	4 (5%)	132321 (64%)	Risk=0.95 (0.69 to 1.31)	0%; 0.82 (p=0.84)
Due to LRTI	3 (4%)	132063 (64%)	Risk=0.86 (0.64 to 1.15)	0%; 0.07 (p=0.96)
Due to malaria	2 (3%)	42818 (21%)	Risk=0.90 (0.77 to 1.06)	0%; 0.01 (p=0.94)
Hospitalisation				
All-cause	7 (9%)	92872 (45%)	Risk=1.04 (0.97 to 1.11)	44%; 14.41 (p=0.07)
Due to diarrhoea	4 (5%)	74039 (36%)	Risk=1.03 (0.87 to 1.22)	42%; 6.91 (p=0.14)
Due to LRTI	3 (4%)	74743 (36%)	Risk=1.10 (0.93 to 1.30)	0%; 0.35 (p=0.95)
Diarrhoea				
Incidence (all cause)	35 (44%)	15042 (7%)	Risk=0.87 (0.85 to 0.89)	88%; 295.56 (p<0.00001)
Prevalence (all cause)	13 (16%)	8519 (4%)	Rate=0.88 (0.86 to 0.90)	88%; 118.88 (p<0.00001)
Incidence (severe)	5 (6%)	4982 (2%)	Risk=0.89 (0.84 to 0.95)	56%; 13.54 (p=0.04)
Incidence (persistent)	7 (9%)	6216 (3%)	Risk=0.73 (0.62 to 0.85)	61%; 20.47 (p=0.009)
Prevalence (persistent)	1 (1%)	666 (0%)	Rate=0.70 (0.64 to 0.76)	91%; 11.76 (p=0.0006)
Lower respiratory tract infection				
Incidence	12 (15%)	9610 (5%)	Risk=1.00 (0.94 to 1.07)	1%; 17.16 (p=0.44)
Prevalence	3 (4%)	1955 (1%)	Rate=1.20 (1.10 to 1.30)	97%; 89.87 (p<0.00001)
Malaria				
Incidence	4 (5%)	2407 (1%)	Risk=1.05 (0.95 to 1.15)	0%; 2.04 (p=0.84)
Prevalence	1 (1%)	661 (0%)	Rate=0.88 (0.47 to 1.64)	Not applicable
Growth				
Height	51 (64%)	13669 (7%)	SMD=0.09 (0.06 to 0.13)	86%; 407.92 (p<0.00001)
Weight	44 (55%)	12305 (6%)	SMD=0.10 (0.07 to 0.14)	76%; 216.64 (p<0.00001)
Weight-to-height ratio	24 (30%)	7901 (4%)	SMD=0.05 (0.01 to 0.10)	20%; 34.96 (p=0.17)
Prevalence of stunting	6 (8%)	3838 (2%)	Risk=0. 94 (0.86 to 1.02)	59%; 19.43 (p=0.01)
Adverse events				
Participants with 1 AE	2 (3%)	850 (0%)	SMD=1.13 (1.00 to 1.27)	0%; 0.49 (p=0.78)
Study withdrawal	6 (8%)	4263 (2%)	Risk=1.75 (0.93 to 3.32)	21%; 5.07 (p=0.28)
Vomiting (incidence)	5 (6%)	4095 (2%)	Risk=1.68 (1.61 to 1.75)	85%; 34.28 (p<0.00001)
Vomiting (prevalence)	4 (5%)	35192 (17%)	Rate=1.29 (1.14 to 1.46)	37%; 6.31 (p=0.18)
Biological indicators				
Zn concentration	46 (58%)	9810 (5%)	SMD=0.62 (0.58 to 0.67)	91%; 582.45 (p<0.00001)
Zn deficiency (prevalence)	15 (19%)	5434 (3%)	Risk=0.49 (0.45 to 0.53)	86%; 144.77 (p<0.00001)
Haemoglobin concentration	27 (34%)	6024 (3%)	SMD=-0.05 (-0.10 to 0.00)	45%; 63.96 (p=0.002)
Anemia (prevalence)	13 (16%)	4287 (2%)	Risk=1.00 (0.95 to 1.06)	37%; 28.52 (p=0.05)
Fe concentration	19 (24%)	4474 (2%)	SMD=0.07 (0.00 to 0.13)	95%; 480.50 (p<0.00001)
Fe deficiency (prevalence)	10 (13%)	3149 (2%)	Risk=0.99 (0.89 to 1.10)	15%; 16.44 (p=0.29)
Cu concentration	11 (14%)	3071 (1%)	SMD=-0.22 (-0.29 to 0.14)	68%; 37.47 (p=0.0002)
Cu deficiency (prevalence)	3 (4%)	1337 (1%)	Risk=2.64 (1.28 to 5.42)	59%; 4.94 (p=0.08)

Table 3: Zinc with iron compared with zinc alone (all outcomes)

Outcomes	Trials	People	ES (95% CI), fixed effects	Heterogeneity I^2; Chi^2 (p value)
All cause mortality	1 (13%)	323 (17%)	Risk=0.33 (0.01 to 8.31)	Not applicable
Hospitalisation				
All-cause	1 (13%)	399 (21%)	Risk=0.92 (0.45 to 1.89)	Not applicable
Due to diarrhoea	1 (13%)	399 (21%)	Risk=0.99 (0.25 to 3.88)	Not applicable
Diarrhoea				
Incidence (all cause)	5 (63%)	1530 (81%)	Risk=1.10 (1.03 to 1.18)	76%; 16.92 (p=0.002)
Prevalence (all cause)	1 (13%)	399 (21%)	Rate=0.90 (0.79 to 1.06)	Not applicable
Incidence (severe)	1 (13%)	323 (17%)	Rate=0.78 (0.59 to 1.04)	Not applicable
Lower respiratory tract infection				
Incidence	3 (38%)	1065 (56%)	Risk=0.93 (0.83 to 1.04)	21%; 2.52 (p=0.28)
Malaria				
Incidence	1 (13%)	410 (22%)	Rate=0.86 (0.59 to 1.24)	Not applicable
Growth				
Height	5 (63%)	1517 (80%)	SMD=0.06 (-0.04 to 0.16)	0%; 3.54 (p=0.47)
Weight	4 (50%)	910 (48%)	SMD=0.12 (-0.01 to 0.25)	0%; 2.29 (p=0.51)
Weight-to-height ratio	4 (50%)	514 (27%)	SMD=-0.06 (-0.07 to 0.19)	0%; 1.36 (p=0.71)
Prevalence of stunting	2 (25%)	462 (24%)	Risk=0.92 (0.85 to 0.99)	45%; 1.82 (p=0.18)
Adverse events				
Study withdrawal	2 (25%)	557 (29%)	Risk=1.41 (0.91 to 2.18)	0%; 0.08 (p=0.78)
Biological indicators				
Zn concentration	8 (100%)	1337 (70%)	SMD=0.16 (0.05 to 0.27)	61%; 17.84 (p=0.01)
Zn deficiency (prevalence)	3 (38%)	350 (18%)	Risk =1.42 (0.75 to 2.68)	5%; 2.10 (p=0.35)
Haemoglobin concentration	8 (100%)	1341 (71%)	SMD=-0.23 (-0.34 to -0.12)	79%; 33.53 (p<0.0001)
Anemia (prevalence)	3 (38%)	482 (25%)	Risk=0.78 (0.67 to 0.92)	0%; 1.25 (p=0.54)
Fe concentration	6 (75%)	945 (50%)	SMD=-1.79 (-1.99 to -1.56)	99%; 927.92 (p<0.00001)
Fe deficiency (prevalence)	2 (25%)	248 (13%)	Risk =0.12 (0.04 to 0.32)	87%; 8.00 (p=0.005)
Cu concentration	2 (25%)	353 (19%)	SMD=-0.06 (-0.27 to 0.15)	0%; 0.11 (p=0.74)

Rate ratio (Rate); Risk ratio (Risk); Odds Ratio (Odds); Standardised Mean Difference (SMD)
Zinc (Zn); Iron (Fe); Copper (Cu).
Effects favour intervention (i.e. zinc rather than iron; zinc plus iron rather than zinc alone) when the relative risk is reduced (RR<1) or the standardised difference is positive (SMD>0).

Table 4: Subgroup analyses

Subgroup	Trials	People	Risk Ratio (95% CI), fixed	I^2; Chi^2 (p value)
Mortality	**13**	**138302**	**0.95 (0.86 to 1.05)**	**0%; 10.57 (p=0.65)**
Iron co-supplementation (I^2=23%; Chi^2=1.30, p=0.25)				
with iron	4	99242	0.99 (0.86 to 1.15)	0%; 0.76 (p=0.86)
without iron	11	64985	0.89 (0.79 to 1.00)	0%; 9.99 (p=0.44)
Age (I^2=59.8%; Chi^2=2.48, p=0.11)				
6m to 1y	6	29879	1.06 (0.88 to 1.27)	0%; 2.56 (p=0.77)
1y to 5y	8	125903	0.89 (0.80 to 0.99)	12%; 10.28 (p=0.33)
Dose (I^2=0%; Chi^2=2.64, p=0.45)				
0mg to 5mg	2	717	0.72 (0.08 to 6.47)	29%; 1.41 (p=0.23)
5mg to 10mg	1	274	3.04 (0.32 to 28.90)	Not applicable
10mg to 15mg	11	152062	0.93 (0.84 to 1.02)	0%; 8.16 (p=0.61)
20mg or more	1	2464	0.14 (0.01 to 2.78)	Not applicable
Duration (I^2=0%; Chi^2=1.20, p=0.55)				
0m to 6m	2	2817	0.59 (0.07 to 5.15)	47%; 1.88. (p=0.17.)
6m to 12m	7	3898	0.68 (0.37 to 1.25)	4%; 6.23 (p=0.40)
12m or more	6	148802	0.93 (0.85 to 1.03)	0%; 2.91 (p=0.71)
Formulation (I^2=0%; Chi^2=0.54, p=0.91)				
Solution	5	3639	0.99 (0.25 to 3.91)	15%; 4.68 (p=0.32)
Pill/ tablet	8	149854	0.93 (0.85 to 1.02)	0%; 6.99 (p=0.43)
Capsule	1	306	0.51 (0.05 to 5.60)	Not applicable
Powder	1	1718	0.71 (0.27 to 1.86)	Not applicable
Incidence of diarrhoea	**35**	**15042**	**0.87 (0.85 to 0.89)**	**88%; 295.56 (p<0.00001)**
Iron co-supplementation (I^2=99%; Chi^2=65.11, p<0.00001)				
with iron	10	4299	1.00 (0.96 to 1.05)	76%; 37.33 (p<0.00001)
without iron	22	11344	0.82 (0.80 to 0.84)	87%; 196.27 (p<0.00001)
Age (I^2=0%; Chi^2=0.32, p=0.85)				
6m to 1y	10	5576	0.88 (0.85 to 0.90)	95%; 252.46 (p<0.00001)
1y to 5y	15	8370	0.87 (0.84 to 0.90)	43%; 31.48 (p=0.03)
5y to 13y	1	842	0.90 (0.81 to 0.98)	Not applicable
Dose (I^2=98%; Chi^2=195.69, p<0.00001)				
0mg to 5mg	4	1784	0.95 (0.89 to 1.01)	73%; 22.46 (p=0.001)
5mg to 10mg	6	2630	0.73 (0.64 to 0.83)	67%; 15.32 (p=0.009)
10mg to 15mg	11	5452	0.96 (0.92 to 0.99)	69%; 38.39 (p=0.0001)
15mg to 20mg	2	477	0.61 (0.58 to 0.65)	0%; 0.21 (p<0.00001)
20mg or more	6	4931	0.90 (0.87 to 0.94)	75%; 28.17 (p<0.00001)
Duration (I^2=0%; Chi^2=1.15, p=0.56)				
0m to 6m	7	4190	0.89 (0.85 to 0.93)	57%; 16.42 (p=0.02)
6m to 12m	14	8971	0.86 (0.84 to 0.89)	93%; 250.92 (p<0.00001)
12m or more	5	1881	0.88 (0.82 to 0.95)	73%; 29.82 (p=0.0002)
Formulation (I^2=94%; Chi^2=51.34, p<0.00001)				
Solution	19	10768	0.84 (0.82 to 0.86)	90%; 236.48 (p<0.00001)
Pill/ tablet	3	1696	0.90 (0.81 to 0.99)	5%; 3.15 (p=0.37)
Capsule	1	612	0.78 (0.60 to 1.01)	Not applicable
Powder	2	1861	1.04 (0.98 to 1.09)	0%; 0.65 (p=0.42)

Appendix 1: Electronic searches

MEDLINE
1 zinc/ or zinc compounds/ or zinc oxide/ or zinc sulfate/ or zinc acetate/
2 (zinc or Zn).tw.
3 1 or 2
4 exp infant/ or exp child/ or adolescent/
5 (newborn$ or neonat$ or neo-nat$ or infan$ or baby or babies or toddler$ or preschool$ or pre-school$ or pediatric$ or paediatric$ or child$ or girl$ or boy$ or preteen$ or pre-teen$ or teen$ or preadolescen$ or pre-adolescen$ or adolescen$ or prepubert$ or pre-pubert$ or pubert$).tw.
6 4 or 5
7 randomized controlled trial.pt.
8 controlled clinical trial.pt.
9 randomized.ab.
10 placebo.ab.
11 drug therapy.fs.
12 randomly.ab.
13 trial.ab.
14 groups.ab.
15 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16 exp animals/ not humans.sh.
17 15 not 16
18 3 and 6 and 17

Cochrane Central Register of Controlled Trials (CENTRAL)
1 MeSH descriptor Zinc explode all trees
2 MeSH descriptor Zinc Compounds explode all trees
3 MeSH descriptor Zinc Oxide explode all trees
4 MeSH descriptor Zinc Sulfate explode all trees
5 MeSH descriptor Zinc Acetate explode all trees
6 (zinc):ti,ab,kw
7 (Zn):ti,ab,kw
8 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7)
9 MeSH descriptor Infant explode all trees
10 MeSH descriptor Child explode all trees
11 MeSH descriptor Adolescent explode all trees
12 (newborn* or neonat* or (neo next nat*) or infan* or baby* or babies or toddler* or preschool* or (pre next school*) or pediatric* or paediatric* or child* or girl* or boy* or preteen* or (pre next teen*) or teen* or preadolescen* or (pre next adolescen*) or adolescen* or prepubert* or (pre next pubert*) or pubert*):ti,ab,kw
13 (#9 OR #10 OR #11 OR #12)
14 (#8 AND #13)

MEDLINE In-Process & Other Non-Indexed Citations
1 (zinc or Zn).tw.
2 (newborn$ or neonat$ or neo-nat$ or infan$ or baby or babies or toddler$ or preschool$ or pre-school$ or pediatric$ or paediatric$ or child$ or girl$ or boy$ or preteen$ or pre-teen$ or teen$ or preadolescen$ or pre-adolescen$ or adolescen$ or prepubert$ or pre-pubert$ or pubert$).tw.
3 randomized controlled trial.pt.
4 controlled clinical trial.pt.
5 randomized.ab.
6 placebo.ab.
7 drug therapy.fs.
8 randomly.ab.
9 trial.ab.
10 groups.ab.
11 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12 exp animals/ not humans.sh.
13 11 not 12
14 1 and 2 and 13

EMBASE
1 zinc/ or zinc derivative/ or zinc oxide/ or zinc sulfate/ or zinc acetate/
2 (zinc or Zn).tw.

3 1 or 2
4 exp infant/ or exp child/ or exp adolescent/
5 (newborn$ or neonat$ or neo-nat$ or infan$ or baby or babies or toddler$ or preschool$ or pre-school$ or pediatric$ or paediatric$ or child$ or girl$ or boy$ or preteen$ or pre-teen$ or teen$ or preadolescen$ or pre-adolescen$ or adolescen$ or prepubert$ or pre-pubert$ or pubert$).tw.
6 4 or 5
7 exp crossover-procedure/ or exp double-blind procedure/ or exp randomized controlled trial/ or exp single-blind procedure/
8 (random$ or factorial$ or crossover$ or cross-over$ or placebo$ or (doubl$ adj blind$) or (singl$ adj blind$) or assign$ or allocat$ or volunteer$).tw.
9 7 or 8
10 3 and 6 and 9
The terms in lines seven through eight are the same as those used by the UK Cochrane Centre to identify randomised controlled trials.

African Index Medicus
zinc or Zn [Key Word] or zinc or Zn [Title] or zinc or Zn [Descriptor]

Global Health
1 zinc/ or zinc sulfate/ or zinc oxide/
2 (zinc or Zn).tw.
3 1 or 2
4 exp infants/ or exp children/ or exp adolescents/
5 (newborn$ or neonat$ or neo-nat$ or infan$ or baby or babies or toddler$ or preschool$ or pre-school$ or pediatric$ or paediatric$ or child$ or girl$ or boy$ or preteen$ or pre-teen$ or teen$ or preadolescen$ or pre-adolescen$ or adolescen$ or prepubert$ or pre-pubert$ or pubert$).tw.
6 4 or 5
7 (random$ or control$ or clinic$ or trial$ or placebo$ or drug therap$ or group$ or crossover$ or cross-over$ or double$-blind$ or single$-blind$ or factorial$ or assign$ or allocat$ or volunteer$).af.
8 3 and 6 and 7

IndMED
zinc or Zn [Title] OR zinc or Zn [Keywords]

Latin American Caribbean Health Sciences Literature (LILACS)
(MH Infant OR MH Child OR MH Adolescent) OR (Tw newborn$ OR Tw neonat$ OR Tw neo-nat$ OR Tw infan$ OR Tw baby$ OR Tw babies OR Tw toddler$ OR Tw preschool$ OR Tw pre-school$ OR Tw pediatric$ OR Tw paediatric$ OR Tw child$ OR Tw girl$ OR Tw boy$ OR Tw preteen$ OR Tw pre-teen$ OR Tw teen$ OR Tw preadolescen$ OR Tw pre-adolescen$ OR Tw adolescen$ OR Tw prepubert$ OR Tw pre-pubert$ OR Tw pubert$ OR Tw niño$ OR Tw niña$ OR Tw bebé$ OR Tw preescolar$ OR Tw prescolar$ OR Tw pre-escolar$ OR Tw pre-scolar$) [Words] and (MH Zinc OR MH Zinc Acetate OR MH Zinc Sulfate OR MH Zinc Compounds OR MH Zinc Oxide) OR Tw Zinc OR Tw Zn [Words]

WHO Library & Information Networks for Knowledge Database (WHOLIS)
zinc or Zn [All indexes] [All sources]

metaRegister of Controlled Trials
(Zinc or Zn) AND (infant or infants or baby or babies or toddler or toddlers or pre-school or preschool or pediatric or paediatric or child or children or girl or girls or boy or boys or pre-teen or pre-adolescent or adolescent or pre-pubertal)

WHO International Clinical Trials Registry Platform (ICTRP)
zinc or Zn [in the Intervention]

Conference Proceedings Citation Index (formerly known as ISI Proceedings)
TS=(zinc or Zn) AND TS=(newborn* or neonat* or neo-nat* or (neo nat*) or infan* or baby or babies or toddler* or preschool* or pre-school* or (pre school*) or pediatric* or paediatric* or child* or girl* or boy* or preteen* or pre-teen* or (pre teen*) or teen* or preadolescen* or pre-adolescen* or (pre adolescen*) or adolescen* or prepubert* or pre-pubert* or (pre pubert*) or pubert*) AND TS=(random* or control* or clinic* or trial* or placebo* or (drug therap*) or group* or crossover* or cross-over* or (cross over*) or double*-blind* or (double* blind*) or single*-blind* or (single* blind*) or factorial* or assign* or allocat* or volunteer*)

ProQuest Dissertations & Theses Database

(zinc or Zn) AND (newborn* or neonat* or neo-nat* or infan* or baby or babies or toddler* or preschool* or pre-school* or pediatric* or paediatric* or child* or girl* or boy* or preteen* or pre-teen* or teen* or preadolescen* or pre-adolescen* or adolescen* or prepubert* or pre-pubert* or pubert*)

Appendix 2: Excluded studies

Study	Reason for exclusion
Ahmed 2009[1]	Non-RCT
Bates 1993[2]	Non-RCT
Behrens 1990[3]	Therapeutic supplementation
Berger 2006[4-6]	Ineligible age
Brooks 2005[7]	Ineligible age
Campos 2004[8]	Non-RCT
Cuevas 2002[9]	No eligible comparison
Duggan 2003[10]	Fortification
Fahmida 2007[11]	Ineligible age
Hashemipour 2009[12-14]	Children were obese
Heinig 2006[15,16]	Ineligible age
Hess 2011[17]	Acceptability study randomizing order of administration
Imamoglu 2005[18]	Non-RCT
Kordas 2005[19-21]	Therapeutic supplementation
NCT01472211[22]	Intervention not eligible (LifeStraw with or without zinc)
Osendarp 2002[23]	Ineligible age
Payne-Robinson 1991[24]	Severe protein-energy malnutrition
Perrone 1999[25]	No eligible comparison
Ronaghy 1969[26]	Ineligible age
Ronaghy 1974[27]	Ineligible age
Roxas 1980[28]	Non-RCT
Shingwekar 1979[29]	Non-RCT
Shrivastava 1993[30]	Non-RCT
Walravens 1992[31]	Ineligible age
Wasantwisut 2006[32]	Ineligible age
Yanfeng 1997[33]	No eligible comparison
Zeba 2008[34]	No eligible comparison

Appendix 3: On-going studies

Study	Reason for exclusion
Arabaci 2010[35]	Awaiting classification
Chicourel 2001[36]	Awaiting classification
CTRI/2010/091/001417[37]	On-going
Jimenez 2000[38]	Awaiting classification
Mitter 2009[39]	Awaiting classification
NCT00133406[40]	On-going
NCT00228254[41]	On-going
NCT00374023[42]	On-going
NCT00421668[43]	On-going
NCT00589264[44]	On-going
NCT00944359[45]	On-going
NCT00967551[46]	On-going
NCT00980421[47]	On-going
NCT01306097[48]	On-going
NCT01616693[49]	On-going
Smith 1985[50]	Awaiting classification

Appendix 4: Included studies

Study	Country	N	Age	Dose	Duration	Form	Height	Co-intervention
Ahmed 2009[51]	BD	40	10 to 18	20mg daily	1.5	Solution	Not reported	Cholera vaccine
Akramuzzaman 1994[52]	BD	256	mean=35	20mg daily	15	Solution	Stunted and non-stunted	Vitamins A, C, D
Alarcon 2004[53]	PE	223	6 to 35	3mg/kg 6d/wk	4.5	Solution	HAZ=-1.04	Iron
Albert 2003[54, 55]	BD	256	24 to 60	20mg daily	1.5	Solution	Not reported	Cholera vaccine
Ba Lo 2011[56]	SN	97	9 to 17	6mg daily	0.5	Solution	Non-stunted only; HAZ=-0.44	Micronutrients
Baqui 2003[57-60]	BD	645	6 to 6	20mg weekly	6	Solution	Stunted and non-stunted; HAZ=-1.2	Vitamin B
Bhandari 2002[61-67]	IN	2482	6 to 30	10mg <1y; 20mg >1y daily	4	Solution	Stunted and non-stunted; HAZ=-1.82	Vitamin A
Bhandari 2007[68, 69]	IN	72,438	6 to 23	10mg daily	12	Tablet	Stunted and non-stunted; HAZ=-1.95	Iron and folic acid
Brown 2007[70-73]	PE	200	6 to 8	3mg daily	6	Solution	Stunted and non-stunted; HAZ=-1.19	Micronutrients
Castillo-Duran 1994[74]	CL	114	72 to 168	10mg daily	12	Capsule	Stunted only	None
*Castillo-Duran 2002[75]	CL	42	17 to 19	5mg daily	12	Solution	Non-stunted only	None
Cavan 1993[76-78]	GT	162	68 to 96	10mg 5d/wk	6.25	Tablet	Stunted and non-stunted; HAZ=-1.51	Micronutrients
Chang 2010[79]	BD	1000	6 to 18	5mg <1y; 10mg >1y alternate days	6	Tablet	Stunted and non-stunted; HAZ=-1.3	None
Chen 2012[80]	CN	361	36 to 72	10mg 5d/wk	6	Tablet	HAZ=-0.264585635	Vitamin A
Chhagan 2009[81-85]	ZA	227	6 to 6	10mg daily	18	Tablet	Stunted and non-stunted; HAZ=-0.45	Vitamin A
Clark 1999[86]	UK	47	mean=146	15mg daily	1.5	Unclear	Non-stunted only	None
Cole 2012[87]	BR	143	6 to 48	5mg daily	3	Powder	Not reported	Micronutrients
Dehbozorgi 2007[88]	IR	60	72 to 144	8mg daily	6	Solution	Not reported	None
DiGirolamo 2010[89, 90]	GT	750	72 to 132	10mg 5d/wk	5.8	Tablet	Stunted and non-stunted; HAZ=-1.2	None
Ebrahimi 2006[91]	IR	804	96 to 132	10mg 6d/wk	7	Solution	Not reported	None
Fallahi 2007[92]	IR	53	132 to 143	20mg 6d/wk	4	Capsule	Not reported	Iron
Fonseca 2002[93]	BR	199	72 to 120	30mg weekly	3	Solution	Stunted and non-stunted	None
Friis 1997[94, 95]	ZW	313	132 to 204	30 mg <29.5 kg; 50 mg >29.5 kg 5d/wk	12	Tablet	HAZ=-1.18	None

Garcia 1998[96]	CL	33	66 to 159.6	20mg daily	6	Unclear	Stunted and non-stunted; HAZ=-2.6	None
Gibson 1989[97]	CA	60	59 to 95	10mg daily	12	Solution	Stunted and non-stunted; HAZ=-1.39	None
Gracia 2005[98]	CO	350	24 to 59	12mg daily	8	Unclear	Stunted and non-stunted; HAZ=0	Micronutrients
Gupta 2003[99]	IN	280	6 to 41	10mg or 50mg 5d/wk or weekly	4	Solution	Not reported	None
Gupta 2007[100]	IN	1,878	6 to 48	50mg weekly	6	Solution	Not reported	Vitamin B
Hambidge 1978[101, 102]	US	75	38 to 61	14mg 5d/wk	6	Solution	Not reported	None
Han 2002[103, 104]	CN	119	36 to 60	3.5mg 5d/wk	12	Tablet	Not reported	Vitamin A and Calcium
Hettiarachchi 2008[105]	LK	341	144 to 155	14mg 5d/wk	6	Capsule	Stunted and non-stunted; HAZ=-1.16	None
Hong 1982[106]	CN	158	4 to 72	Daily	2.4	Solution	Stunted and non-stunted	Vitamin B
Ince 1995[107]	TR	25	25 to 76	10mg daily	12	Solution	Non-stunted only; HAZ=-1.55	None
Kartasurya 2012[108]	ID	826	24 to 60	10mg daily	4	Solution	Non-stunted only; HAZ=-1.730145278	Vitamin A
Kikafunda 1998[109-111]	UG	155	33 to 89	10mg 5d/wk	6	Tablet	HAZ=-0.7	None
Kurugöl 2006[112]	TR	200	24 to 120	15mg daily	7	Solution	Not reported	None
Larson 2010[113, 114]	BD	353	6 to 24	10mg daily	3	Solution	HAZ=-1.72	None
Lind 2003[115-118]	ID	680	6 to 6	10mg daily	6	Solution	Stunted and non-stunted; HAZ=-0.34	Vitamin C
Long 2006[119-122]	MX	786	6 to 15	20mg daily	12	Solution	Stunted and non-stunted; HAZ=0.1	None
Mahloudji 1975[123]	IR	50	72 to 144	20mg 6d/wk	16	Capsule	Not reported	Micronutrients
Malik 2013[124]	IN	158	6 to 11	20mg daily	0.46	Solution	Not reported	None
*Marinho 1991[125]	BR	240	36 to 84	5mg daily	1	Unclear	Stunted and non-stunted	None
Mazariegos 2010[126]	GT	412	6 to 6	5mg daily	6	Tablet	Stunted and non-stunted; HAZ=-2.09	Low-phytate maize
Meeks Gardner 1998[127, 128]	JM	61	6 to 24	5mg daily	3	Solution	Stunted only; HAZ=-2.9	Micronutrients
Meeks Gardner 2005[129]	JM	126	9 to 30	10mg daily	6	Solution	HAZ=-1.42	Micronutrients
Mozaffari-Khosravi 2009[130, 131]	IR	90	25 to 69	5mg daily	6	Solution	Stunted and non-stunted; HAZ=-1.59	None
Muller 2001[132-134]	BF	709	6 to 30	12.5mg 6d/wk	6	Tablet	Stunted and non-stunted; HAZ=-1.6	None
Nakamura 1993[135]	JP	21	mean=70	5mg/kg daily	6	Unclear	Stunted only; HAZ=-2.44	None
Ninh 1996[136]	VN	210	4 to 36	10mg daily	5	Solution	Stunted only; HAZ=-2.61	None

Penny 2004[137, 138]	PE	164	6 to 35	10mg daily	6	Solution	Stunted and non-stunted; HAZ=-1.56	None
Rahman 2001[139-142]	BD	800	12 to 35	20mg daily	0.5	Solution	Stunted and non-stunted; HAZ=-2.41	None
Richard 2006[143]	PE	855	6 to 180	20mg daily	7	Solution	Stunted and non-stunted; HAZ=-2.08	None
Rosado 1997[144-146]	MX	219	18 to 36	20mg 6d/wk	12	Solution	Stunted and non-stunted; HAZ=-1.6	None
Rosales 2004[147]	GT	76	96 to 132	42.5mg 5d/wk	2	Solution	Not reported	None
Ruel 1997[148-150]	GT	108	6 to 9	10mg daily	7	Solution	Stunted and non-stunted; HAZ=-2.16	None
Ruz 1997[151]	CL	98	27 to 50	10mg daily	14	Solution	Stunted and non-stunted; HAZ=-0.52	None
*Sandstead 1998[152, 153]	CN	NR	72 to 108	20mg 6d/wk	2.5	Tablet	Not reported	Micronutrients
Sandstead 2008[154]	US	54	72 to 84	20mg 5d/wk	2.5	Unclear	Not reported	Micronutrients
*Sanjur 1990[155]	US	NR	12 to 24	Daily	6	Tablet	Not reported	Micronutrients
Sayeg Porto 2000[156]	BR	21	84 to 120	5mg/kg daily	6	Solution	Stunted only; HAZ=-2.67	None
Sazawal 1996[157-166]	IN	609	6 to 35	10mg daily	6	Solution	Stunted and non-stunted	Micronutrients
Sazawal 2006[167-176]	TZ	60,225	1 to 35	5mg <1y; 10mg >1y daily	16	Tablet	Stunted and non-stunted; HAZ=-1.5	Micronutrients
Schultink 1997[177]	ID	85	24 to 60	15mg daily	2	Solution	Stunted and non-stunted; HAZ=-2.5	Iron
Sempertegui 1996[178, 179]	EC	50	12 to 59	10mg daily	2	Solution	Stunted and non-stunted; HAZ=-2	None
*Shah 2011[180]	IN	NR	6 to 59	10mg daily	2	Unclear	Not reported	None
Shankar 2000[181, 182]	PG	274	6 to 60	10mg 6d/wk	11.5	Tablet	Stunted and non-stunted; HAZ=-1.9	None
Silva 2006[183]	BR	60	12 to 59	10mg daily	4	Solution	Stunted and non-stunted; HAZ=-1.9	Iron-fortified milk
Smith 1999[184]	BZ	51	Preschool	70mg weekly	6	Solution	Stunted and non-stunted	None
Soofi 2013[185]	PK	1305	6 to 6	10mg daily	12	Powder	Stunted and non-stunted	Micronutrients
Tielsch 2006[186-193]	NP	49,205	1 to 35	5mg < 1y; 10mg >1y daily	to 36m	Tablet	Stunted and non-stunted	Iron and folic acid
Tupe 2009[194, 195]	IN	88	120 to 155	16.6mg 6d/wk	2.5	Tablet	Stunted and non-stunted; HAZ=-1.3	None
Uckardes 2009[196-198]	TR	226	89 to 140	15mg 5d/wk	2.5	Solution	Not reported	None
Udomkesmalee 1992[199, 200]	TH	133	72 to 156	25mg 5d/wk	6	Capsule	Stunted and non-stunted	Vitamin A
Umeta 2000[201-203]	ET	200	6 to 12	10mg 6d/wk	6	Solution	Stunted and non-stunted; HAZ=-1.7	None
*Vakili 2009[204]	IR	200	78 to 120	10mg 6d/wk	5	Tablet	Not reported	None

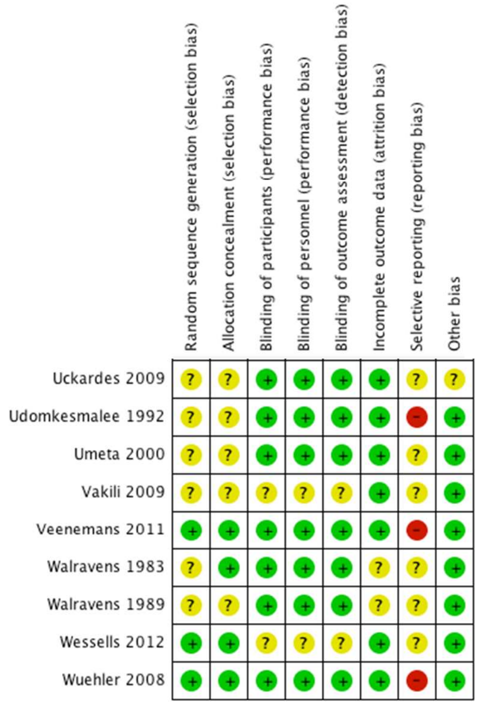
Veenemans 2011[205-208]	TZ	612	6 to 60	10mg daily	11	Capsule	Stunted and non-stunted; HAZ=-2.43	Micronutrients
Walravens 1983[209, 210]	US	57	24 to 72	5mg 2x daily	12	Solution	Stunted and non-stunted; HAZ=-2.07	None
Walravens 1989[211]	US	NR	8 to 27	25mg (frequency unclear)	6	Solution	HAZ=-1.35	None
Wessells 2012[212, 213]	BF	451	6 to 23	5mg daily	0.75	Solution	HAZ=-1.5	None
Wuehler 2008[214, 215]	EC	503	12 to 30	3, 7, or 10mg daily	6	Solution	Stunted and non-stunted; HAZ=-2.3	None

*Not included in meta-analysis; Age and duration reported in months

Appendix 5: Risk of bias

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants (performance bias)	Blinding of personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Ahmed 2009	?	?	?	?	?	+	?	+
Akramuzzaman 1994	?	?	?	?	?	?	?	+
Alarcon 2004	?	?	+	+	+	+	?	+
Albert 2003	?	+	+	+	+	+	−	+
Ba Lo 2011	+	?	+	+	+	−	+	+
Baqui 2003	?	?	+	+	+	+	−	+
Bhandari 2002	+	+	+	+	+	+	−	+
Bhandari 2007	+	+	+	+	+	+	−	+
Brown 2007	+	+	+	+	+	?	+	+
Castillo-Duran 1994	?	?	+	+	+	?	−	+
Castillo-Duran 2002	?	?	?	?	?	?	−	+
Cavan 1993	+	+	+	+	+	+	−	+
Chang 2010	+	+	+	+	+	+	?	+
Chen 2012	?	?	−	−	?	?	?	+
Chhagan 2009	+	+	+	+	+	?	−	?
Clark 1999	?	?	+	+	+	+	?	+
Cole 2012	+	?	+	−	+	+	?	+
Dehbozorgi 2007	?	?	+	+	+	?	−	+
DiGirolamo 2010	+	+	+	+	+	+	?	+
Ebrahimi 2006	?	?	+	+	+	?	?	+
Fallahi 2007	?	?	?	?	?	+	?	+
Fonseca 2002	+	?	+	+	+	?	−	+
Friis 1997	?	?	+	+	+	?	−	+
Garcia 1998	?	?	+	+	+	+	?	+
Gibson 1989	?	+	+	+	+	+	?	+
Gracia 2005	?	?	+	+	+	?	−	+
Gupta 2003	+	+	+	+	+	+	−	+
Gupta 2007	?	?	+	+	+	−	−	+
Hambidge 1978	?	?	?	?	?	?	?	+
Han 2002	?	?	+	+	+	?	?	+
Hettiarachchi 2008	?	?	+	+	+	?	?	+
Hong 1982	?	?	?	?	?	?	?	+
Ince 1995	+	?	+	+	+	+	?	+
Kartasurya 2012	+	+	+	+	+	+	−	+
Kikafunda 1998	?	?	+	+	+	?	−	+
Kurugöl 2006	+	+	+	+	+	+	?	+
Larson 2010	+	+	+	+	+	+	−	+

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants (performance bias)	Blinding of personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Lind 2003	?	+	+	+	+	+	+	+
Long 2006	+	+	+	+	+	+	?	+
Mahloudji 1975	?	?	+	+	+	?	-	+
Malik 2013	+	+	+	+	+	+	-	+
Marinho 1991	?	?	?	?	?	?	?	+
Mazariegos 2010	+	+	+	+	+	+	-	+
Meeks Gardner 1998	?	?	+	+	+	?	?	+
Meeks Gardner 2005	?	?	+	+	+	+	?	?
Mozaffari-Khosravi 2009	+	+	+	+	+	?	?	+
Muller 2001	+	+	+	+	+	+	?	+
Nakamura 1993	?	?	?	?	?	?	?	+
Ninh 1996	?	?	+	+	+	?	-	+
Penny 2004	+	?	+	+	+	+	?	+
Rahman 2001	+	+	+	+	+	+	-	+
Richard 2006	+	?	+	+	+	+	?	+
Rosado 1997	?	?	+	+	+	+	?	+
Rosales 2004	+	?	+	+	+	+	?	+
Ruel 1997	?	?	+	+	+	+	?	+
Ruz 1997	?	+	+	+	+	?	-	+
Sandstead 1998	?	?	+	+	+	?	-	+
Sandstead 2008	?	+	+	+	+	?	?	+
Sanjur 1990	?	?	+	+	+	?	?	+
Sayeg Porto 2000	?	+	+	+	+	?	-	+
Sazawal 1996	+	+	+	+	+	+	-	+
Sazawal 2006	+	+	+	+	+	+	-	+
Schultink 1997	?	?	+	+	+	?	?	+
Sempertegui 1996	+	?	+	+	+	+	?	+
Shah 2011	?	?	?	?	?	?	-	+
Shankar 2000	+	+	+	+	+	+	-	+
Silva 2006	?	?	?	?	?	+	-	+
Smith 1999	?	?	?	?	?	+	?	?
Soofi 2013	+	+	+	+	+	+	+	+
Tielsch 2006	+	+	+	+	+	+	?	+
Tupe 2009	+	?	?	?	+	+	?	+


Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants (performance bias)
Blinding of personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
Uckardes 2009
Udomkesmalee 1992
Umeta 2000
Vakili 2009
Veenemans 2011
Walravens 1983
Walravens 1989
Wessells 2012
Wuehler 2008

Appendix 6: Subgroup analyses

Subgroup	Trials	People	Effect size (95% CI), fixed	I^2; Chi^2 (p value)
Prevalence of diarrhoea (RR)	**13**	**8519**	**0.88 (0.86 to 0.90)**	**88%; 118.88 (p<0.00001)**
Iron co-supplementation (I^2=75%; Chi^2=3.97, p=0.05)				
with iron	3	1024	0.96 (0.88 to 1.05)	96%; 46.97 (p<0.00001)
without iron	11	7495	0.88 (0.86 to 0.90)	84%; 67.94 (p<0.00001)
Age (I^2=97%; Chi^2=30.52, p<0.00001)				
6m to 1y	7	3714	0.96 (0.93 to 1.00)	94%; 112.81 (p<0.00001)
1y to 5y	7	4805	0.85 (0.83 to 0.87)	37%; 11.03 (p=0.14)
Dose (I^2=94%; Chi^2=61.69, p<0.00001)				
0mg to 5mg	2	1200	1.00 (0.92 to 1.08)	94%; 33.41 (p<0.00001)
5mg to 10mg	1	274	1.17 (0.60 to 2.28)	Not applicable
10mg to 15mg	6	3434	0.93 (0.90 to 0.96)	66%; 14.53 (p=0.01)
15mg to 20mg	1	258	0.61 (0.54 to 0.69)	Not applicable
20mg or more	3	3353	0.85 (0.82 to 0.87)	68%; 9.24 (p=0.03)
Duration (I^2=86%; Chi^2=13.98, p=0.0009)				
0m to 6m	3	3353	0.85 (0.82 to 0.87)	68%; 9.24 (p=0.03)
6m to 12m	9	4957	0.92 (0.89 to 0.95)	91%; 95.66 (p<0.00001)
12m or more	1	209	0.88 (0.74 to 1.03)	Not applicable
Formulation (I^2=86%; Chi^2=13.99, p=0.0009)				
Solution	8	4657	0.88 (0.85 to 0.90)	92%; 97.84 (p<0.00001)
Pill/ tablet	4	2144	0.86 (0.81 to 0.92)	43%; 7.05 (p=0.13)
Capsule	1	1718	1.03 (0.95 to 1.12)	Not applicable
Incidence of LRTI (RR)	**12**	**9610**	**1.00 (0.94 to 1.07)**	**1%; 17.16 (p=0.44)**
Iron co-supplementation (I^2=0%; Chi^2=0.06, p=0.80)				
with iron	5	2896	0.99 (0.87 to 1.12)	0%; 2.92 (p=0.71)
without iron	10	6714	1.01 (0.93 to 1.08)	22%; 14.17 (p=0.22)
Age (I^2=0%; Chi^2=1.50, p=0.47)				
6m to 1y	5	3566	0.97 (0.88 to 1.07)	0%; 2.12 (p=0.95)
1y to 5y	5	4605	1.05 (0.96 to 1.16)	25%; 8.01 (p=0.24)
5y to 13y	1	836	1.00 (0.72 to 1.40)	Not applicable
Dose (I^2=0%; Chi^2=0.60, p=0.74)				
0mg to 5mg	3	845	0.94 (0.78 to 1.13)	0%; 0.93 (p=0.63)
10mg to 15mg	8	4045	1.00 (0.91 to 1.10)	25%; 9.32 (p=0.23)
20mg or more	7	4720	1.02 (0.92 to 1.13)	5%; 6.31 (p=0.39)
Duration (I^2=0%; Chi^2=0.79, p=0.67)				
0m to 6m	2	3148	1.03 (0.92 to 1.14)	67%; 6.05 (p=0.05)
6m to 12m	8	5114	0.98 (0.90 to 1.06)	0%; 9.69 (p=0.47)
12m or more	2	1348	1.08 (0.83 to 1.42)	0%; 0.64 (p=0.89)
Formulation (I^2=20%; Chi^2=3.73, p=0.29)				
Solution	9	7007	0.98 (0.91 to 1.05)	2%; 13.25 (p=0.43)
Pill/ tablet	1	686	1.19 (0.93 to 1.51)	Not applicable
Capsule	1	612	1.12 (0.84 to 1.51)	Not applicable
Powder	1	1305	1.25 (0.75 to 2.09)	Not applicable
Height (SMD)	**51**	**13669**	**0.09 (0.06 to 0.13)**	**86%; 407.92 (p<0.00001)**
Iron co-supplementation (I^2=85%; Chi^2=6.60, p=0.01)				
with iron	12	2929	0.01 (-0.07 to 0.08)	29%; 15.48 (p=0.16)
without iron	44	10510	0.12 (0.08 to 0.16)	88%; 385.12 (p<0.00001)
Age (I^2=98%; Chi^2=117.89, p<0.00001)				
6m to 1y	9	3730	-0.26 (-0.33 to 0.19)	94%; 204.70 (p<0.00001)
1y to 5y	24	6155	0.09 (0.04 to 0.14)	42%; 44.94 (p=0.01)
5y to 13y	16	3449	0.25 (0.18 to 0.32)	94%; 277.24 (p<0.00001)
Dose (I^2=91%; Chi^2=43.60, p<0.00001)				
0mg to 5mg	5	1170	0.02 (0.10 to 0.13)	58%; 14.30 (p=0.03)
5mg to 10mg	8	2978	0.29 (0.22 to 0.37)	96%; 271.49 (p<0.00001)
10mg to 15mg	22	4344	0.06 (0.00 to 0.12)	29%; 33.90 (p=0.09)
15mg to 20mg	2	240	-0.01 (-0.26 to 0.24)	39%; 3.26 (p=0.20)
20mg or more	3	4675	-0.01 (0.07 to 0.05)	11%; 11.22 (p=0.34)
Duration (I^2=91%; Chi^2=21.62, p<0.00001)				
0m to 6m	12	4475	-0.01 (-0.07 to 0.04)	76%; 50.43 (p<0.00001)
6m to 12m	26	6479	0.17 (0.12 to 0.22)	91%; 313.67 (p<0.00001)
12m or more	12	2715	0.10 (0.02 to 0.17)	32%; 22.21 (p=0.10)
Iron co-supplementation (I^2=85%; Chi^2=6.60, p=0.01)				
with iron	12	2929	0.01 (-0.07 to 0.08)	29%; 15.48 (p=0.16)
without iron	44	10510	0.12 (0.08 to 0.16)	88%; 385.12 (p<0.00001)
Formulation (I^2=75%; Chi^2=8.03, p=0.02)				
Solution	32	9030	0.12 (0.07 to 0.16)	90%; 367.20 (p<0.00001)
Pill/ tablet	11	3868	0.02 (-0.04 to 0.09)	9%; 12.11 (p=0.36)
Capsule	2	322	0.31 (0.03 to 0.59)	0%; 0.90 (p=0.64)
Weight (SMD)	**44**	**12305**	**0.10 (0.07 to 0.14)**	**76%; 216.64 (p<0.00001)**
Iron co-supplementation (I^2=34%; Chi^2=1.50, p=0.22)				
with iron	10	2494	0.06 (-0.02 to 0.14)	5%; 9.50 (p=0.39)
without iron	39	9811	0.12 (0.08 to 0.16)	80%; 205.63 (p<0.00001)

Age (I^2=99%; Chi^2=136.86, p<0.00001)				
6m to 1y	9	3730	-0.31 (-0.38 to -0.25)	97%; 387.48 (p<0.00001)
1y to 5y	20	5565	0.06 (0.01 to 0.11)	43%; 38.72 (p=0.02)
5y to 13y	13	2654	0.28 (0.20 to 0.36)	89%; 117.28 (p<0.00001)
Dose (I^2=89%; Chi^2=35.38, p<0.00001)				
0mg to 5mg	5	1170	0.00 (-0.11 to 0.12)	0%; 2.79 (p=0.83)
5mg to 10mg	10	2766	0.27 (0.20 to 0.35)	92%; 108.31 (p<0.00001)
10mg to 15mg	19	3969	0.11 (0.04 to 0.17)	34%; 31.75 (p=0.06)
15mg to 20mg	2	240	-0.20 (-0.45 to 0.06)	13%; 2.30 (p=0.32)
20mg or more	7	3919	0.01 (-0.05 to 0.08)	36%; 12.43 (p=0.13)
Duration (I^2=92%; Chi^2=23.59, p<0.00001)				
0m to 6m	11	4417	0.05 (0.00 to 0.11)	76%; 44.95 (p<0.00001)
6m to 12m	22	5289	0.20 (0.15 to 0.26)	82%; 131.52 (p<0.00001)
12m or more	11	2599	-0.01 (-0.07 to 0.09)	16%; 16.58 (p=0.28)
Formulation (I^2=87%; Chi^2=15.43, p=0.0004)				
Solution	29	8147	0.14 (0.10 to 0.19)	82%; 182.72 (p<0.00001)
Pill/ tablet	10	3656	0.01 (-0.06 to 0.08]	13%; 11.51 (p=0.32)
Capsule	2	304	0.41 (0.12 to 0.71)	0%; 1.21 (p=0.55)
Weight-to-height ratio (SMD)	**24**	**7901**	**0.05 (0.01 to 0.10)**	**20%; 34.96 (p=0.17)**
Iron co-supplementation (I^2=72%; Chi^2=3.51, p=0.06)				
with iron	8	1409	0.14 (0.03 to 0.24)	14%; 8.10 (p=0.32)
without iron	19	6262	0.03 (-0.02 to 0.08)	16%; 22.67 (p=0.25)
Age (I^2=30%; Chi^2=11.45, p=0.18)				
6m to 1y	7	2559	0.03 (-0.04 to 0.11)	30%; 11.45 (p=0.18)
1y to 5y	12	4302	0.02 (-0.05 to 0.08)	7%; 13.95 (p=0.38)
5y to 13y	5	857	0.07 (-0.06 to 0.20)	0%; 3.20 (p=0.67)
Dose (I^2=11%; Chi^2=4.52, p=0.34)				
0mg to 5mg	4	671	0.07 (-0.08 to 0.22)	0%; 1.02 (p=0.91)
5mg to 10mg	6	1229	0.01 (-0.01 to 0.12)	30%; 7.16 (p=0.21)
10mg to 15mg	10	2389	0.08 (-0.01 to 0.16)	47%; 18.79 (p=0.04)
15mg to 20mg	1	194	-0.22 (-0.50 to 0.06)	Not applicable
20mg or more	4	3576	0.06 (0.00 to 0.13)	0%; 2.43 (p=0.79)
Duration (I^2=18.2%; Chi^2=2.45, p=0.29)				
0m to 6m	5	3337	0.07 (0.00 to 0.14)	0%; 2.14 (p=0.83)
6m to 12m	15	4212	0.05 (-0.01 to 0.11)	38%; 27.40 (p=0.05)
12m or more	4	352	-0.10 (-0.31 to 0.11)	0%; 2.98 (p=0.56)
Formulation (I^2=49%; Chi^2=1.97, p=0.16)				
Solution	17	6019	0.06 (0.01 to 0.12)	0%; 20.92 (p=0.46)
Pill/ tablet	6	1652	-0.01 (-0.11 to 0.08)	56%; 11.38 (p=0.04)
Plasma zinc (SMD)	**46**	**9810**	**0.62 (0.58 to 0.67)**	**91%; 582.45 (p<0.00001)**
Iron co-supplementation (I^2=96%; Chi^2=27.07, p<0.00001)				
with iron	17	3231	0.47 (0.39 to 0.54)	82%; 90.82 (p<0.00001)
without iron	37	6579	0.70 (0.65 to 0.75)	92%; 464.56 (p<0.00001)
Age (I^2=95%; Chi^2=40.84, p<0.00001)				
6m to 1y	8	2042	0.46 (0.37 to 0.55)	87%; 74.18 (p<0.00001)
1y to 5y	19	4911	0.75 (0.69 to 0.81)	93%; 309.84 (p<0.00001)
5y to 13y	17	2375	0.47 (0.38 to 0.55)	83%; 116.75 (p<0.00001)
Dose (I^2=92%; Chi^2=49.94, p<0.00001)				
0mg to 5mg	4	855	0.35 (0.21 to 0.49)	26%; 6.72 (p=0.24)
5mg to 10mg	8	1762	0.49 (0.40 to 0.59)	93%; 102.83 (p<0.00001)
10mg to 15mg	20	4596	0.62 (0.56 to 0.68)	86%; 158.02 (p<0.00001)
15mg to 20mg	6	535	0.76 (0.58 to 0.94)	86%; 51.51 (p<0.00001)
20mg or more	6	1724	0.88 (0.78 to 0.98)	95%; 161.54 (p<0.00001)
Duration (I^2=94%; Chi^2=32.98, p<0.00001)				
0m to 6m	15	3079	0.81 (0.73 to 0.88)	94%; 285.66 (p<0.00001)
6m to 12m	22	4347	0.52 (0.46 to 0.58)	85%; 178.87 (p<0.00001)
12m or more	9	2384	0.59 (0.50 to 0.67)	88%; 84.94 (p<0.00001)
Formulation (I^2=98%; Chi^2=149.23, p<0.00001)				
Solution	25	4741	0.78 (0.72 to 0.84)	90%; 293.32 (p<0.00001)
Pill/ tablet	12	3553	0.42 (0.35 to 0.49)	88%; 96.60 (p<0.00001)
Capsule	5	1115	1.07 (0.94 to 1.21)	88%; 56.53 (p<0.00001)
Powder	1	401	-0.06 (-0.25 to 0.14)	Not applicable
Prevalence of zinc deficiency (RR)	**15**	**5434**	**0.49 (0.45 to 0.53)**	**86%; 144.77 (p<0.00001)**
Iron co-supplementation (I^2=97%; Chi^2=34.27, p<0.00001)				
with iron	6	1704	0.62 (0.55 to 0.69)	69%; 16.19 (p=0.006)
without iron	14	3840	0.37 (0.33 to 0.42)	85%; 94.31 (p<0.00001)
Age (I^2=92%; Chi^2=24.36, p<0.00001)				
6m to 1y	1	549	0.62 (0.54 to 0.70)	0%; 0.07 (p=0.79)
1y to 5y	9	3761	0.41 (0.37 to 0.47)	91%; 116.81 (p<0.00001)
5y to 13y	5	1234	0.31 (0.20 to 0.49)	0%; 3.53 (p=0.74)
Dose (I^2=96%; Chi^2=74.93, p<0.00001)				
5mg to 10mg	3	1181	0.34 (0.27 to 0.44)	71%; 6.81 (p=0.03)
10mg to 15mg	7	2890	0.57 (0.52 to 0.63)	81%; 48.40 (p<0.00001)
15mg to 20mg	1	194	0.46 (0.24 to 0.89)	0%; 0.26 (p=0.61)
20mg or more	4	1279	0.14 (0.10 to 0.19)	65%; 14.28 (p=0.01)

Duration (I^2=97%; Chi^2=71.67, p<0.00001)				
0m to 6m	6	2554	0.22 (0.18 to 0.27)	72%; 24.89 (p=0.0008)
6m to 12m	5	1043	0.59 (0.53 to 0.67)	35%; 9.19 (p=0.16)
12m or more	4	1947	0.55 (0.48 to 0.64)	87%; 39.02 (p<0.00001)
Formulation (I^2=91%; Chi^2=22.12, p<0.00001)				
Solution	7	2415	0.49 (0.44 to 0.54)	89%; 87.85 (p<0.00001)
Pill/ tablet	7	2392	0.59 (0.50 to 0.68)	80%; 29.32 (p<0.0001)
Capsule	2	883	0.29 (0.23 to 0.37)	60%; 7.43 (p=0.06)
Blood haemoglobin (SMD)	**27**	**6024**	**-0.05 (-0.10 to 0.00)**	**45%; 63.96 (p=0.002)**
Iron co-supplementation (I^2=0%; Chi^2=0.70, p=0.40)				
with iron	17	3098	-0.01 (-0.08 to 0.07)	63%; 42.74 (p=0.0003)
without iron	19	2913	0.04 (-0.04 to 0.11)	54%; 39.06 (p=0.003)
Age (I^2=0%; Chi^2=1.53, p=0.46)				
6m to 1y	7	2192	-0.04 (-0.12 to 0.05)	69%; 32.49 (p=0.0003)
1y to 5y	12	2332	0.04 (-0.04 to 0.12)	62%; 33.89 (p=0.001)
5y to 13y	6	1286	0.01 (-0.11 to 0.13)	10%; 8.93 (p=0.35)
Dose (I^2=0%; Chi^2=2.12, p=0.71)				
0mg to 5mg	4	966	0.01 (-0.12 to 0.14)	39%; 8.16 (p=0.15)
5mg to 10mg	2	306	-0.01 (-0.23 to 0.21)	0%; 0.56 (p=0.45)
10mg to 15mg	16	3452	0.01 (-0.06 to 0.08)	58%; 44.83 (p=0.0007)
15mg to 20mg	4	364	-0.04 (-0.24 to 0.17)	25%; 5.31 (p=0.26)
20mg or more	3	1025	0.10 (-0.02 to 0.22)	83%; 23.74 (p<0.00001)
Duration (I^2=52%; Chi^2=4.20, p=0.12)				
0m to 6m	7	672	0.17 (0.01 to 0.33)	74%; 27.23 (p=0.0003)
6m to 12m	14	3738	-0.01 (-0.08 to 0.06)	39%; 27.71 (p=0.05)
12m or more	7	1601	0.01 (-0.09 to 0.11)	61%; 23.36 (p=0.005)
Formulation (I^2=0%; Chi^2=1.38, p=0.71)				
Solution	15	2990	0.01 (-0.06 to 0.08)	64%; 52.48 (p<0.00001)
Pill/ tablet	8	1605	0.01 (-0.09 to 0.12)	67%; 24.34 (p=0.002)
Capsule	4	989	0.07 (-0.06 to 0.20)	0%; 4.31 (p=0.51)
Powder	1	427	-0.07 (-0.26 to 0.12)	Not applicable
Prevalence of anaemia (RR)	**13**	**4287**	**1.00 (0.95 to 1.06)**	**37%; 28.52 (p=0.05)**
Iron co-supplementation (I^2=0%; Chi^2=0.01, p=0.93)				
with iron	10	2755	1.00 (0.91 to 1.09)	58%; 21.20 (p=0.01)
without iron	9	1532	1.00 (0.93 to 1.08)	0%; 7.31 (p=0.50)
Age (I^2=8%; Chi^2=2.17, p=0.34)				
6m to 1y	6	1726	1.01 (0.95 to 1.08)	39%; 11.43 (p=0.12)
1y to 5y	6	2161	0.99 (0.88 to 1.12)	50%; 14.07 (p=0.05)
5y to 13y	2	400	0.73 (0.47 to 1.12)	0%; 0.84 (p=0.66)
Dose (I^2=68%; Chi^2=12.56, p=0.01)				
0mg to 5mg	2	616	1.01 (0.94 to 1.09)	31%; 2.91 (p=0.23)
5mg to 10mg	1	208	0.94 (0.47 to 1.87)	Not applicable
10mg to 15mg	8	3069	1.01 (0.92 to 1.11)	15%; 13.00 (p=0.29)
15mg to 20mg	1	181	0.76 (0.40 to 1.46)	Not applicable
20mg or more	1	213	0.17 (0.06 to 0.46)	Not applicable
Duration (I^2=83%; Chi^2=11.42, p=0.003)				
0m to 6m	2	325	0.18 (0.06 to 0.48)	0%; 0.39 (p=0.53)
6m to 12m	7	1989	1.01 (0.94 to 1.08)	40%; 13.33 (p=0.10)
12m or more	5	1973	1.00 (0.90 to 1.12)	0%; 3.38 (p=0.85)
Formulation (I^2=7%; Chi^2=3.21, p=0.36)				
Solution	4	1115	0.90 (0.78 to 1.04)	73%; 18.87 (p=0.002)
Pill/ tablet	6	1958	1.02 (0.95 to 1.10)	0%; 3.36 (p=0.85)
Capsule	2	886	1.00 (0.88 to 1.13)	3%; 3.08 (p=0.38)
Powder	1	328	1.19 (0.81 to 1.73)	Not applicable
Plasma ferritin (SMD)	**19**	**4474**	**0.07 (0.00 to 0.13)**	**95%; 480.50 (p<0.00001)**
Iron co-supplementation (I^2=91%; Chi^2=11.08, p=0.0009)				
with iron	14	2765	-0.05 (-0.13 to 0.02)	80%; 64.00 (p<0.00001)
without iron	11	1709	-0.27 (-0.38 to 0.17)	97%; 389.92 (p<0.00001)
Age (I^2=0%; Chi^2=1.02, p=0.60)				
6m to 1y	4	1166	-0.14 (-0.26 to 0.03)	20%; 6.26 (p=0.28)
1y to 5y	9	2716	-0.16 (-0.24 to 0.08)	98%; 439.66 (p<0.00001)
5y to 13y	5	534	-0.05 (-0.24 to 0.15)	47%; 11.30 (p=0.08)
Dose (I^2=79%; Chi^2=18.71, p=0.0009)				
0mg to 5mg	3	371	-0.07 (-0.28 to 0.14)	29%; 4.21 (p=0.24)
5mg to 10mg	1	78	-0.15 (-0.63 to 0.34)	Not applicable
10mg to 15mg	11	3171	-0.20 (-0.28 to -0.13)	97%; 428.29 (p<0.00001)
15mg to 20mg	3	314	-0.14 (-0.36 to 0.08)	0%; 2.05 (p=0.56)
20mg or more	3	652	0.17 (0.02 to 0.33)	79%; 14.57 (p=0.002)
Duration (I^2=92%; Chi^2=26.28, p<0.00001)				
0m to 6m	7	902	0.06 (-0.07 to 0.20)	79%; 32.68 (p<0.0001)
6m to 12m	7	1735	-0.07 (-0.17 to 0.03)	28%; 12.55 (p=0.18)
12m or more	4	1779	-0.34 (-0.45 to 0.24)	99%; 386.75 (p<0.00001)
Formulation (I^2=92%; Chi^2=35.34, p<0.00001)				
Solution	10	2043	0.01 (-0.08 to 0.10)	62%; 34.20 (p=0.001)
Pill/ tablet	3	1070	-0.16 (-0.29 to -0.04)	89%; 17.89 (p=0.0001)

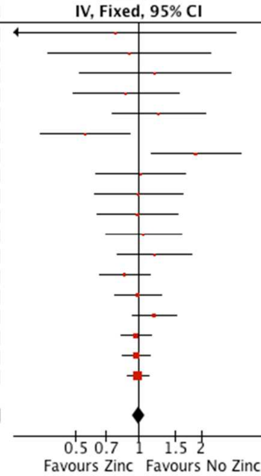
Capsule	3	939	-0.54 (-0.69 to -0.38)	99%; 364.74 (p<0.00001)
Powder	1	317	-0.18 (-0.40 to 0.04)	Not applicable
Prevalence of iron deficiency (RR)	**10**	**3149**	**0.99 (0.89 to 1.10)**	**15%; 16.44 (p=0.29)**
Iron co-supplementation (I^2=0%; Chi^2=0.51, p=0.48)				
with iron	9	2301	1.02 (0.89 to 1.17)	47%; 15.03 (p=0.06)
without iron	6	947	0.94 (0.79 to 1.11)	0%; 0.90 (p=0.97)
Age (I^2=44%; Chi^2=3.56, p=0.17)				
6m to 1y	3	905	0.92 (0.82 to 1.05)	25%; 5.34 (p=0.25)
1y to 5y	4	1992	1.16 (0.94 to 1.44)	13%; 5.75 (p=0.33)
5y to 13y	2	351	1.12 (0.61 to 2.04)	0%; 1.80 (p=0.62)
Dose (I^2=49%; Chi^2=5.86, p=0.12)				
0mg to 5mg	1	144	0.78 (0.61 to 1.00)	Not applicable
10mg to 15mg	6	2634	1.03 (0.91 to 1.16)	14%; 10.42 (p=0.32)
15mg to 20mg	1	194	1.07 (0.52 to 2.18)	Not applicable
20mg or more	2	276	2.16 (0.72 to 6.44)	0%; 0.15 (p=0.93)
Duration (I^2=52%; Chi^2=4.12, p=0.13)				
0m to 6m	2	276	2.16 (0.72 to 6.44)	0%; 0.15 (p=0.93)
6m to 12m	3	981	0.88 (0.73 to 1.05)	22%; 5.13 (p=0.27)
12m or more	4	1991	1.04 (0.91 to 1.18)	15%; 7.04 (p=0.32)
Formulation (I^2=0%; Chi^2=1.87, p=0.39)				
Solution	4	1163	0.90 (0.75 to 1.08)	18%; 7.31 (p=0.29)
Pill/ tablet	3	1199	1.05 (0.91 to 1.20)	51%; 6.17 (p=0.10)
Capsule	2	886	0.88 (0.56 to 1.37)	0%; 1.09 (p=0.78)
Plasma copper (SMD)	**11**	**3071**	**-0.22 (-0.29 to 0.14)**	**68%; 37.47 (p=0.0002)**
Iron co-supplementation (I^2=64.1%; Chi^2=2.71, p=0.09)				
with iron	4	650	-0.10 (-0.25 to 0.05)	0%; 2.45 (p=0.49)
without iron	9	2421	-0.25 (-0.33 to -0.17)	75%; 32.34 (p<0.00001)
Age (I^2=71%; Chi^2=3.46, p=0.06)				
6m to 1y	3	865	-0.11 (-0.24 to 0.02)	0%; 1.27 (p=0.87)
5y to 13y	8	2206	-0.26 (-0.35 to -0.17)	79%; 32.74 (p<0.00001)
Dose (I^2=90%; Chi^2=29.23, p<0.00001)				
0mg to 5mg	3	410	-0.08 (-0.27 to 0.12)	25%; 4.00 (p=0.26)
5mg to 10mg	2	519	-0.31 (-0.49 to -0.13)	75%; 3.98 (p=0.05)
10mg to 15mg	7	1310	-0.01 (-0.12 to 0.10)	0%; 5.40 (p=0.61)
20mg or more	1	930	-0.46 (-0.59 to -0.33)	Not applicable
Duration (I^2=94%; Chi^2=30.84, p<0.00001)				
0m to 6m	2	1355	-0.44 (-0.55 to -0.33)	0%; 0.17 (p=0.68)
6m to 12m	5	1168	-0.08 (-0.20 to 0.04)	0%; 3.23 (p=0.78)
12m or more	4	548	0.06 (-0.11 to 0.24)	7%; 3.23 (p=0.36)
Formulation (I^2=95%; Chi^2=20.76, p<0.00001)				
Solution	9	2490	-0.37 (-0.46 to -0.29)	97%; 370.26 (p<0.00001)
Pill/ tablet	3	439	-0.83 (-1.01 to -0.65)	99%; 277.02 (p<0.00001)

Appendix 7: Additional forest plots

Incidence of lower respiratory tract infection

Study or Subgroup	log[Risk Ratio]	SE	Zinc Total	No Zinc Total	Weight	Risk Ratio IV, Fixed, 95% CI
Long 2006 (2)	−0.24816892	0.67082039	192	180	0.2%	0.78 [0.21, 2.91]
Long 2006	−0.10536052	0.45946829	181	183	0.5%	0.90 [0.37, 2.21]
Brown 2007	0.18232156	0.42839042	101	99	0.6%	1.20 [0.52, 2.78]
Penny 2004	−0.14058195	0.29777877	80	79	1.2%	0.87 [0.48, 1.56]
Soofi 2013	0.22314355	0.2627712	659	646	1.6%	1.25 [0.75, 2.09]
Sazawal 1996	−0.59000642	0.25375961	297	306	1.7%	0.55 [0.34, 0.91]
Rahman 2001	0.63062682	0.25241624	170	161	1.7%	1.88 [1.15, 3.08]
Richard 2006 (2)	0.02032	0.25200806	210	208	1.7%	1.02 [0.62, 1.67]
Rahman 2001 (2)	0	0.24928541	175	160	1.7%	1.00 [0.61, 1.63]
Richard 2006	−0.01129956	0.22645541	209	209	2.1%	0.99 [0.63, 1.54]
Veenemans 2011	0.05383699	0.2132558	153	153	2.4%	1.06 [0.69, 1.60]
Veenemans 2011 (2)	0.17745056	0.20798032	151	155	2.5%	1.19 [0.79, 1.80]
Baqui 2003 (2)	−0.15645218	0.14256197	162	165	5.3%	0.86 [0.65, 1.13]
Baqui 2003	−0.00673403	0.13486419	161	157	5.9%	0.99 [0.76, 1.29]
Muller 2001	0.17162318	0.12304944	342	344	7.1%	1.19 [0.93, 1.51]
Lind 2003 (2)	−0.02898754	0.08383997	170	170	15.4%	0.97 [0.82, 1.14]
Lind 2003	−0.02739897	0.08077837	170	170	16.6%	0.97 [0.83, 1.14]
Bhandari 2002	−0.00591199	0.05834957	1241	1241	31.7%	0.99 [0.89, 1.11]
Total (95% CI)			**4824**	**4786**	**100.0%**	**1.00 [0.94, 1.07]**

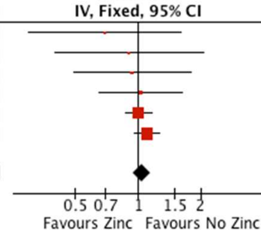
Heterogeneity: $Chi^2 = 17.16$, df = 17 (P = 0.44); $I^2 = 1\%$
Test for overall effect: Z = 0.03 (P = 0.98)



Incidence of malaria

Study or Subgroup	log[Risk Ratio]	SE	Zinc Total	No Zinc Total	Weight	Risk Ratio IV, Fixed, 95% CI
Shankar 2000	−0.37018553	0.42956235	136	138	1.3%	0.69 [0.30, 1.60]
Richard 2006 (2)	−0.09844007	0.41742355	210	208	1.3%	0.91 [0.40, 2.05]
Richard 2006	−0.06536678	0.32891813	209	209	2.1%	0.94 [0.49, 1.78]
Muller 2001	0.02817088	0.23737988	341	344	4.1%	1.03 [0.65, 1.64]
Veenemans 2011	0.00837462	0.0727393	153	153	43.9%	1.01 [0.87, 1.16]
Veenemans 2011 (2)	0.10019023	0.07006137	151	155	47.3%	1.11 [0.96, 1.27]
Total (95% CI)			**1200**	**1207**	**100.0%**	**1.05 [0.95, 1.15]**

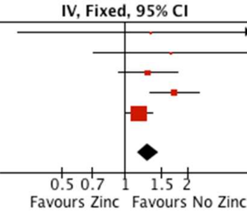
Heterogeneity: $Chi^2 = 2.04$, df = 5 (P = 0.84); $I^2 = 0\%$
Test for overall effect: Z = 0.93 (P = 0.35)



Participants with ≥1 vomiting episode

Study or Subgroup	log[Risk Ratio]	SE	Zinc Total	No Zinc Total	Weight	Risk Ratio IV, Fixed, 95% CI
Kurugöl 2006	0.28768207	0.75055535	100	100	0.7%	1.33 [0.31, 5.81]
Gupta 2007	0.51549853	0.44177764	854	858	2.0%	1.67 [0.70, 3.98]
Lind 2003	0.25343215	0.16826769	162	164	13.9%	1.29 [0.93, 1.79]
Lind 2003 (2)	0.55134234	0.14130384	161	163	19.7%	1.74 [1.32, 2.29]
Bhandari 2007	0.15688142	0.0785542	16289	16341	63.7%	1.17 [1.00, 1.36]
Total (95% CI)			**17566**	**17626**	**100.0%**	**1.29 [1.14, 1.46]**

Heterogeneity: $Chi^2 = 6.31$, df = 4 (P = 0.18); $I^2 = 37\%$
Test for overall effect: Z = 4.08 (P < 0.0001)

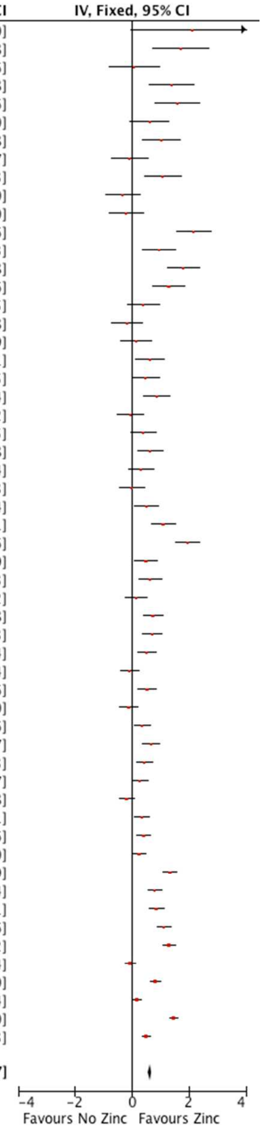


Plasma zinc

Study or Subgroup	Std. Mean Difference	SE	No Zinc Total	Zinc Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Silva 2006	2.12757492	1.10761519	30	28	0.0%	2.13 [−0.04, 4.30]
Nakamura 1993	1.7108436	0.49561271	11	10	0.2%	1.71 [0.74, 2.68]
Sayeg Porto 2000	0.07926742	0.44915102	9	9	0.2%	0.08 [−0.80, 0.96]
Rosales 2004	1.39772302	0.39918356	14	16	0.3%	1.40 [0.62, 2.18]
Rosales 2004 (2)	1.59178434	0.393349	15	18	0.3%	1.59 [0.82, 2.36]
Garcia 1998	0.61895336	0.34825576	17	16	0.4%	0.62 [−0.06, 1.30]
Smith 1999	1.02871696	0.33059672	20	20	0.4%	1.03 [0.38, 1.68]
Gibson 1989	−0.07887671	0.33058919	18	17	0.4%	−0.08 [−0.73, 0.57]
Clark 1999	1.08857292	0.32653377	19	23	0.4%	1.09 [0.45, 1.73]
Walravens 1989	−0.32044174	0.3159476	25	16	0.5%	−0.32 [−0.94, 0.30]
Walravens 1983	−0.21002838	0.31083333	20	20	0.5%	−0.21 [−0.82, 0.40]
Udomkesmalee 1992	2.16724629	0.30343932	35	33	0.5%	2.17 [1.57, 2.76]
Sempertegui 1996	0.94195962	0.30001048	25	23	0.5%	0.94 [0.35, 1.53]
Udomkesmalee 1992 (2)	1.80519359	0.29181765	33	32	0.5%	1.81 [1.23, 2.38]
Tupe 2009	1.2972891	0.28675374	40	43	0.6%	1.30 [0.74, 1.86]
Fallahi 2007	0.39627284	0.28402418	25	24	0.6%	0.40 [−0.16, 0.95]
Mahloudji 1975	−0.165458	0.2788914	25	25	0.6%	−0.17 [−0.71, 0.38]
Sandstead 2008	0.14492933	0.27877714	25	25	0.6%	0.14 [−0.40, 0.69]
Ba Lo 2011	0.62542586	0.24941159	32	34	0.7%	0.63 [0.14, 1.11]
Schultink 1997	0.47144486	0.24494512	34	33	0.8%	0.47 [−0.01, 0.95]
Hettiarachchi 2008 (2)	0.86739385	0.24267158	30	114	0.8%	0.87 [0.39, 1.34]
Ruz 1997	−0.04794779	0.23832669	33	36	0.8%	−0.05 [−0.52, 0.42]
Mazariegos 2010	0.3998476	0.23138369	40	35	0.9%	0.40 [−0.05, 0.85]
Muller 2001	0.63830688	0.22576313	40	41	0.9%	0.64 [0.20, 1.08]
Baqui 2003	0.30706347	0.22305208	38	42	0.9%	0.31 [−0.13, 0.74]
Baqui 2003 (2)	0	0.21750534	42	41	1.0%	0.00 [−0.43, 0.43]
Hettiarachchi 2008	0.51369923	0.21562749	41	100	1.0%	0.51 [0.09, 0.94]
Umeta 2000	1.09640714	0.21307062	50	50	1.0%	1.10 [0.68, 1.51]
Hong 1982	1.94421305	0.21124116	67	64	1.0%	1.94 [1.53, 2.36]
Rosado 1997	0.49001387	0.20662869	47	48	1.1%	0.49 [0.09, 0.89]
Rosado 1997 (2)	0.62774877	0.20438775	50	49	1.1%	0.63 [0.23, 1.03]
Uckardes 2009	0.14435311	0.18964639	54	56	1.3%	0.14 [−0.23, 0.52]
Penny 2004	0.73471063	0.17762983	69	65	1.4%	0.73 [0.39, 1.08]
Wuehler 2008	0.70122941	0.16887846	49	142	1.6%	0.70 [0.37, 1.03]
Cavan 1993	0.51245133	0.1679712	74	71	1.6%	0.51 [0.18, 0.84]
Rahman 2001 (2)	−0.08998801	0.16760985	70	71	1.6%	−0.09 [−0.42, 0.24]
Brown 2007	0.53520617	0.16389707	84	70	1.7%	0.54 [0.21, 0.86]
Rahman 2001	−0.11598147	0.16210648	77	74	1.7%	−0.12 [−0.43, 0.20]
Chang 2010	0.36204843	0.15223956	89	85	2.0%	0.36 [0.06, 0.66]
Richard 2006	0.67063373	0.15053466	92	93	2.0%	0.67 [0.38, 0.97]
Chen 2012	0.43585676	0.14985294	93	88	2.0%	0.44 [0.14, 0.73]
Richard 2006 (2)	0.27769813	0.14757993	90	94	2.1%	0.28 [−0.01, 0.57]
Shankar 2000	−0.18954625	0.13723333	109	103	2.4%	−0.19 [−0.46, 0.08]
Tielsch 2006	0.35339326	0.13023913	146	152	2.7%	0.35 [0.10, 0.61]
Friis 1997	0.40647134	0.1292236	121	122	2.7%	0.41 [0.15, 0.66]
Chang 2010 (2)	0.2481705	0.12815887	93	177	2.8%	0.25 [−0.00, 0.50]
Veenemans 2011	1.33657691	0.1276632	150	149	2.8%	1.34 [1.09, 1.59]
Lind 2003 (2)	0.7946871	0.12563884	136	136	2.9%	0.79 [0.55, 1.04]
Lind 2003	0.86027128	0.12535047	143	134	2.9%	0.86 [0.61, 1.11]
Veenemans 2011 (2)	1.11626145	0.12407823	151	148	3.0%	1.12 [0.87, 1.36]
Wessells 2012	1.30076381	0.11129748	146	279	3.7%	1.30 [1.08, 1.52]
Soofi 2013	−0.05814114	0.09971627	203	198	4.6%	−0.06 [−0.25, 0.14]
Sazawal 1996	0.8263088	0.08664303	292	285	6.1%	0.83 [0.66, 1.00]
DiGirolamo 2010	0.18538814	0.07877571	318	328	7.4%	0.19 [0.03, 0.34]
Bhandari 2002	1.46023697	0.07309568	499	450	8.6%	1.46 [1.32, 1.60]
Bhandari 2007	0.49031017	0.0714016	419	438	9.0%	0.49 [0.35, 0.63]
Total (95% CI)			**4717**	**5093**	**100.0%**	**0.62 [0.58, 0.67]**

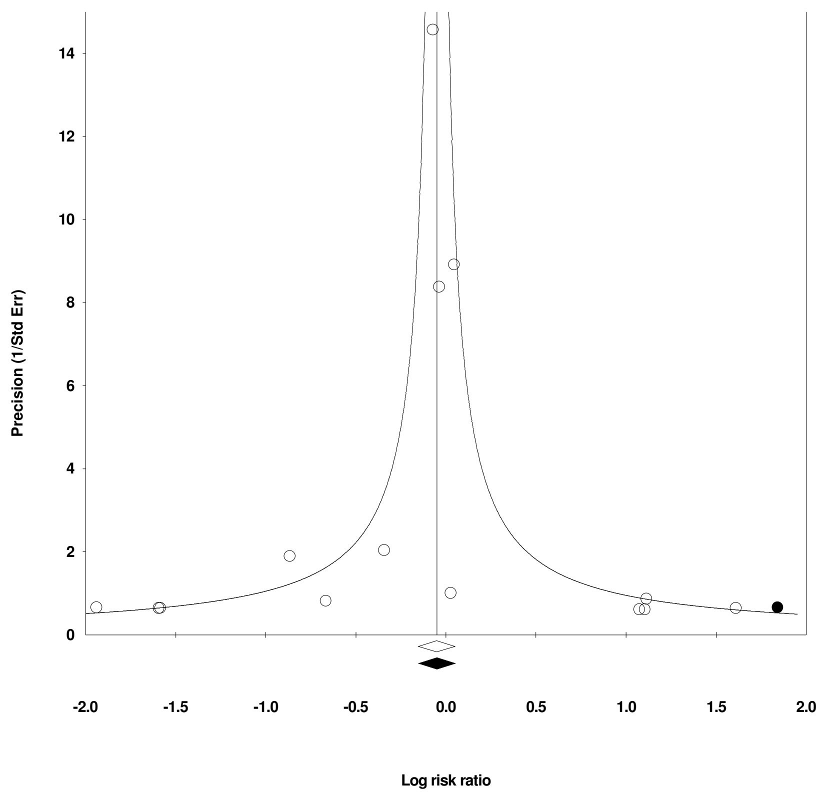
Heterogeneity: $Chi^2 = 582.45$, $df = 55$ ($P < 0.00001$); $I^2 = 91\%$
Test for overall effect: $Z = 29.16$ ($P < 0.00001$)

Std. Mean Difference IV, Fixed, 95% CI

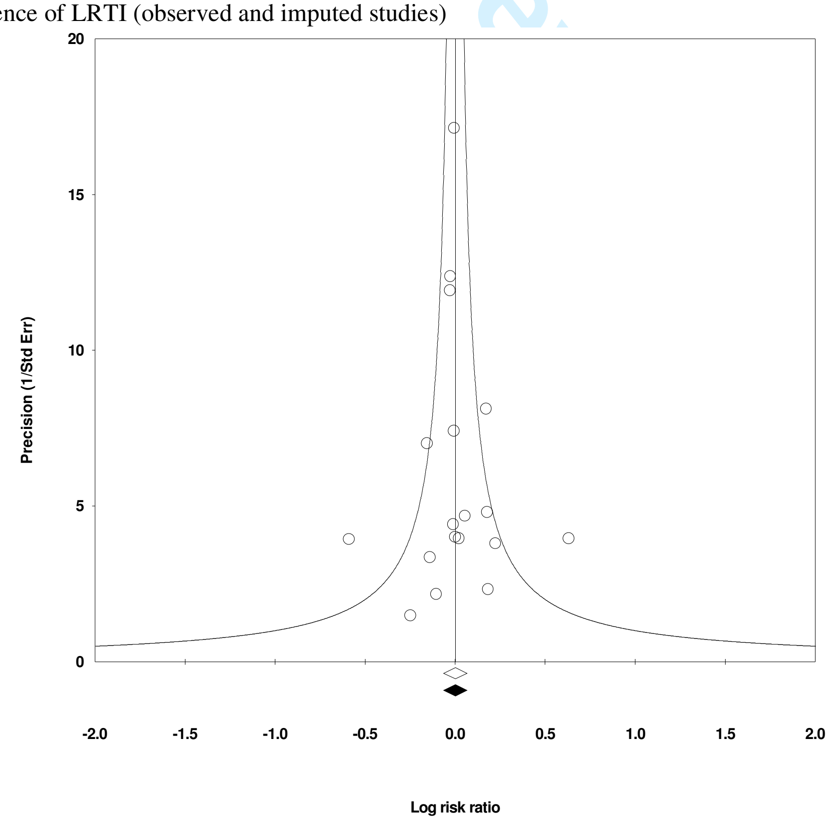


Appendix 8: Tests for reporting bias

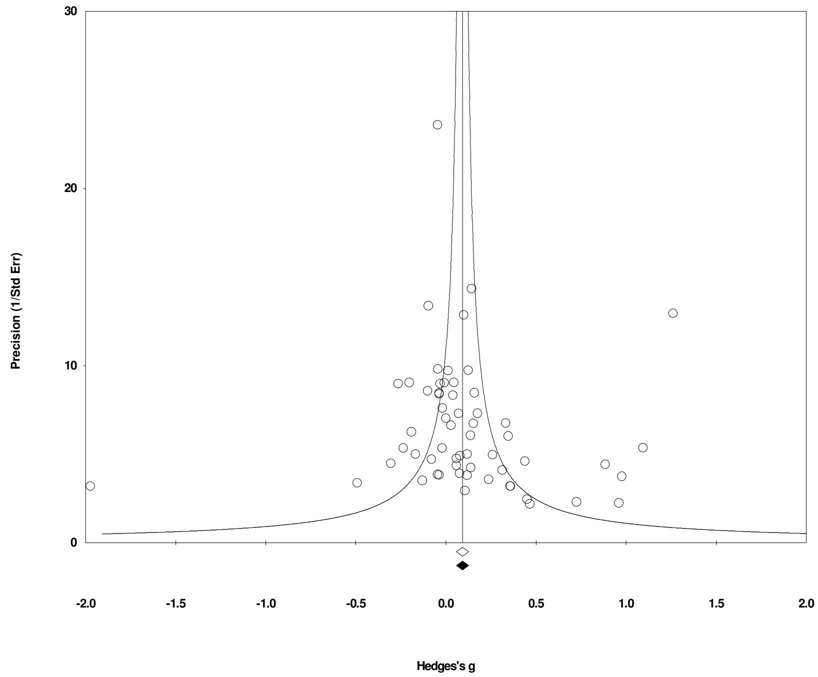
All cause mortality funnel plot (observed and imputed studies)



Incidence of LRTI (observed and imputed studies)



Height (observed and imputed studies)



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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3, App 1
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	App 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	3
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	3
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	3, 5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	3
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	3

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	4
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	3, 5-6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	4, Fig 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	App 4
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	App 5
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Fig 3 to 5, App 7
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	4-5, Table 2-3
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	4, Fig 2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	5-6, Table 4, App 6 and 8
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	6-7
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	6-7
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	7
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	2

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Preventive zinc supplementation for children, and the effect of additional iron: A systematic review and meta-analysis

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Preventive zinc supplementation for children, and the effect of additional iron: A systematic review and meta-analysis

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ABSTRACT

Objective

Zinc deficiency is widespread, and preventive supplementation may have benefits in young children. Effects for children over 5 years of age, and effects when coadministered with other micronutrients are uncertain. These are obstacles to scale-up. This review seeks to determine if preventive supplementation reduces mortality and morbidity for children ages 6 months to 12 years.

Design

Systematic review conducted with the Cochrane Developmental, Psychosocial and Learning Problems Group. Two reviewers independently assessed studies. Meta-analyses were performed for mortality, illness, and side effects.

Data sources

We searched multiple databases, including CENTRAL and Medline in January 2013. Authors were contacted for missing information.

Eligibility criteria for selecting studies

Randomised trials of preventive zinc supplementation. Hospitalised children and children with chronic diseases were excluded.

Results

Eighty randomised trials with 205401 participants were included. There was a small but non-significant effect on all-cause mortality (risk ratio 0.95 [95% CI 0.86 to 1.05]). Supplementation may reduce incidence of all-cause diarrhoea (risk ratio 0.87 [0.85 to 0.89]), but there was evidence of reporting bias. There was no evidence of an effect of incidence or prevalence of respiratory infections or malaria. There was moderate quality evidence of a very small effect on linear growth (SMD 0.09 [0.06 to 0.13]) and an increase in vomiting (RR 1.29 [1.14 to 1.46]). There was no evidence of an effect on iron status. Comparing zinc with and without iron co-supplementation and direct comparisons of zinc plus iron versus zinc administered alone favoured co-intervention for some outcomes and zinc alone for other outcomes. Effects may be larger for children over one year of age, but most differences were not significant.

Conclusions

Benefits of preventive zinc supplementation may outweigh any potential adverse effects in areas where risk of zinc deficiency is high. Further research should determine optimal intervention characteristics and delivery strategies.

STRENGTHS AND LIMITATIONS OF THIS STUDY

This large review was conducted according to best practices and includes the highest quality current evidence about the effects of zinc supplementation.

We investigated several outcomes made multiple comparisons to explore the most important main effects and interactions.

The analyses in this review could not identify the best way to deliver zinc supplements to children in need.

INTRODUCTION

Regular dietary zinc intake is required because zinc cannot be produced or stored.[1,2] In 2011, 116000 deaths in children under 5 years were attributable to zinc deficiency (1.7% of mortalities in this group).[3]

Previous reviews reach disparate conclusions about the benefits of zinc supplementation for young children,[4-12] and most have not examined evidence for children over 5 years of age. Zinc deficiency is prevalent in areas with other micronutrient deficiencies. Concerns about the administration of zinc with iron have been an obstacle to widespread delivery.[13] Understanding the effects of preventive zinc supplementation alone and with iron is crucially important to the future of global health policy.

To evaluate the effects of zinc with or without iron on illness and mortality, as well as growth, we analysed direct comparisons (i.e. zinc plus iron versus zinc alone) as well as subgroups within an overall analysis.

METHODS

Selection criteria and search strategy

Following a published protocol,[14] we conducted a systematic review of randomised clinical trials (RCTs) of orally administered zinc compared with placebo and non-zinc co-interventions received by both groups (e.g. vitamin A). We also compared zinc with and without iron co-supplementation. Participants were six months to 12 years of age. We excluded studies of food fortification and children who were acutely ill.

We searched African Index Medicus, CENTRAL, Conference Proceedings Citation Index, EMBASE, Global Health, ICTRP, IndMED, LILACS, MEDLINE, metaRegister of Controlled Trials, ProQuest Dissertations & Theses Database, and WHOLIS in December 2012 and January 2013 (Appendix 1). Reference lists from previous reviews and from included studies were examined, and trial authors were contacted for unpublished data. Two authors independently reviewed citations and extracted data, including participant demographics, details of the intervention, outcomes, and risk of bias.[15]

Data synthesis

Relative risks and 95% confidence intervals (CIs) were calculated using Mantel-Haenszel methods. Standardised mean differences (SMDs) and 95% CIs were calculated for continuous measures using Hedges *g* and combined using inverse variance methods. When studies reported data in multiple formats, we calculated the SMD and its standard error in Comprehensive Meta-Analysis (CMA) Version 2 before entering data in Review Manager (RevMan) Version 5.2. For incidence data, we combined risk ratios (events per child) and rate ratios (events per child year) because trials were relatively short and we did not anticipate interactions between the intervention and time at risk. For cluster-randomised trials, we used effects controlling for clustering, or we used a intra-cluster correlation coefficient (ICC) to estimate robust standard errors.[15] We used fixed-effect methods for all meta-analyses. Effects favour intervention when the relative risk is reduced (RR<1) or the standardised difference is positive (SMD>0).

When 10 or more studies reported an outcome, we conducted subgroup analyses to explore the effects of iron co-supplementation, national income (low-income countries compared with others), stunting, age (6-12 months, more than 12 months), dose (0-5mg, 5-10mg, etc.), duration (0-6 months, 6-12 months, more than 12 months), and formulation.

Quality of the evidence

Quality of the evidence was judged independently using GRADE.[16] The GRADE system rates evidence from each analysis (i.e., pooled data where possible) as “high”, “moderate”, “low” or “very low”. A “high” rating suggests that evidence is unlikely to be affected by further studies; a “low” rating suggests that further research is required to confirm the direction and magnitude of the true effect. Ratings for meta-analyses of randomised controlled trials start at “high” and may be downgraded for threats to internal validity (i.e. within-study bias), inconsistency (i.e. heterogeneity in results across studies), indirectness (e.g. measures are proxies for the true outcome of interest), imprecision (e.g. few participants, wide confidence intervals), and reporting bias (i.e. publication bias and selective outcome reporting). Because GRADE considers several domains in addition to internal validity, confidence in overall effects may be “low” or “very low” even when all studies were conducted rigorously. The following sections include both significant and non-significant statistical results, and GRADE ratings in the text and tables provide further information about our confidence in these estimates.

RESULTS

Results of the search

From 6384 records, 80 studies were included (Figure 1). Seventy-five studies were published in English, two each in Spanish and Portuguese, one in Chinese. Reasons for excluding 27 studies were enumerated (Appendix 2); additionally, 11 on-going studies were identified, and 5 studies could not be obtained. Seven included studies did not contribute to any meta-analysis because they did not report sufficient data (Appendix 3).

Study characteristics

Included studies assigned 205923 eligible participants (Appendix 4). Twenty trials used factorial designs; there were 100 independent comparisons isolating zinc, and co-interventions were provided to both groups in 51 comparisons. There were 8 independent comparisons of iron with zinc versus zinc alone including 1898 eligible participants. Sample sizes ranged from 21 to 72438 eligible participants (median=200). Nine studies were cluster-randomised, including two randomising households. Three studies included 88% of participants.[17-19] Forty-six studies reported the mean baseline plasma or serum zinc concentration of their participants; the median of these mean concentrations was 72.5 µg/dL.

Thirty-two countries are represented; most studies were conducted in low- or middle-income countries: 37 in Asia, 26 in Latin America and the Caribbean, and 10 in sub-Saharan Africa. The median of mean age at baseline was 28 months, and 22 studies included children over 5 years of age. Both stunted and non-stunted children were included in 42 studies; 5 included only stunted children, 5 included only non-stunted children, and 28 did not specify if participants were stunted.

Studies provided zinc for less than 6 months (30), 6 to 12 months (33), and 12 months or more (16). Of those reporting frequency of zinc supplementation, 48 provided zinc daily and 11 provided zinc weekly. Where reported, daily dose was 0 to 5 mg (5), 5 to 10 mg (19), 10 to 15 mg (30), 15 to 20 mg (8), and 20 mg or more (12). Studies reporting the chemical compound of their zinc supplements provided zinc as sulfate (45), gluconate (12), acetate (six), and other compounds (8). Studies comparing zinc with iron versus zinc alone provided daily dose equivalents of 3 to 36 mg of iron. Outcomes were observed for about 26 weeks (median) after randomisation, with follow-up from 2 to 80 weeks.

Risk of bias

Randomisation and allocation concealment were adequate in 34 and 32 studies; 46 and 48 studies were unclear (Figure 2). For blinding of participants and personnel, 63 studies were at low risk of bias. For blinding of outcome assessment, 65 studies were at low risk of bias. For both types of blinding, 15 studies were unclear.

For all analyses, we attempted to include all randomised study participants; 47 studies were at low risk of bias for incomplete data, 31 were unclear, and 2 were at high risk. For selective reporting, 3 studies were at low risk of bias, 44 were at unclear risk, and 32 were at high risk (Appendix 5).

Bias may affect secondary outcomes in this review, but it does not appear to be important for the primary outcome. For example, mortality and other objective measures are not vulnerable to bias related to blinding, and many missing outcomes were biomarkers or growth related.

Effects of zinc supplementation

In addition to outcomes included in the Summary of Findings Table (Table 1), we analysed results for hospitalisation; prevalence of morbidities; additional measures of growth; as well as biological indicators of zinc, haemoglobin, iron, and copper status (Table 2). Subgroup analyses compare the effects of zinc supplementation with and without iron coadministration (Table 4, Appendix 6).

Fourteen studies including 138302 participants were analysed for all-cause mortality, though other studies included no deaths in either group (Figure 3), and there was high quality evidence of a small effect (risk ratio 0.95 [0.86 to 1.05]). There were similar effects for mortality due to diarrhoea (RR 0.95 [0.69 to 1.31]), mortality due to LRTI (RR 0.86 [0.64 to 1.15]), and mortality due to malaria (RR 0.90 [0.77 to 1.06]), and the evidence for these outcomes was moderate quality.

In 25 studies including 15042 participants, there was low quality evidence of a 13% reduction in incidence of all-cause diarrhoea (Figure 4; RR 0.87 [0.85 to 0.89]). Other measures of diarrhoea were consistent with no difference or with a small reduction in morbidity, including: prevalence of all-cause diarrhoea, hospitalisation due to all-cause diarrhoea, incidence of severe diarrhoea, prevalence of severe diarrhoea, incidence of persistent diarrhoea, and prevalence of persistent diarrhoea.

In twelve trials (9610 participants), there was high quality evidence of no effect on LRTI incidence (Appendix 7; RR 1.00 [0.94 to 1.07]). One trial reported no LRTI in either group.[20] Results for prevalence were consistent with no difference in respiratory morbidity.

Four trials (2407 participants) found moderate quality evidence that would be consistent with no effect or a harmful effect on malaria incidence (RR 1.04 [0.94, 1.14]). One study reported no significant effect on malaria prevalence.

Fifty studies reported height for 13669 participants (Figure 5). There was moderate quality evidence of a very small but statistically significant increase in linear growth (SMD 0.09 [0.06 to 0.13]). Results for weight, weight-to-height ratio and prevalence of stunting were consistent with no difference or a small effect on growth.

Forty-six studies reported serum zinc for 9810 participants. There was evidence of a medium effect (SMD 0.62 [0.58 to 0.67]) on zinc concentration. Results consistently favoured zinc rather than no-intervention, but they were extremely inconsistent in magnitude, possibly due to differences in participants and settings (Chi^2=582.45, df=47 ($P < 0.00001$); I^2=91%). Eleven studies reported serum copper for 3071 participants (1% of participants in this review). There was very low quality evidence of a small reduction in copper (SMD -0.22 [-0.29 to 0.14]); as above, the results were inconsistent (Chi^2=37.47, df=10 ($P < 0.0002$); I^2=68%). There was no evidence of an effect on haemoglobin, prevalence of anaemia, or iron status.

In five trials (35192 participants) there was high quality evidence of increased vomiting (RR 1.29 [1.14 to 1.46]). Two trials reported no adverse events in either group (i.e. supplemented or non-supplemented).[21,22] Results for study withdrawal, participants with one or more side effects, and number of vomiting episodes indicate some short-term side effects; there was no evidence of serious adverse events.

Effects of zinc plus iron compared with zinc alone

Effects on mortality were not significantly different between subgroups with and without iron (Chi^2=1.30, p=0.25); however, there was no mortality effect in groups receiving iron (RR 0.99 [0.86 to 1.15]) while the effect for groups that did not receive iron was nearly significant (RR 0.89 [0.79 to 1.00]). Effects on incidence of diarrhoea differed between groups (Figure 4; Chi^2=65.11, $p<0.00001$), with no benefit for the group that received iron (RR 1.00 [0.96 to 1.05]) and a significant benefit for the group that did not receive iron (RR 0.82 [0.80 to 0.84]). There were significant effects with and without iron co-supplementation on zinc status; these were greater in the studies without iron for serum zinc (Chi^2=27.07, $p<0.00001$) and prevalence of zinc deficiency (Chi^2=34.27, $p<0.00001$). There were also differences between these groups of studies for serum ferritin and serum copper; zinc had no effect in studies with iron co-intervention, but zinc without iron co-intervention reduced ferritin and copper. Overall effects on growth were small; there was a significant difference between subgroups for height but not weight, and the difference for weight-to-height ratio favoured the group that received iron (i.e. the opposite of other results). There were no significant effects in either subgroup for lower respiratory tract infections, serum haemoglobin, prevalence of anaemia, or prevalence of iron deficiency.

Several trials compared zinc coadministered with iron versus zinc given alone (Appendix 6). One trial reported no significant difference in all-cause mortality (323 participants; RR 0.33 [0.01 to 8.39]). In five trials (1530 participants), effects on incidence of all-cause diarrhoea favoured zinc alone (RR 1.10 [1.03 to 1.18]). In one trial (399 participants), effects on prevalence of all-cause diarrhoea favoured zinc with iron, but this was not significant (RR 0.90 [0.79 to 1.06]). Five trials (1329 participants) reported no difference in height (SMD 0.06 [-0.04 to 0.16]). There was similarly low quality evidence and mixed results for other outcomes (Table 3).

Additional subgroup analyses

Studies in high-income countries did not evaluate most outcomes, so we were unable to explore differences in effect by national income. Effects on weight and weight–to-height ratio were not statistically different, and there was no evidence of consistent differences in biological outcomes (Appendix 6).

Most studies included both stunted and non-stunted children, and it was not possible to compare effects between studies for most outcomes. Differences between groups were not significant for growth, but these would be consistent with larger effects in studies of stunted children.

Age was not significantly associated with effects on mortality or incidence diarrhoea, but results would be consistent with greater benefits in children over 1 year of age (Figure 3). Effects on weight were greatest in studies of older children, and there was a similar pattern for height, though the largest study of children over 5 years of age included only 804 participants. The effect of supplementation on zinc deficiency was greater in studies of older children, as was the negative effect on copper. There was no evidence of consistent differences in other biological outcomes.

Dose was not significantly associated with effects on mortality, incidence of LRTI, haemoglobin, or weight-to-height ratio. The pattern of results was inconsistent for incidence and prevalence of diarrhoea, height, weight, and plasma ferritin (Appendix 6). Subgroups were significantly different for serum zinc, prevalence of zinc deficiency, prevalence of iron deficiency, and plasma copper; only these results are consistent with a dose-response relationship.

Duration of supplementation was not significantly associated with effects on mortality, incidence of diarrhoea, incidence of LRTI, or weight-to-height ratio, or prevalence of iron deficiency (Appendix 6). There was a significant difference for prevalence of diarrhoea, but the magnitude of this difference may not be important. Studies of longer supplementation were associated with greater effects on height; the pattern of results was not consistent for weight. By contrast, the largest benefits for biological markers (serum zinc and prevalence of zinc deficiency) were reported in the shortest studies.

Formulation was associated with differences among subgroups, though few studies included capsules or powder. Comparing solution and tablets, differences were not significant for mortality, incidence and prevalence of diarrhoea, incidence of LRTI, blood haemoglobin, prevalence of anaemia, or prevalence of iron deficiency. There were significant differences in the effects of serum ferritin and serum copper, but only three studies of each outcome used tablets, and they were highly heterogeneous. Effects on height, weight, and serum zinc were greater in studies using solution compared with tablet, but all effects were small (Appendix 6).

Reporting bias

For outcomes included in the Summary of Findings Table with 10 or more studies, we also conducted a trim-and-fill analysis to investigate reporting bias (Appendix 8).[23] There was some evidence of small study bias—studies were trimmed for all-cause mortality (1 trimmed) and incidence of all-cause diarrhoea (13 trimmed; Figure 6). None were trimmed for incidence of LRTI, nor were any trimmed for height. The adjusted effect for mortality was not importantly different from the observed effect, but the observed effect for diarrhoea (RR 0.87 [0.85 to 0.89]) was larger than the adjusted value (RR 0.95 [0.93 to 0.97]).

DISCUSSION

Consistent with previous reviews, this review finds high quality evidence from several large, well-conducted trials.[5,7,10] We believe that these results suggest zinc supplementation is probably associated with a small reduction in all-cause mortality for children at risk of deficiency. In interpreting these results, we considered that the results of this meta-analysis are drawn from 13 trials including almost 140,000 participants. The results of those studies are statistically consistent, the overall confidence intervals are relatively small, and the balance of probability favours zinc supplementation rather than placebo. Small reductions in cause-specific mortality were consistent with effects on illness and cause-specific mortality, and the results were biologically plausible. Benefits in any specific are may be related to level of deficiency; countries with very high levels of deficiency could expect the largest reductions in mortality as a result of supplementation.[24] This review also suggests that benefits may not be restricted to young children; there is some evidence of benefits on secondary outcomes in trials including children over 5 years of age, but there is a lack of evidence about effects on mortality in this group.

Results for secondary outcomes suggest modest benefits. Main results for diarrhoea morbidity were consistent with previous reviews,[4,5,7,10] but an asymmetrical funnel plot was indicative of small-study bias. After adjustment, the effect for diarrhoea was halved, and the reduced estimate was consistent with other critical outcomes in this review. Previous reviews have also suggested beneficial effects on respiratory infections[4,5,9-12] and malaria,[10] which this review does not confirm. Previous reviews have reported variable effects on growth;[5,6,8] this review suggests that preventive zinc supplementation alone is unlikely to have large effects on linear growth and morbidity. Supplementation is associated with increased risk of vomiting, but there is no evidence of lasting adverse effects.

Critical outcomes included data for 2407 to 138302 participants, so further placebo-controlled trials of preventive zinc supplementation for young children may not be necessary. However, subgroup analyses did not identify an optimal supplementation strategy (i.e. dose, formulation, and frequency), and large trials comparing active interventions could inform clinical guidelines. Subgroup analyses identify some sources of observed heterogeneity; however, subgroups that were statistically different included a large amount of residual heterogeneity, which is reflected in our judgements about the quality of the evidence (Table 1). Analyses of group-level data are of limited value for identifying moderators, particularly in analyses dominated by a few large studies. Further analyses of individual patient data would be more conclusive.

Effects on biological indicators were inconsistent across studies, but large effects on these measures were not always reflected in clinical outcomes. Supplementation may increase serum zinc, but the magnitude of the effect appears to differ across populations and interventions. Effects on other micronutrients, including iron and copper, are uncertain. Researchers have suggested that iron supplementation may interfere with the absorption of zinc and, conversely, that zinc may interfere with iron and copper absorption;[25,26] however, the relationships between these biomarkers and clinical outcomes (i.e. mortality and morbidities) have not been established.

Subgroup analyses comparing zinc with and without iron did not resolve uncertainty about the effect of co-supplementation. Only four studies with iron co-supplementation reported mortality outcomes, and evidence of outcome reporting bias for diarrhoea incidence leads to cautious interpretation of differences in this outcome. There was no evidence that larger doses or increased duration were associated with increased iron deficiency, but these comparisons are observational and could be affected by uncontrolled covariates.

Direct comparisons within trials provide the only experimental evidence about the effects of co-supplementation with iron. For rare events like mortality, effects of zinc and iron can only be detected in large studies, so studies of interaction effects will need to be very large to detect real differences. Future studies are needed to identify main effects and to explore how administration (i.e. separate or combined) affects uptake and costs.

Dietary intake and supplementation have reduced micronutrient deficiencies in Asia, but micronutrient deficiencies remain common.[3,27] The prevalence of micronutrient deficiencies is declining in Africa, but the absolute number of deficient children is increasing.[3] This review suggests that the overall benefits of preventive zinc supplementation outweigh potential harms in areas with a high risk of zinc deficiency. Further research is needed to determine if these benefits extend to children over 5 years of age. Current estimates suggest that delivering 10 evidence-based nutrition-specific interventions, including preventive zinc supplements, could reduce global mortality in children under 5 years of age by 15%.[28] To that end, research is needed to identify the most effective strategies for delivering zinc supplements to populations in need.[29]

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Contributors

All authors contributed to the background. EMW and JJ were responsible for the methods. JJ executed the first literature search, and EMW and AI executed the update. JJ, EMW, AI, and EC reviewed citations for inclusion. JJ, EMW, AI, SD, XHC, and AJ extracted data. JJ and EMW entered outcome data into RevMan and analysed the data. EMW, JJ, and AI wrote the results and discussion. EMW and AI drafted the summary of findings table, which was agreed on by all authors. ZB contributed to the writing and interpretation of findings. EMW is the guarantor.

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Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years. ZAB is an author of some of the included trials. ZAB and AI have published previous reviews about zinc.

Ethical approval

Not required.

Data sharing

Data are provided in the appendices and available from the authors upon request.

APPENDICIES

Appendix 1: Electronic searches
Appendix 2: Excluded studies
Appendix 3: On-going studies
Appendix 4: Included studies
Appendix 5: Risk of bias
Appendix 6: Subgroup analyses
Appendix 7: Additional forest plots
Appendix 8: Tests for reporting bias

Figure legends

Figure 1: PRISMA flowchart
Figure 2: Risk of bias summary
Figure 3: All-cause mortality by age
Figure 4: Incidence of all cause diarrhoea with and without iron co-supplementation
Figure 5: Height
Figure 6: Incidence of diarrhoea funnel plot (trim-and-fill analysis)

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Table 1: Summary of findings

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk Control	Corresponding risk Zinc	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
All-cause mortality Follow-up: 17 to 72 weeks	Low 2,400 per 1,000,000 High 34,900 per 1,000,000	 2,280 per 1,000,000 (2,064 to 2,520) 33,155 per 1,000,000 (30,014 to 36,645)	RR 0.95 (0.86 to 1.05)	138,302 (13 studies)	⊕⊕⊕⊕ high
Mortality due to all-cause diarrhoea Follow-up: 52 to 69 weeks	Low 800 per 1,000,000 High 3,000 per 1,000,000	 760 per 1,000,000 (552 to 1,048) 2,850 per 1,000,000 (2,070 to 3,930)	RR .95 (0.69 to 1.31)	132,321 (4 studies)	⊕⊕⊕⊖ moderate[1]
Mortality due to LRTI Follow-up: 52 to 69 weeks	Low 1,200 per 1,000,000 High 3,000 per 1,000,000	 1,032 per 1,000,000 (768 to 1,380) 2,580 per 1,000,000 (1,920 to 3,450)	RR 0.86 (0.64 to 1.15)	132,063 (3 studies)	⊕⊕⊕⊖ moderate[1]
Mortality due to malaria Follow-up: 46 to 69 weeks	Low 7,400 per 1,000,000 High 14,200 per 1,000,000	 6,660 per 1,000,000 (5,698 to 7,844) 12,780 per 1,000,000 (10,934 to 15,052)	RR 0.90 (0.77 to 1.06)	42,818 (2 study)	⊕⊕⊕⊖ moderate[1]
Incidence of all-cause diarrhoea Follow-up: 12 to 72 weeks	Low 20,000 per 1,000,000 High 1,770,000 per 1,000,000	 17,400 per 1,000,000 (17,000 to 17,800) 1,539,900 per 1,000,000 (1,504,500 to 1,575,300)	RR 0.87 (0.85 to 0.89)	15,042 (35 studies)	⊕⊕⊖⊖ low[2,3]
Incidence of LRTI Follow-up: 12 to 52 weeks	Low 30,000 per 1,000,000 High 370,000 per 1,000,000	 30,000 per 1,000,000 (28,200 to 32,100) 370,000 per 1,000,000 (347,800 to 395,900)	RR 1.00 (0.94 to 1.07)	9,610 (12 studies)	⊕⊕⊕⊕ high
Incidence of malaria Follow-up: 24 to 47 weeks	Low 140,000 per 1,000,000 High 2,950,000 per 1,000,000	 147,000 per 1,000,000 (133,000 to 161,000) 3,097,500 per 1,000,000 (2,802,500 to 3,392,500)	RR 1.05 (0.95 to 1.15)	2,407 (4 studies)	⊕⊕⊕⊖ moderate[4]
Height Follow-up: 10 to 60 weeks	The mean height in the control groups was -1 HAZ	The mean height in the intervention groups was 0.1 HAZ better (0 to 0.2 better)	SMD 0.09 (0.06 to 0.13)	13,669 (51 studies)	⊕⊕⊕⊖ moderate[5]
Participants with 1 vomiting episode Follow-up: 24 to 52 weeks	Low 17,500 per 1,000,000 High 300,600 per 1,000,000	 22,575 per 1,000,000 (19,950 to 25,550) 387,774 per 1,000,000 (342,684 to 438,876)	RR 1.29 (1.14 to 1.46)	35,192 (4 studies)	⊕⊕⊕⊕ high

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval; RR: Risk ratio; SMD: Standardised Mean Difference

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Footnotes
[1] Few deaths observed overall.
[2] I^2=88%
[3] Trim and fill analysis suggests the effect may be overestimated due to publication bias.
[4] I^2=44%
[5] I^2=86%

Table 2: Zinc compared with no zinc (all outcomes)

Outcomes	Trials	People	ES (95% CI), fixed effects	Heterogeneity I^2; Chi^2 (p value)
ZINC VERSUS NO ZINC				
Mortality				
All-cause	13 (16%)	138302 (67%)	Risk=0.95 (0.86 to 1.05)	0%; 10.57 (p=0.65)
Due to diarrhoea	4 (5%)	132321 (64%)	Risk=0.95 (0.69 to 1.31)	0%; 0.82 (p=0.84)
Due to LRTI	3 (4%)	132063 (64%)	Risk=0.86 (0.64 to 1.15)	0%; 0.07 (p=0.96)
Due to malaria	2 (3%)	42818 (21%)	Risk=0.90 (0.77 to 1.06)	0%; 0.01 (p=0.94)
Hospitalisation				
All-cause	7 (9%)	92872 (45%)	Risk=1.04 (0.97 to 1.11)	44%; 14.41 (p=0.07)
Due to diarrhoea	4 (5%)	74039 (36%)	Risk=1.03 (0.87 to 1.22)	42%; 6.91 (p=0.14)
Due to LRTI	3 (4%)	74743 (36%)	Risk=1.10 (0.93 to 1.30)	0%; 0.35 (p=0.95)
Diarrhoea				
Incidence (all cause)	35 (44%)	15042 (7%)	Risk=0.87 (0.85 to 0.89)	88%; 295.56 (p<0.00001)
Prevalence (all cause)	13 (16%)	8519 (4%)	Rate=0.88 (0.86 to 0.90)	88%; 118.88 (p<0.00001)
Incidence (severe)	5 (6%)	4982 (2%)	Risk=0.89 (0.84 to 0.95)	56%; 13.54 (p=0.04)
Incidence (persistent)	7 (9%)	6216 (3%)	Risk=0.73 (0.62 to 0.85)	61%; 20.47 (p=0.009)
Prevalence (persistent)	1 (1%)	666 (0%)	Rate=0.70 (0.64 to 0.76)	91%; 11.76 (p=0.0006)
Lower respiratory tract infection				
Incidence	12 (15%)	9610 (5%)	Risk=1.00 (0.94 to 1.07)	1%; 17.16 (p=0.44)
Prevalence	3 (4%)	1955 (1%)	Rate=1.20 (1.10 to 1.30)	97%; 89.87 (p<0.00001)
Malaria				
Incidence	4 (5%)	2407 (1%)	Risk=1.05 (0.95 to 1.15)	0%; 2.04 (p=0.84)
Prevalence	1 (1%)	661 (0%)	Rate=0.88 (0.47 to 1.64)	Not applicable
Growth				
Height	51 (64%)	13669 (7%)	SMD=0.09 (0.06 to 0.13)	86%; 407.92 (p<0.00001)
Weight	44 (55%)	12305 (6%)	SMD=0.10 (0.07 to 0.14)	76%; 216.64 (p<0.00001)
Weight-to-height ratio	24 (30%)	7901 (4%)	SMD=0.05 (0.01 to 0.10)	20%; 34.96 (p=0.17)
Prevalence of stunting	6 (8%)	3838 (2%)	Risk=0. 94 (0.86 to 1.02)	59%; 19.43 (p=0.01)
Adverse events				
Participants with 1 AE	2 (3%)	850 (0%)	SMD=1.13 (1.00 to 1.27)	0%; 0.49 (p=0.78)
Study withdrawal	6 (8%)	4263 (2%)	Risk=1.75 (0.93 to 3.32)	21%; 5.07 (p=0.28)
Vomiting (incidence)	5 (6%)	4095 (2%)	Risk=1.68 (1.61 to 1.75)	85%; 34.28 (p<0.00001)
Vomiting (prevalence)	4 (5%)	35192 (17%)	Rate=1.29 (1.14 to 1.46)	37%; 6.31 (p=0.18)
Biological indicators				
Zn concentration	46 (58%)	9810 (5%)	SMD=0.62 (0.58 to 0.67)	91%; 582.45 (p<0.00001)
Zn deficiency (prevalence)	15 (19%)	5434 (3%)	Risk=0.49 (0.45 to 0.53)	86%; 144.77 (p<0.00001)
Haemoglobin concentration	27 (34%)	6024 (3%)	SMD=-0.05 (-0.10 to 0.00)	45%; 63.96 (p=0.002)
Anemia (prevalence)	13 (16%)	4287 (2%)	Risk=1.00 (0.95 to 1.06)	37%; 28.52 (p=0.05)
Fe concentration	19 (24%)	4474 (2%)	SMD=0.07 (0.00 to 0.13)	95%; 480.50 (p<0.00001)
Fe deficiency (prevalence)	10 (13%)	3149 (2%)	Risk=0.99 (0.89 to 1.10)	15%; 16.44 (p=0.29)
Cu concentration	11 (14%)	3071 (1%)	SMD=-0.22 (-0.29 to 0.14)	68%; 37.47 (p=0.0002)
Cu deficiency (prevalence)	3 (4%)	1337 (1%)	Risk=2.64 (1.28 to 5.42)	59%; 4.94 (p=0.08)

Table 3: Zinc with iron compared with zinc alone (all outcomes)

Outcomes	Trials	People	ES (95% CI), fixed effects	Heterogeneity I^2; Chi^2 (p value)
All cause mortality	1 (13%)	323 (17%)	Risk=0.33 (0.01 to 8.31)	Not applicable
Hospitalisation				
All-cause	1 (13%)	399 (21%)	Risk=0.92 (0.45 to 1.89)	Not applicable
Due to diarrhoea	1 (13%)	399 (21%)	Risk=0.99 (0.25 to 3.88)	Not applicable
Diarrhoea				
Incidence (all cause)	5 (63%)	1530 (81%)	Risk=1.10 (1.03 to 1.18)	76%; 16.92 (p=0.002)
Prevalence (all cause)	1 (13%)	399 (21%)	Rate=0.90 (0.79 to 1.06)	Not applicable
Incidence (severe)	1 (13%)	323 (17%)	Rate=0.78 (0.59 to 1.04)	Not applicable
Lower respiratory tract infection				
Incidence	3 (38%)	1065 (56%)	Risk=0.93 (0.83 to 1.04)	21%; 2.52 (p=0.28)
Malaria				
Incidence	1 (13%)	410 (22%)	Rate=0.86 (0.59 to 1.24)	Not applicable
Growth				
Height	5 (63%)	1517 (80%)	SMD=0.06 (-0.04 to 0.16)	0%; 3.54 (p=0.47)
Weight	4 (50%)	910 (48%)	SMD=0.12 (-0.01 to 0.25)	0%; 2.29 (p=0.51)
Weight-to-height ratio	4 (50%)	514 (27%)	SMD=-0.06 (-0.07 to 0.19)	0%; 1.36 (p=0.71)
Prevalence of stunting	2 (25%)	462 (24%)	Risk=0.92 (0.85 to 0.99)	45%; 1.82 (p=0.18)
Adverse events				
Study withdrawal	2 (25%)	557 (29%)	Risk=1.41 (0.91 to 2.18)	0%; 0.08 (p=0.78)
Biological indicators				
Zn concentration	8 (100%)	1337 (70%)	SMD=0.16 (0.05 to 0.27)	61%; 17.84 (p=0.01)
Zn deficiency (prevalence)	3 (38%)	350 (18%)	Risk =1.42 (0.75 to 2.68)	5%; 2.10 (p=0.35)
Haemoglobin concentration	8 (100%)	1341 (71%)	SMD=-0.23 (-0.34 to -0.12)	79%; 33.53 (p<0.0001)
Anemia (prevalence)	3 (38%)	482 (25%)	Risk=0.78 (0.67 to 0.92)	0%; 1.25 (p=0.54)
Fe concentration	6 (75%)	945 (50%)	SMD=-1.79 (-1.99 to -1.56)	99%; 927.92 (p<0.00001)
Fe deficiency (prevalence)	2 (25%)	248 (13%)	Risk =0.12 (0.04 to 0.32)	87%; 8.00 (p=0.005)
Cu concentration	2 (25%)	353 (19%)	SMD=-0.06 (-0.27 to 0.15)	0%; 0.11 (p=0.74)

Rate ratio (Rate); Risk ratio (Risk); Odds Ratio (Odds); Standardised Mean Difference (SMD)
Zinc (Zn); Iron (Fe); Copper (Cu).
Effects favour intervention (i.e. zinc rather than iron; zinc plus iron rather than zinc alone) when the relative risk is reduced (RR<1) or the standardised difference is positive (SMD>0).

Table 4: Subgroup analyses

Subgroup	Trials	People	Risk Ratio (95% CI), fixed	I^2; Chi^2 (p value)
Mortality	**13**	**138302**	**0.95 (0.86 to 1.05)**	**0%; 10.57 (p=0.65)**
Iron co-supplementation (I^2=23%; Chi^2=1.30, p=0.25)				
with iron	4	99242	0.99 (0.86 to 1.15)	0%; 0.76 (p=0.86)
without iron	11	64985	0.89 (0.79 to 1.00)	0%; 9.99 (p=0.44)
Age (I^2=59.8%; Chi^2=2.48, p=0.11)				
6m to 1y	6	29879	1.06 (0.88 to 1.27)	0%; 2.56 (p=0.77)
1y to 5y	8	125903	0.89 (0.80 to 0.99)	12%; 10.28 (p=0.33)
Dose (I^2=0%; Chi^2=2.64, p=0.45)				
0mg to 5mg	2	717	0.72 (0.08 to 6.47)	29%; 1.41 (p=0.23)
5mg to 10mg	1	274	3.04 (0.32 to 28.90)	Not applicable
10mg to 15mg	11	152062	0.93 (0.84 to 1.02)	0%; 8.16 (p=0.61)
20mg or more	1	2464	0.14 (0.01 to 2.78)	Not applicable
Duration (I^2=0%; Chi^2=1.20, p=0.55)				
0m to 6m	2	2817	0.59 (0.07 to 5.15)	47%; 1.88. (p=0.17.)
6m to 12m	7	3898	0.68 (0.37 to 1.25)	4%; 6.23 (p=0.40)
12m or more	6	148802	0.93 (0.85 to 1.03)	0%; 2.91 (p=0.71)
Formulation (I^2=0%; Chi^2=0.54, p=0.91)				
Solution	5	3639	0.99 (0.25 to 3.91)	15%; 4.68 (p=0.32)
Pill/ tablet	8	149854	0.93 (0.85 to 1.02)	0%; 6.99 (p=0.43)
Capsule	1	306	0.51 (0.05 to 5.60)	Not applicable
Powder	1	1718	0.71 (0.27 to 1.86)	Not applicable
Incidence of diarrhoea	**35**	**15042**	**0.87 (0.85 to 0.89)**	**88%; 295.56 (p<0.00001)**
Iron co-supplementation (I^2=99%; Chi^2=65.11, p<0.00001)				
with iron	10	4299	1.00 (0.96 to 1.05)	76%; 37.33 (p<0.00001)
without iron	22	11344	0.82 (0.80 to 0.84)	87%; 196.27 (p<0.00001)
Age (I^2=0%; Chi^2=0.32, p=0.85)				
6m to 1y	10	5576	0.88 (0.85 to 0.90)	95%; 252.46 (p<0.00001)
1y to 5y	15	8370	0.87 (0.84 to 0.90)	43%; 31.48 (p=0.03)
5y to 13y	1	842	0.90 (0.81 to 0.98)	Not applicable
Dose (I^2=98%; Chi^2=195.69, p<0.00001)				
0mg to 5mg	4	1784	0.95 (0.89 to 1.01)	73%; 22.46 (p=0.001)
5mg to 10mg	6	2630	0.73 (0.64 to 0.83)	67%; 15.32 (p=0.009)
10mg to 15mg	11	5452	0.96 (0.92 to 0.99)	69%; 38.39 (p=0.0001)
15mg to 20mg	2	477	0.61 (0.58 to 0.65)	0%; 0.21 (p<0.00001)
20mg or more	6	4931	0.90 (0.87 to 0.94)	75%; 28.17 (p<0.00001)
Duration (I^2=0%; Chi^2=1.15, p=0.56)				
0m to 6m	7	4190	0.89 (0.85 to 0.93)	57%; 16.42 (p=0.02)
6m to 12m	14	8971	0.86 (0.84 to 0.89)	93%; 250.92 (p<0.00001)
12m or more	5	1881	0.88 (0.82 to 0.95)	73%; 29.82 (p=0.0002)
Formulation (I^2=94%; Chi^2=51.34, p<0.00001)				
Solution	19	10768	0.84 (0.82 to 0.86)	90%; 236.48 (p<0.00001)
Pill/ tablet	3	1696	0.90 (0.81 to 0.99)	5%; 3.15 (p=0.37)
Capsule	1	612	0.78 (0.60 to 1.01)	Not applicable
Powder	2	1861	1.04 (0.98 to 1.09)	0%; 0.65 (p=0.42)

Appendix 1: Electronic searches

MEDLINE

1 zinc/ or zinc compounds/ or zinc oxide/ or zinc sulfate/ or zinc acetate/
2 (zinc or Zn).tw.
3 1 or 2
4 exp infant/ or exp child/ or adolescent/
5 (newborn$ or neonat$ or neo-nat$ or infan$ or baby or babies or toddler$ or preschool$ or pre-school$ or pediatric$ or paediatric$ or child$ or girl$ or boy$ or preteen$ or pre-teen$ or teen$ or preadolescen$ or pre-adolescen$ or adolescen$ or prepubert$ or pre-pubert$ or pubert$).tw.
6 4 or 5
7 randomized controlled trial.pt.
8 controlled clinical trial.pt.
9 randomized.ab.
10 placebo.ab.
11 drug therapy.fs.
12 randomly.ab.
13 trial.ab.
14 groups.ab.
15 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16 exp animals/ not humans.sh.
17 15 not 16
18 3 and 6 and 17

Cochrane Central Register of Controlled Trials (CENTRAL)

1 MeSH descriptor Zinc explode all trees
2 MeSH descriptor Zinc Compounds explode all trees
3 MeSH descriptor Zinc Oxide explode all trees
4 MeSH descriptor Zinc Sulfate explode all trees
5 MeSH descriptor Zinc Acetate explode all trees
6 (zinc):ti,ab,kw
7 (Zn):ti,ab,kw
8 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7)
9 MeSH descriptor Infant explode all trees
10 MeSH descriptor Child explode all trees
11 MeSH descriptor Adolescent explode all trees
12 (newborn* or neonat* or (neo next nat*) or infan* or baby* or babies or toddler* or preschool* or (pre next school*) or pediatric* or paediatric* or child* or girl* or boy* or preteen* or (pre next teen*) or teen* or preadolescen* or (pre next adolescen*) or adolescen* or prepubert* or (pre next pubert*) or pubert*):ti,ab,kw
13 (#9 OR #10 OR #11 OR #12)
14 (#8 AND #13)

MEDLINE In-Process & Other Non-Indexed Citations

1 (zinc or Zn).tw.
2 (newborn$ or neonat$ or neo-nat$ or infan$ or baby or babies or toddler$ or preschool$ or pre-school$ or pediatric$ or paediatric$ or child$ or girl$ or boy$ or preteen$ or pre-teen$ or teen$ or preadolescen$ or pre-adolescen$ or adolescen$ or prepubert$ or pre-pubert$ or pubert$).tw.
3 randomized controlled trial.pt.
4 controlled clinical trial.pt.
5 randomized.ab.
6 placebo.ab.
7 drug therapy.fs.
8 randomly.ab.
9 trial.ab.
10 groups.ab.
11 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12 exp animals/ not humans.sh.
13 11 not 12
14 1 and 2 and 13

EMBASE

1 zinc/ or zinc derivative/ or zinc oxide/ or zinc sulfate/ or zinc acetate/
2 (zinc or Zn).tw.

3 1 or 2
4 exp infant/ or exp child/ or exp adolescent/
5 (newborn$ or neonat$ or neo-nat$ or infan$ or baby or babies or toddler$ or preschool$ or pre-school$ or pediatric$ or paediatric$ or child$ or girl$ or boy$ or preteen$ or pre-teen$ or teen$ or preadolescen$ or pre-adolescen$ or adolescen$ or prepubert$ or pre-pubert$ or pubert$).tw.
6 4 or 5
7 exp crossover-procedure/ or exp double-blind procedure/ or exp randomized controlled trial/ or exp single-blind procedure/
8 (random$ or factorial$ or crossover$ or cross-over$ or placebo$ or (doubl$ adj blind$) or (singl$ adj blind$) or assign$ or allocat$ or volunteer$).tw.
9 7 or 8
10 3 and 6 and 9
The terms in lines seven through eight are the same as those used by the UK Cochrane Centre to identify randomised controlled trials.

African Index Medicus
zinc or Zn [Key Word] or zinc or Zn [Title] or zinc or Zn [Descriptor]

Global Health
1 zinc/ or zinc sulfate/ or zinc oxide/
2 (zinc or Zn).tw.
3 1 or 2
4 exp infants/ or exp children/ or exp adolescents/
5 (newborn$ or neonat$ or neo-nat$ or infan$ or baby or babies or toddler$ or preschool$ or pre-school$ or pediatric$ or paediatric$ or child$ or girl$ or boy$ or preteen$ or pre-teen$ or teen$ or preadolescen$ or pre-adolescen$ or adolescen$ or prepubert$ or pre-pubert$ or pubert$).tw.
6 4 or 5
7 (random$ or control$ or clinic$ or trial$ or placebo$ or drug therap$ or group$ or crossover$ or cross-over$ or double$-blind$ or single$-blind$ or factorial$ or assign$ or allocat$ or volunteer$).af.
8 3 and 6 and 7

IndMED
zinc or Zn [Title] OR zinc or Zn [Keywords]

Latin American Caribbean Health Sciences Literature (LILACS)
(MH Infant OR MH Child OR MH Adolescent) OR (Tw newborn$ OR Tw neonat$ OR Tw neo-nat$ OR Tw infan$ OR Tw baby$ OR Tw babies OR Tw toddler$ OR Tw preschool$ OR Tw pre-school$ OR Tw pediatric$ OR Tw paediatric$ OR Tw child$ OR Tw girl$ OR Tw boy$ OR Tw preteen$ OR Tw pre-teen$ OR Tw teen$ OR Tw preadolescen$ OR Tw pre-adolescen$ OR Tw adolescen$ OR Tw prepubert$ OR Tw pre-pubert$ OR Tw pubert$ OR Tw niño$ OR Tw niña$ OR Tw bebé$ OR Tw preescolar$ OR Tw prescolar$ OR Tw pre-escolar$ OR Tw pre-scolar$) [Words] and (MH Zinc OR MH Zinc Acetate OR MH Zinc Sulfate OR MH Zinc Compounds OR MH Zinc Oxide) OR Tw Zinc OR Tw Zn [Words]

WHO Library & Information Networks for Knowledge Database (WHOLIS)
zinc or Zn [All indexes] [All sources]

metaRegister of Controlled Trials
(Zinc or Zn) AND (infant or infants or baby or babies or toddler or toddlers or pre-school or preschool or pediatric or paediatric or child or children or girl or girls or boy or boys or pre-teen or pre-adolescent or adolescent or pre-pubertal)

WHO International Clinical Trials Registry Platform (ICTRP)
zinc or Zn [in the Intervention]

Conference Proceedings Citation Index (formerly known as ISI Proceedings)
TS=(zinc or Zn) AND TS=(newborn* or neonat* or neo-nat* or (neo nat*) or infan* or baby or babies or toddler* or preschool* or pre-school* or (pre school*) or pediatric* or paediatric* or child* or girl* or boy* or preteen* or pre-teen* or (pre teen*) or teen* or preadolescen* or pre-adolescen* or (pre adolescen*) or adolescen* or prepubert* or pre-pubert* or (pre pubert*) or pubert*) AND TS=(random* or control* or clinic* or trial* or placebo* or (drug therap*) or group* or crossover* or cross-over* or (cross over*) or double*-blind* or (double* blind*) or single*-blind* or (single* blind*) or factorial* or assign* or allocat* or volunteer*)

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(zinc or Zn) AND (newborn* or neonat* or neo-nat* or infan* or baby or babies or toddler* or preschool* or pre-school* or pediatric* or paediatric* or child* or girl* or boy* or preteen* or pre-teen* or teen* or preadolescen* or pre-adolescen* or adolescen* or prepubert* or pre-pubert* or pubert*)

Appendix 2: Excluded studies

Study	Reason for exclusion
Ahmed 2009[1]	Non-RCT
Bates 1993[2]	Non-RCT
Behrens 1990[3]	Therapeutic supplementation
Berger 2006[4-6]	Ineligible age
Brooks 2005[7]	Ineligible age
Campos 2004[8]	Non-RCT
Cuevas 2002[9]	No eligible comparison
Duggan 2003[10]	Fortification
Fahmida 2007[11]	Ineligible age
Hashemipour 2009[12-14]	Children were obese
Heinig 2006[15,16]	Ineligible age
Hess 2011[17]	Acceptability study randomizing order of administration
Imamoglu 2005[18]	Non-RCT
Kordas 2005[19-21]	Therapeutic supplementation
NCT01472211[22]	Intervention not eligible (LifeStraw with or without zinc)
Osendarp 2002[23]	Ineligible age
Payne-Robinson 1991[24]	Severe protein-energy malnutrition
Perrone 1999[25]	No eligible comparison
Ronaghy 1969[26]	Ineligible age
Ronaghy 1974[27]	Ineligible age
Roxas 1980[28]	Non-RCT
Shingwekar 1979[29]	Non-RCT
Shrivastava 1993[30]	Non-RCT
Walravens 1992[31]	Ineligible age
Wasantwisut 2006[32]	Ineligible age
Yanfeng 1997[33]	No eligible comparison
Zeba 2008[34]	No eligible comparison

Appendix 3: On-going studies

Study	Reason for exclusion
Arabaci 2010[35]	Awaiting classification
Chicourel 2001[36]	Awaiting classification
CTRI/2010/091/001417[37]	On-going
Jimenez 2000[38]	Awaiting classification
Mitter 2009[39]	Awaiting classification
NCT00133406[40]	On-going
NCT00228254[41]	On-going
NCT00374023[42]	On-going
NCT00421668[43]	On-going
NCT00589264[44]	On-going
NCT00944359[45]	On-going
NCT00967551[46]	On-going
NCT00980421[47]	On-going
NCT01306097[48]	On-going
NCT01616693[49]	On-going
Smith 1985[50]	Awaiting classification

Appendix 4: Included studies

Study	Country	N	Age	Dose	Duration	Form	Height	Co-intervention
Ahmed 2009[51]	BD	40	10 to 18	20mg daily	1.5	Solution	Not reported	Cholera vaccine
Akramuzzaman 1994[52]	BD	256	mean=35	20mg daily	15	Solution	Stunted and non-stunted	Vitamins A, C, D
Alarcon 2004[53]	PE	223	6 to 35	3mg/kg 6d/wk	4.5	Solution	HAZ=-1.04	Iron
Albert 2003[54, 55]	BD	256	24 to 60	20mg daily	1.5	Solution	Not reported	Cholera vaccine
Ba Lo 2011[56]	SN	97	9 to 17	6mg daily	0.5	Solution	Non-stunted only; HAZ=-0.44	Micronutrients
Baqui 2003[57-60]	BD	645	6 to 6	20mg weekly	6	Solution	Stunted and non-stunted; HAZ=-1.2	Vitamin B
Bhandari 2002[61-67]	IN	2482	6 to 30	10mg <1y; 20mg >1y daily	4	Solution	Stunted and non-stunted; HAZ=-1.82	Vitamin A
Bhandari 2007[68, 69]	IN	72,438	6 to 23	10mg daily	12	Tablet	Stunted and non-stunted; HAZ=-1.95	Iron and folic acid
Brown 2007[70-73]	PE	200	6 to 8	3mg daily	6	Solution	Stunted and non-stunted; HAZ=-1.19	Micronutrients
Castillo-Duran 1994[74]	CL	114	72 to 168	10mg daily	12	Capsule	Stunted only	None
*Castillo-Duran 2002[75]	CL	42	17 to 19	5mg daily	12	Solution	Non-stunted only	None
Cavan 1993[76-78]	GT	162	68 to 96	10mg 5d/wk	6.25	Tablet	Stunted and non-stunted; HAZ=-1.51	Micronutrients
Chang 2010[79]	BD	1000	6 to 18	5mg <1y; 10mg >1y alternate days	6	Tablet	Stunted and non-stunted; HAZ=-1.3	None
Chen 2012[80]	CN	361	36 to 72	10mg 5d/wk	6	Tablet	HAZ=-0.264585635	Vitamin A
Chhagan 2009[81-85]	ZA	227	6 to 6	10mg daily	18	Tablet	Stunted and non-stunted; HAZ=-0.45	Vitamin A
Clark 1999[86]	UK	47	mean=146	15mg daily	1.5	Unclear	Non-stunted only	None
Cole 2012[87]	BR	143	6 to 48	5mg daily	3	Powder	Not reported	Micronutrients
Dehbozorgi 2007[88]	IR	60	72 to 144	8mg daily	6	Solution	Not reported	None
DiGirolamo 2010[89, 90]	GT	750	72 to 132	10mg 5d/wk	5.8	Tablet	Stunted and non-stunted; HAZ=-1.2	None
Ebrahimi 2006[91]	IR	804	96 to 132	10mg 6d/wk	7	Solution	Not reported	None
Fallahi 2007[92]	IR	53	132 to 143	20mg 6d/wk	4	Capsule	Not reported	Iron
Fonseca 2002[93]	BR	199	72 to 120	30mg weekly	3	Solution	Stunted and non-stunted	None
Friis 1997[94, 95]	ZW	313	132 to 204	30 mg <29.5 kg; 50 mg >29.5 kg 5d/wk	12	Tablet	HAZ=-1.18	None

Garcia 1998[96]	CL	33	66 to 159.6	20mg daily	6	Unclear	Stunted and non-stunted; HAZ=-2.6	None
Gibson 1989[97]	CA	60	59 to 95	10mg daily	12	Solution	Stunted and non-stunted; HAZ=-1.39	None
Gracia 2005[98]	CO	350	24 to 59	12mg daily	8	Unclear	Stunted and non-stunted; HAZ=0	Micronutrients
Gupta 2003[99]	IN	280	6 to 41	10mg or 50mg 5d/wk or weekly	4	Solution	Not reported	None
Gupta 2007[100]	IN	1,878	6 to 48	50mg weekly	6	Solution	Not reported	Vitamin B
Hambidge 1978[101, 102]	US	75	38 to 61	14mg 5d/wk	6	Solution	Not reported	None
Han 2002[103, 104]	CN	119	36 to 60	3.5mg 5d/wk	12	Tablet	Not reported	Vitamin A and Calcium
Hettiarachchi 2008[105]	LK	341	144 to 155	14mg 5d/wk	6	Capsule	Stunted and non-stunted; HAZ=-1.16	None
Hong 1982[106]	CN	158	4 to 72	Daily	2.4	Solution	Stunted and non-stunted	Vitamin B
Ince 1995[107]	TR	25	25 to 76	10mg daily	12	Solution	Non-stunted only; HAZ=-1.55	None
Kartasurya 2012[108]	ID	826	24 to 60	10mg daily	4	Solution	Non-stunted only; HAZ=-1.730145278	Vitamin A
Kikafunda 1998[109-111]	UG	155	33 to 89	10mg 5d/wk	6	Tablet	HAZ=-0.7	None
Kurugöl 2006[112]	TR	200	24 to 120	15mg daily	7	Solution	Not reported	None
Larson 2010[113, 114]	BD	353	6 to 24	10mg daily	3	Solution	HAZ=-1.72	None
Lind 2003[115-118]	ID	680	6 to 6	10mg daily	6	Solution	Stunted and non-stunted; HAZ=-0.34	Vitamin C
Long 2006[119-122]	MX	786	6 to 15	20mg daily	12	Solution	Stunted and non-stunted; HAZ=0.1	None
Mahloudji 1975[123]	IR	50	72 to 144	20mg 6d/wk	16	Capsule	Not reported	Micronutrients
Malik 2013[124]	IN	158	6 to 11	20mg daily	0.46	Solution	Not reported	None
*Marinho 1991[125]	BR	240	36 to 84	5mg daily	1	Unclear	Stunted and non-stunted	None
Mazariegos 2010[126]	GT	412	6 to 6	5mg daily	6	Tablet	Stunted and non-stunted; HAZ=-2.09	Low-phytate maize
Meeks Gardner 1998[127, 128]	JM	61	6 to 24	5mg daily	3	Solution	Stunted only; HAZ=-2.9	Micronutrients
Meeks Gardner 2005[129]	JM	126	9 to 30	10mg daily	6	Solution	HAZ=-1.42	Micronutrients
Mozaffari-Khosravi 2009[130, 131]	IR	90	25 to 69	5mg daily	6	Solution	Stunted and non-stunted; HAZ=-1.59	None
Muller 2001[132-134]	BF	709	6 to 30	12.5mg 6d/wk	6	Tablet	Stunted and non-stunted; HAZ=-1.6	None
Nakamura 1993[135]	JP	21	mean=70	5mg/kg daily	6	Unclear	Stunted only; HAZ=-2.44	None
Ninh 1996[136]	VN	210	4 to 36	10mg daily	5	Solution	Stunted only; HAZ=-2.61	None

Penny 2004[137, 138]	PE	164	6 to 35	10mg daily	6	Solution	Stunted and non-stunted; HAZ=-1.56	None
Rahman 2001[139-142]	BD	800	12 to 35	20mg daily	0.5	Solution	Stunted and non-stunted; HAZ=-2.41	None
Richard 2006[143]	PE	855	6 to 180	20mg daily	7	Solution	Stunted and non-stunted; HAZ=-2.08	None
Rosado 1997[144-146]	MX	219	18 to 36	20mg 6d/wk	12	Solution	Stunted and non-stunted; HAZ=-1.6	None
Rosales 2004[147]	GT	76	96 to 132	42.5mg 5d/wk	2	Solution	Not reported	None
Ruel 1997[148-150]	GT	108	6 to 9	10mg daily	7	Solution	Stunted and non-stunted; HAZ=-2.16	None
Ruz 1997[151]	CL	98	27 to 50	10mg daily	14	Solution	Stunted and non-stunted; HAZ=-0.52	None
*Sandstead 1998[152, 153]	CN	NR	72 to 108	20mg 6d/wk	2.5	Tablet	Not reported	Micronutrients
Sandstead 2008[154]	US	54	72 to 84	20mg 5d/wk	2.5	Unclear	Not reported	Micronutrients
*Sanjur 1990[155]	US	NR	12 to 24	Daily	6	Tablet	Not reported	Micronutrients
Sayeg Porto 2000[156]	BR	21	84 to 120	5mg/kg daily	6	Solution	Stunted only; HAZ=-2.67	None
Sazawal 1996[157-166]	IN	609	6 to 35	10mg daily	6	Solution	Stunted and non-stunted	Micronutrients
Sazawal 2006[167-176]	TZ	60,225	1 to 35	5mg <1y; 10mg >1y daily	16	Tablet	Stunted and non-stunted; HAZ=-1.5	Micronutrients
Schultink 1997[177]	ID	85	24 to 60	15mg daily	2	Solution	Stunted and non-stunted; HAZ=-2.5	Iron
Sempertegui 1996[178, 179]	EC	50	12 to 59	10mg daily	2	Solution	Stunted and non-stunted; HAZ=-2	None
*Shah 2011[180]	IN	NR	6 to 59	10mg daily	2	Unclear	Not reported	None
Shankar 2000[181, 182]	PG	274	6 to 60	10mg 6d/wk	11.5	Tablet	Stunted and non-stunted; HAZ=-1.9	None
Silva 2006[183]	BR	60	12 to 59	10mg daily	4	Solution	Stunted and non-stunted; HAZ=-1.9	Iron-fortified milk
Smith 1999[184]	BZ	51	Preschool	70mg weekly	6	Solution	Stunted and non-stunted	None
Soofi 2013[185]	PK	1305	6 to 6	10mg daily	12	Powder	Stunted and non-stunted	Micronutrients
Tielsch 2006[186-193]	NP	49,205	1 to 35	5mg < 1y; 10mg >1y daily	to 36m	Tablet	Stunted and non-stunted	Iron and folic acid
Tupe 2009[194, 195]	IN	88	120 to 155	16.6mg 6d/wk	2.5	Tablet	Stunted and non-stunted; HAZ=-1.3	None
Uckardes 2009[196-198]	TR	226	89 to 140	15mg 5d/wk	2.5	Solution	Not reported	None
Udomkesmalee 1992[199, 200]	TH	133	72 to 156	25mg 5d/wk	6	Capsule	Stunted and non-stunted	Vitamin A
Umeta 2000[201-203]	ET	200	6 to 12	10mg 6d/wk	6	Solution	Stunted and non-stunted; HAZ=-1.7	None
*Vakili 2009[204]	IR	200	78 to 120	10mg 6d/wk	5	Tablet	Not reported	None

Veenemans 2011[205-208]	TZ	612	6 to 60	10mg daily	11	Capsule	Stunted and non-stunted; HAZ=-2.43	Micronutrients
Walravens 1983[209, 210]	US	57	24 to 72	5mg 2x daily	12	Solution	Stunted and non-stunted; HAZ=-2.07	None
Walravens 1989[211]	US	NR	8 to 27	25mg (frequency unclear)	6	Solution	HAZ=-1.35	None
Wessells 2012[212, 213]	BF	451	6 to 23	5mg daily	0.75	Solution	HAZ=-1.5	None
Wuehler 2008[214, 215]	EC	503	12 to 30	3, 7, or 10mg daily	6	Solution	Stunted and non-stunted; HAZ=-2.3	None

*Not included in meta-analysis; Age and duration reported in months

Appendix 5: Risk of bias

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants (performance bias)	Blinding of personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Ahmed 2009	?	?	?	?	?	+	?	+
Akramuzzaman 1994	?	?	?	?	?	?	?	+
Alarcon 2004	?	?	+	+	+	+	?	+
Albert 2003	?	+	+	+	+	+	−	+
Ba Lo 2011	+	?	+	+	+	−	+	+
Baqui 2003	?	?	+	+	+	+	−	+
Bhandari 2002	+	+	+	+	+	+	−	+
Bhandari 2007	+	+	+	+	+	+	−	+
Brown 2007	+	+	+	+	+	?	+	+
Castillo-Duran 1994	?	?	+	+	+	?	−	+
Castillo-Duran 2002	?	?	?	?	?	?	−	+
Cavan 1993	+	+	+	+	+	+	−	+
Chang 2010	+	+	+	+	+	+	?	+
Chen 2012	?	?	−	−	?	?	?	+
Chhagan 2009	+	+	+	+	+	?	−	?
Clark 1999	?	?	+	+	+	+	?	+
Cole 2012	+	?	+	−	+	+	?	+
Dehbozorgi 2007	?	?	+	+	+	?	−	+
DiGirolamo 2010	+	+	+	+	+	+	?	+
Ebrahimi 2006	?	?	+	+	+	?	?	+
Fallahi 2007	?	?	?	?	?	+	?	+
Fonseca 2002	+	?	+	+	+	?	−	+
Friis 1997	?	?	+	+	+	?	−	+
Garcia 1998	?	?	+	+	+	+	?	+
Gibson 1989	?	+	+	+	+	+	?	+
Gracia 2005	?	?	+	+	+	?	−	+
Gupta 2003	+	+	+	+	+	+	−	+
Gupta 2007	?	?	+	+	+	−	−	+
Hambidge 1978	?	?	?	?	?	?	?	+
Han 2002	?	?	+	+	+	?	?	+
Hettiarachchi 2008	?	?	+	+	+	?	?	+
Hong 1982	?	?	?	?	?	?	?	+
Ince 1995	+	?	+	+	+	+	?	+
Kartasurya 2012	+	+	+	+	+	+	−	+
Kikafunda 1998	?	?	+	+	+	?	−	+
Kurugöl 2006	+	+	+	+	+	+	?	+
Larson 2010	+	+	+	+	+	+	−	+

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants (performance bias)	Blinding of personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Lind 2003	?	+	+	+	+	+	+	+
Long 2006	+	+	+	+	+	+	?	+
Mahloudji 1975	?	?	+	+	+	?	-	+
Malik 2013	+	+	+	+	+	+	-	+
Marinho 1991	?	?	?	?	?	?	?	+
Mazariegos 2010	+	+	+	+	+	+	-	+
Meeks Gardner 1998	?	?	+	+	+	?	?	+
Meeks Gardner 2005	?	?	+	+	+	+	?	?
Mozaffari-Khosravi 2009	+	+	+	+	+	?	?	+
Muller 2001	+	+	+	+	+	+	?	+
Nakamura 1993	?	?	?	?	?	?	?	+
Ninh 1996	?	?	+	+	+	?	-	+
Penny 2004	+	?	+	+	+	+	?	+
Rahman 2001	+	+	+	+	+	+	-	+
Richard 2006	+	?	+	+	+	+	?	+
Rosado 1997	?	?	+	+	+	+	?	+
Rosales 2004	+	?	+	+	+	+	?	+
Ruel 1997	?	?	+	+	+	+	?	+
Ruz 1997	?	+	+	+	+	?	-	+
Sandstead 1998	?	?	+	+	+	?	-	+
Sandstead 2008	?	+	+	+	+	?	?	+
Sanjur 1990	?	?	+	+	+	?	?	+
Sayeg Porto 2000	?	+	+	+	+	?	-	+
Sazawal 1996	+	+	+	+	+	+	-	+
Sazawal 2006	+	+	+	+	+	+	-	+
Schultink 1997	?	?	+	+	+	?	?	+
Sempertegui 1996	+	?	+	+	+	+	?	+
Shah 2011	?	?	?	?	?	?	-	+
Shankar 2000	+	+	+	+	+	+	-	+
Silva 2006	?	?	?	?	?	+	-	+
Smith 1999	?	?	?	?	?	+	?	?
Soofi 2013	+	+	+	+	+	+	+	+
Tielsch 2006	+	+	+	+	+	+	?	+
Tupe 2009	+	?	?	?	+	+	?	+

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants (performance bias)	Blinding of personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Uckardes 2009	?	?	+	+	+	+	?	?
Udomkesmalee 1992	?	?	+	+	+	+	-	+
Umeta 2000	?	?	+	+	+	+	?	+
Vakili 2009	?	?	?	?	?	+	?	+
Veenemans 2011	+	+	+	+	+	+	-	+
Walravens 1983	?	+	+	+	+	?	?	+
Walravens 1989	?	?	+	+	+	?	?	+
Wessells 2012	+	+	?	?	?	+	?	+
Wuehler 2008	+	+	+	+	+	+	-	+

Appendix 6: Subgroup analyses

Subgroup	Trials	People	Effect size (95% CI), fixed	I^2; Chi^2 (p value)
Prevalence of diarrhoea (RR)	**13**	**8519**	**0.88 (0.86 to 0.90)**	**88%; 118.88 (p<0.00001)**
Iron co-supplementation (I^2=75%; Chi^2=3.97, p=0.05)				
with iron	3	1024	0.96 (0.88 to 1.05)	96%; 46.97 (p<0.00001)
without iron	11	7495	0.88 (0.86 to 0.90)	84%; 67.94 (p<0.00001)
Age (I^2=97%; Chi^2=30.52, p<0.00001)				
6m to 1y	7	3714	0.96 (0.93 to 1.00)	94%; 112.81 (p<0.00001)
1y to 5y	7	4805	0.85 (0.83 to 0.87)	37%; 11.03 (p=0.14)
Dose (I^2=94%; Chi^2=61.69, p<0.00001)				
0mg to 5mg	2	1200	1.00 (0.92 to 1.08)	94%; 33.41 (p<0.00001)
5mg to 10mg	1	274	1.17 (0.60 to 2.28)	Not applicable
10mg to 15mg	6	3434	0.93 (0.90 to 0.96)	66%; 14.53 (p=0.01)
15mg to 20mg	1	258	0.61 (0.54 to 0.69)	Not applicable
20mg or more	3	3353	0.85 (0.82 to 0.87)	68%; 9.24 (p=0.03)
Duration (I^2=86%; Chi^2=13.98, p=0.0009)				
0m to 6m	3	3353	0.85 (0.82 to 0.87)	68%; 9.24 (p=0.03)
6m to 12m	9	4957	0.92 (0.89 to 0.95)	91%; 95.66 (p<0.00001)
12m or more	1	209	0.88 (0.74 to 1.03)	Not applicable
Formulation (I^2=86%; Chi^2=13.99, p=0.0009)				
Solution	8	4657	0.88 (0.85 to 0.90)	92%; 97.84 (p<0.00001)
Pill/ tablet	4	2144	0.86 (0.81 to 0.92)	43%; 7.05 (p=0.13)
Capsule	1	1718	1.03 (0.95 to 1.12)	Not applicable
Incidence of LRTI (RR)	**12**	**9610**	**1.00 (0.94 to 1.07)**	**1%; 17.16 (p=0.44)**
Iron co-supplementation (I^2=0%; Chi^2=0.06, p=0.80)				
with iron	5	2896	0.99 (0.87 to 1.12)	0%; 2.92 (p=0.71)
without iron	10	6714	1.01 (0.93 to 1.08)	22%; 14.17 (p=0.22)
Age (I^2=0%; Chi^2=1.50, p=0.47)				
6m to 1y	5	3566	0.97 (0.88 to 1.07)	0%; 2.12 (p=0.95)
1y to 5y	5	4605	1.05 (0.96 to 1.16)	25%; 8.01 (p=0.24)
5y to 13y	1	836	1.00 (0.72 to 1.40)	Not applicable
Dose (I^2=0%; Chi^2=0.60, p=0.74)				
0mg to 5mg	3	845	0.94 (0.78 to 1.13)	0%; 0.93 (p=0.63)
10mg to 15mg	8	4045	1.00 (0.91 to 1.10)	25%; 9.32 (p=0.23)
20mg or more	7	4720	1.02 (0.92 to 1.13)	5%; 6.31 (p=0.39)
Duration (I^2=0%; Chi^2=0.79, p=0.67)				
0m to 6m	2	3148	1.03 (0.92 to 1.14)	67%; 6.05 (p=0.05)
6m to 12m	8	5114	0.98 (0.90 to 1.06)	0%; 9.69 (p=0.47)
12m or more	2	1348	1.08 (0.83 to 1.42)	0%; 0.64 (p=0.89)
Formulation (I^2=20%; Chi^2=3.73, p=0.29)				
Solution	9	7007	0.98 (0.91 to 1.05)	2%; 13.25 (p=0.43)
Pill/ tablet	1	686	1.19 (0.93 to 1.51)	Not applicable
Capsule	1	612	1.12 (0.84 to 1.51)	Not applicable
Powder	1	1305	1.25 (0.75 to 2.09)	Not applicable
Height (SMD)	**51**	**13669**	**0.09 (0.06 to 0.13)**	**86%; 407.92 (p<0.00001)**
Iron co-supplementation (I^2=85%; Chi^2=6.60, p=0.01)				
with iron	12	2929	0.01 (-0.07 to 0.08)	29%; 15.48 (p=0.16)
without iron	44	10510	0.12 (0.08 to 0.16)	88%; 385.12 (p<0.00001)
Age (I^2=98%; Chi^2=117.89, p<0.00001)				
6m to 1y	9	3730	-0.26 (-0.33 to 0.19)	94%; 204.70 (p<0.00001)
1y to 5y	24	6155	0.09 (0.04 to 0.14)	42%; 44.94 (p=0.01)
5y to 13y	16	3449	0.25 (0.18 to 0.32)	94%; 277.24 (p<0.00001)
Dose (I^2=91%; Chi^2=43.60, p<0.00001)				
0mg to 5mg	5	1170	0.02 (0.10 to 0.13)	58%; 14.30 (p=0.03)
5mg to 10mg	8	2978	0.29 (0.22 to 0.37)	96%; 271.49 (p<0.00001)
10mg to 15mg	22	4344	0.06 (0.00 to 0.12)	29%; 33.90 (p=0.09)
15mg to 20mg	2	240	-0.01 (-0.26 to 0.24)	39%; 3.26 (p=0.20)
20mg or more	3	4675	-0.01 (0.07 to 0.05)	11%; 11.22 (p=0.34)
Duration (I^2=91%; Chi^2=21.62, p<0.00001)				
0m to 6m	12	4475	-0.01 (-0.07 to 0.04)	76%; 50.43 (p<0.00001)
6m to 12m	26	6479	0.17 (0.12 to 0.22)	91%; 313.67 (p<0.00001)
12m or more	12	2715	0.10 (0.02 to 0.17)	32%; 22.21 (p=0.10)
Iron co-supplementation (I^2=85%; Chi^2=6.60, p=0.01)				
with iron	12	2929	0.01 (-0.07 to 0.08)	29%; 15.48 (p=0.16)
without iron	44	10510	0.12 (0.08 to 0.16)	88%; 385.12 (p<0.00001)
Formulation (I^2=75%; Chi^2=8.03, p=0.02)				
Solution	32	9030	0.12 (0.07 to 0.16)	90%; 367.20 (p<0.00001)
Pill/ tablet	11	3868	0.02 (-0.04 to 0.09)	9%; 12.11 (p=0.36)
Capsule	2	322	0.31 (0.03 to 0.59)	0%; 0.90 (p=0.64)
Weight (SMD)	**44**	**12305**	**0.10 (0.07 to 0.14)**	**76%; 216.64 (p<0.00001)**
Iron co-supplementation (I^2=34%; Chi^2=1.50, p=0.22)				
with iron	10	2494	0.06 (-0.02 to 0.14)	5%; 9.50 (p=0.39)
without iron	39	9811	0.12 (0.08 to 0.16)	80%; 205.63 (p<0.00001)

Age (I^2=99%; Chi^2=136.86, p<0.00001)				
6m to 1y	9	3730	-0.31 (-0.38 to -0.25)	97%; 387.48 (p<0.00001)
1y to 5y	20	5565	0.06 (0.01 to 0.11)	43%; 38.72 (p=0.02)
5y to 13y	13	2654	0.28 (0.20 to 0.36)	89%; 117.28 (p<0.00001)
Dose (I^2=89%; Chi^2=35.38, p<0.00001)				
0mg to 5mg	5	1170	0.00 (-0.11 to 0.12)	0%; 2.79 (p=0.83)
5mg to 10mg	10	2766	0.27 (0.20 to 0.35)	92%; 108.31 (p<0.00001)
10mg to 15mg	19	3969	0.11 (0.04 to 0.17)	34%; 31.75 (p=0.06)
15mg to 20mg	2	240	-0.20 (-0.45 to 0.06)	13%; 2.30 (p=0.32)
20mg or more	7	3919	0.01 (-0.05 to 0.08)	36%; 12.43 (p=0.13)
Duration (I^2=92%; Chi^2=23.59, p<0.00001)				
0m to 6m	11	4417	0.05 (0.00 to 0.11)	76%; 44.95 (p<0.00001)
6m to 12m	22	5289	0.20 (0.15 to 0.26)	82%; 131.52 (p<0.00001)
12m or more	11	2599	-0.01 (-0.07 to 0.09)	16%; 16.58 (p=0.28)
Formulation (I^2=87%; Chi^2=15.43, p=0.0004)				
Solution	29	8147	0.14 (0.10 to 0.19)	82%; 182.72 (p<0.00001)
Pill/ tablet	10	3656	0.01 (-0.06 to 0.08]	13%; 11.51 (p=0.32)
Capsule	2	304	0.41 (0.12 to 0.71)	0%; 1.21 (p=0.55)
Weight-to-height ratio (SMD)	**24**	**7901**	**0.05 (0.01 to 0.10)**	**20%; 34.96 (p=0.17)**
Iron co-supplementation (I^2=72%; Chi^2=3.51, p=0.06)				
with iron	8	1409	0.14 (0.03 to 0.24)	14%; 8.10 (p=0.32)
without iron	19	6262	0.03 (-0.02 to 0.08)	16%; 22.67 (p=0.25)
Age (I^2=30%; Chi^2=11.45, p=0.18)				
6m to 1y	7	2559	0.03 (-0.04 to 0.11)	30%; 11.45 (p=0.18)
1y to 5y	12	4302	0.02 (-0.05 to 0.08)	7%; 13.95 (p=0.38)
5y to 13y	5	857	0.07 (-0.06 to 0.20)	0%; 3.20 (p=0.67)
Dose (I^2=11%; Chi^2=4.52, p=0.34)				
0mg to 5mg	4	671	0.07 (-0.08 to 0.22)	0%; 1.02 (p=0.91)
5mg to 10mg	6	1229	0.01 (-0.01 to 0.12)	30%; 7.16 (p=0.21)
10mg to 15mg	10	2389	0.08 (-0.01 to 0.16)	47%; 18.79 (p=0.04)
15mg to 20mg	1	194	-0.22 (-0.50 to 0.06)	Not applicable
20mg or more	4	3576	0.06 (0.00 to 0.13)	0%; 2.43 (p=0.79)
Duration (I^2=18.2%; Chi^2=2.45, p=0.29)				
0m to 6m	5	3337	0.07 (0.00 to 0.14)	0%; 2.14 (p=0.83)
6m to 12m	15	4212	0.05 (-0.01 to 0.11)	38%; 27.40 (p=0.05)
12m or more	4	352	-0.10 (-0.31 to 0.11)	0%; 2.98 (p=0.56)
Formulation (I^2=49%; Chi^2=1.97, p=0.16)				
Solution	17	6019	0.06 (0.01 to 0.12)	0%; 20.92 (p=0.46)
Pill/ tablet	6	1652	-0.01 (-0.11 to 0.08)	56%; 11.38 (p=0.04)
Plasma zinc (SMD)	**46**	**9810**	**0.62 (0.58 to 0.67)**	**91%; 582.45 (p<0.00001)**
Iron co-supplementation (I^2=96%; Chi^2=27.07, p<0.00001)				
with iron	17	3231	0.47 (0.39 to 0.54)	82%; 90.82 (p<0.00001)
without iron	37	6579	0.70 (0.65 to 0.75)	92%; 464.56 (p<0.00001)
Age (I^2=95%; Chi^2=40.84, p<0.00001)				
6m to 1y	8	2042	0.46 (0.37 to 0.55)	87%; 74.18 (p<0.00001)
1y to 5y	19	4911	0.75 (0.69 to 0.81)	93%; 309.84 (p<0.00001)
5y to 13y	17	2375	0.47 (0.38 to 0.55)	83%; 116.75 (p<0.00001)
Dose (I^2=92%; Chi^2=49.94, p<0.00001)				
0mg to 5mg	4	855	0.35 (0.21 to 0.49)	26%; 6.72 (p=0.24)
5mg to 10mg	8	1762	0.49 (0.40 to 0.59)	93%; 102.83 (p<0.00001)
10mg to 15mg	20	4596	0.62 (0.56 to 0.68)	86%; 158.02 (p<0.00001)
15mg to 20mg	6	535	0.76 (0.58 to 0.94)	86%; 51.51 (p<0.00001)
20mg or more	6	1724	0.88 (0.78 to 0.98)	95%; 161.54 (p<0.00001)
Duration (I^2=94%; Chi^2=32.98, p<0.00001)				
0m to 6m	15	3079	0.81 (0.73 to 0.88)	94%; 285.66 (p<0.00001)
6m to 12m	22	4347	0.52 (0.46 to 0.58)	85%; 178.87 (p<0.00001)
12m or more	9	2384	0.59 (0.50 to 0.67)	88%; 84.94 (p<0.00001)
Formulation (I^2=98%; Chi^2=149.23, p<0.00001)				
Solution	25	4741	0.78 (0.72 to 0.84)	90%; 293.32 (p<0.00001)
Pill/ tablet	12	3553	0.42 (0.35 to 0.49)	88%; 96.60 (p<0.00001)
Capsule	5	1115	1.07 (0.94 to 1.21)	88%; 56.53 (p<0.00001)
Powder	1	401	-0.06 (-0.25 to 0.14)	Not applicable
Prevalence of zinc deficiency (RR)	**15**	**5434**	**0.49 (0.45 to 0.53)**	**86%; 144.77 (p<0.00001)**
Iron co-supplementation (I^2=97%; Chi^2=34.27, p<0.00001)				
with iron	6	1704	0.62 (0.55 to 0.69)	69%; 16.19 (p=0.006)
without iron	14	3840	0.37 (0.33 to 0.42)	85%; 94.31 (p<0.00001)
Age (I^2=92%; Chi^2=24.36, p<0.00001)				
6m to 1y	1	549	0.62 (0.54 to 0.70)	0%; 0.07 (p=0.79)
1y to 5y	9	3761	0.41 (0.37 to 0.47)	91%; 116.81 (p<0.00001)
5y to 13y	5	1234	0.31 (0.20 to 0.49)	0%; 3.53 (p=0.74)
Dose (I^2=96%; Chi^2=74.93, p<0.00001)				
5mg to 10mg	3	1181	0.34 (0.27 to 0.44)	71%; 6.81 (p=0.03)
10mg to 15mg	7	2890	0.57 (0.52 to 0.63)	81%; 48.40 (p<0.00001)
15mg to 20mg	1	194	0.46 (0.24 to 0.89)	0%; 0.26 (p=0.61)
20mg or more	4	1279	0.14 (0.10 to 0.19)	65%; 14.28 (p=0.01)

Duration (I^2=97%; Chi^2=71.67, p<0.00001)				
0m to 6m	6	2554	0.22 (0.18 to 0.27)	72%; 24.89 (p=0.0008)
6m to 12m	5	1043	0.59 (0.53 to 0.67)	35%; 9.19 (p=0.16)
12m or more	4	1947	0.55 (0.48 to 0.64)	87%; 39.02 (p<0.00001)
Formulation (I^2=91%; Chi^2=22.12, p<0.00001)				
Solution	7	2415	0.49 (0.44 to 0.54)	89%; 87.85 (p<0.00001)
Pill/ tablet	7	2392	0.59 (0.50 to 0.68)	80%; 29.32 (p<0.0001)
Capsule	2	883	0.29 (0.23 to 0.37)	60%; 7.43 (p=0.06)
Blood haemoglobin (SMD)	**27**	**6024**	**-0.05 (-0.10 to 0.00)**	**45%; 63.96 (p=0.002)**
Iron co-supplementation (I^2=0%; Chi^2=0.70, p=0.40)				
with iron	17	3098	-0.01 (-0.08 to 0.07)	63%; 42.74 (p=0.0003)
without iron	19	2913	0.04 (-0.04 to 0.11)	54%; 39.06 (p=0.003)
Age (I^2=0%; Chi^2=1.53, p=0.46)				
6m to 1y	7	2192	-0.04 (-0.12 to 0.05)	69%; 32.49 (p=0.0003)
1y to 5y	12	2332	0.04 (-0.04 to 0.12)	62%; 33.89 (p=0.001)
5y to 13y	6	1286	0.01 (-0.11 to 0.13)	10%; 8.93 (p=0.35)
Dose (I^2=0%; Chi^2=2.12, p=0.71)				
0mg to 5mg	4	966	0.01 (-0.12 to 0.14)	39%; 8.16 (p=0.15)
5mg to 10mg	2	306	-0.01 (-0.23 to 0.21)	0%; 0.56 (p=0.45)
10mg to 15mg	16	3452	0.01 (-0.06 to 0.08)	58%; 44.83 (p=0.0007)
15mg to 20mg	4	364	-0.04 (-0.24 to 0.17)	25%; 5.31 (p=0.26)
20mg or more	3	1025	0.10 (-0.02 to 0.22)	83%; 23.74 (p<0.00001)
Duration (I^2=52%; Chi^2=4.20, p=0.12)				
0m to 6m	7	672	0.17 (0.01 to 0.33)	74%; 27.23 (p=0.0003)
6m to 12m	14	3738	-0.01 (-0.08 to 0.06)	39%; 27.71 (p=0.05)
12m or more	7	1601	0.01 (-0.09 to 0.11)	61%; 23.36 (p=0.005)
Formulation (I^2=0%; Chi^2=1.38, p=0.71)				
Solution	15	2990	0.01 (-0.06 to 0.08)	64%; 52.48 (p<0.00001)
Pill/ tablet	8	1605	0.01 (-0.09 to 0.12)	67%; 24.34 (p=0.002)
Capsule	4	989	0.07 (-0.06 to 0.20)	0%; 4.31 (p=0.51)
Powder	1	427	-0.07 (-0.26 to 0.12)	Not applicable
Prevalence of anaemia (RR)	**13**	**4287**	**1.00 (0.95 to 1.06)**	**37%; 28.52 (p=0.05)**
Iron co-supplementation (I^2=0%; Chi^2=0.01, p=0.93)				
with iron	10	2755	1.00 (0.91 to 1.09)	58%; 21.20 (p=0.01)
without iron	9	1532	1.00 (0.93 to 1.08)	0%; 7.31 (p=0.50)
Age (I^2=8%; Chi^2=2.17, p=0.34)				
6m to 1y	6	1726	1.01 (0.95 to 1.08)	39%; 11.43 (p=0.12)
1y to 5y	6	2161	0.99 (0.88 to 1.12)	50%; 14.07 (p=0.05)
5y to 13y	2	400	0.73 (0.47 to 1.12)	0%; 0.84 (p=0.66)
Dose (I^2=68%; Chi^2=12.56, p=0.01)				
0mg to 5mg	2	616	1.01 (0.94 to 1.09)	31%; 2.91 (p=0.23)
5mg to 10mg	1	208	0.94 (0.47 to 1.87)	Not applicable
10mg to 15mg	8	3069	1.01 (0.92 to 1.11)	15%; 13.00 (p=0.29)
15mg to 20mg	1	181	0.76 (0.40 to 1.46)	Not applicable
20mg or more	1	213	0.17 (0.06 to 0.46)	Not applicable
Duration (I^2=83%; Chi^2=11.42, p=0.003)				
0m to 6m	2	325	0.18 (0.06 to 0.48)	0%; 0.39 (p=0.53)
6m to 12m	7	1989	1.01 (0.94 to 1.08)	40%; 13.33 (p=0.10)
12m or more	5	1973	1.00 (0.90 to 1.12)	0%; 3.38 (p=0.85)
Formulation (I^2=7%; Chi^2=3.21, p=0.36)				
Solution	4	1115	0.90 (0.78 to 1.04)	73%; 18.87 (p=0.002)
Pill/ tablet	6	1958	1.02 (0.95 to 1.10)	0%; 3.36 (p=0.85)
Capsule	2	886	1.00 (0.88 to 1.13)	3%; 3.08 (p=0.38)
Powder	1	328	1.19 (0.81 to 1.73)	Not applicable
Plasma ferritin (SMD)	**19**	**4474**	**0.07 (0.00 to 0.13)**	**95%; 480.50 (p<0.00001)**
Iron co-supplementation (I^2=91%; Chi^2=11.08, p=0.0009)				
with iron	14	2765	-0.05 (-0.13 to 0.02)	80%; 64.00 (p<0.00001)
without iron	11	1709	-0.27 (-0.38 to 0.17)	97%; 389.92 (p<0.00001)
Age (I^2=0%; Chi^2=1.02, p=0.60)				
6m to 1y	4	1166	-0.14 (-0.26 to 0.03)	20%; 6.26 (p=0.28)
1y to 5y	9	2716	-0.16 (-0.24 to 0.08)	98%; 439.66 (p<0.00001)
5y to 13y	5	534	-0.05 (-0.24 to 0.15)	47%; 11.30 (p=0.08)
Dose (I^2=79%; Chi^2=18.71, p=0.0009)				
0mg to 5mg	3	371	-0.07 (-0.28 to 0.14)	29%; 4.21 (p=0.24)
5mg to 10mg	1	78	-0.15 (-0.63 to 0.34)	Not applicable
10mg to 15mg	11	3171	-0.20 (-0.28 to -0.13)	97%; 428.29 (p<0.00001)
15mg to 20mg	3	314	-0.14 (-0.36 to 0.08)	0%; 2.05 (p=0.56)
20mg or more	3	652	0.17 (0.02 to 0.33)	79%; 14.57 (p=0.002)
Duration (I^2=92%; Chi^2=26.28, p<0.00001)				
0m to 6m	7	902	0.06 (-0.07 to 0.20)	79%; 32.68 (p<0.0001)
6m to 12m	7	1735	-0.07 (-0.17 to 0.03)	28%; 12.55 (p=0.18)
12m or more	4	1779	-0.34 (-0.45 to 0.24)	99%; 386.75 (p<0.00001)
Formulation (I^2=92%; Chi^2=35.34, p<0.00001)				
Solution	10	2043	0.01 (-0.08 to 0.10)	62%; 34.20 (p=0.001)
Pill/ tablet	3	1070	-0.16 (-0.29 to -0.04)	89%; 17.89 (p=0.0001)

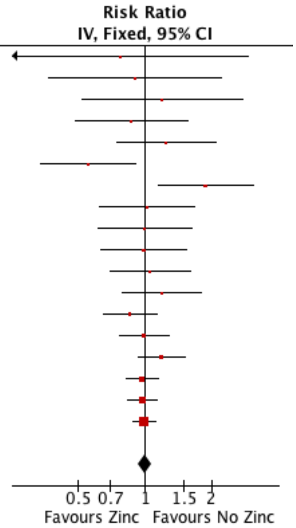
Capsule	3	939	-0.54 (-0.69 to -0.38)	99%; 364.74 (p<0.00001)
Powder	1	317	-0.18 (-0.40 to 0.04)	Not applicable
Prevalence of iron deficiency (RR)	**10**	**3149**	**0.99 (0.89 to 1.10)**	**15%; 16.44 (p=0.29)**
Iron co-supplementation (I^2=0%; Chi^2=0.51, p=0.48)				
with iron	9	2301	1.02 (0.89 to 1.17)	47%; 15.03 (p=0.06)
without iron	6	947	0.94 (0.79 to 1.11)	0%; 0.90 (p=0.97)
Age (I^2=44%; Chi^2=3.56, p=0.17)				
6m to 1y	3	905	0.92 (0.82 to 1.05)	25%; 5.34 (p=0.25)
1y to 5y	4	1992	1.16 (0.94 to 1.44)	13%; 5.75 (p=0.33)
5y to 13y	2	351	1.12 (0.61 to 2.04)	0%; 1.80 (p=0.62)
Dose (I^2=49%; Chi^2=5.86, p=0.12)				
0mg to 5mg	1	144	0.78 (0.61 to 1.00)	Not applicable
10mg to 15mg	6	2634	1.03 (0.91 to 1.16)	14%; 10.42 (p=0.32)
15mg to 20mg	1	194	1.07 (0.52 to 2.18)	Not applicable
20mg or more	2	276	2.16 (0.72 to 6.44)	0%; 0.15 (p=0.93)
Duration (I^2=52%; Chi^2=4.12, p=0.13)				
0m to 6m	2	276	2.16 (0.72 to 6.44)	0%; 0.15 (p=0.93)
6m to 12m	3	981	0.88 (0.73 to 1.05)	22%; 5.13 (p=0.27)
12m or more	4	1991	1.04 (0.91 to 1.18)	15%; 7.04 (p=0.32)
Formulation (I^2=0%; Chi^2=1.87, p=0.39)				
Solution	4	1163	0.90 (0.75 to 1.08)	18%; 7.31 (p=0.29)
Pill/ tablet	3	1199	1.05 (0.91 to 1.20)	51%; 6.17 (p=0.10)
Capsule	2	886	0.88 (0.56 to 1.37)	0%; 1.09 (p=0.78)
Plasma copper (SMD)	**11**	**3071**	**-0.22 (-0.29 to 0.14)**	**68%; 37.47 (p=0.0002)**
Iron co-supplementation (I^2=64.1%; Chi^2=2.71, p=0.09)				
with iron	4	650	-0.10 (-0.25 to 0.05)	0%; 2.45 (p=0.49)
without iron	9	2421	-0.25 (-0.33 to -0.17)	75%; 32.34 (p<0.00001)
Age (I^2=71%; Chi^2=3.46, p=0.06)				
6m to 1y	3	865	-0.11 (-0.24 to 0.02)	0%; 1.27 (p=0.87)
5y to 13y	8	2206	-0.26 (-0.35 to -0.17)	79%; 32.74 (p<0.00001)
Dose (I^2=90%; Chi^2=29.23, p<0.00001)				
0mg to 5mg	3	410	-0.08 (-0.27 to 0.12)	25%; 4.00 (p=0.26)
5mg to 10mg	2	519	-0.31 (-0.49 to -0.13)	75%; 3.98 (p=0.05)
10mg to 15mg	7	1310	-0.01 (-0.12 to 0.10)	0%; 5.40 (p=0.61)
20mg or more	1	930	-0.46 (-0.59 to -0.33)	Not applicable
Duration (I^2=94%; Chi^2=30.84, p<0.00001)				
0m to 6m	2	1355	-0.44 (-0.55 to -0.33)	0%; 0.17 (p=0.68)
6m to 12m	5	1168	-0.08 (-0.20 to 0.04)	0%; 3.23 (p=0.78)
12m or more	4	548	0.06 (-0.11 to 0.24)	7%; 3.23 (p=0.36)
Formulation (I^2=95%; Chi^2=20.76, p<0.00001)				
Solution	9	2490	-0.37 (-0.46 to -0.29)	97%; 370.26 (p<0.00001)
Pill/ tablet	3	439	-0.83 (-1.01 to -0.65)	99%; 277.02 (p<0.00001)

Appendix 7: Additional forest plots

Incidence of lower respiratory tract infection

Study or Subgroup	log[Risk Ratio]	SE	Zinc Total	No Zinc Total	Weight	Risk Ratio IV, Fixed, 95% CI
Long 2006 (2)	−0.24816892	0.67082039	192	180	0.2%	0.78 [0.21, 2.91]
Long 2006	−0.10536052	0.45946829	181	183	0.5%	0.90 [0.37, 2.21]
Brown 2007	0.18232156	0.42839042	101	99	0.6%	1.20 [0.52, 2.78]
Penny 2004	−0.14058195	0.29777877	80	79	1.2%	0.87 [0.48, 1.56]
Soofi 2013	0.22314355	0.2627712	659	646	1.6%	1.25 [0.75, 2.09]
Sazawal 1996	−0.59000642	0.25375961	297	306	1.7%	0.55 [0.34, 0.91]
Rahman 2001	0.63062682	0.25241624	170	161	1.7%	1.88 [1.15, 3.08]
Richard 2006 (2)	0.02032	0.25200806	210	208	1.7%	1.02 [0.62, 1.67]
Rahman 2001 (2)	0	0.24928541	175	160	1.7%	1.00 [0.61, 1.63]
Richard 2006	−0.01129956	0.22645541	209	209	2.1%	0.99 [0.63, 1.54]
Veenemans 2011	0.05383699	0.2132558	153	153	2.4%	1.06 [0.69, 1.60]
Veenemans 2011 (2)	0.17745056	0.20798032	151	155	2.5%	1.19 [0.79, 1.80]
Baqui 2003 (2)	−0.15645218	0.14256197	162	165	5.3%	0.86 [0.65, 1.13]
Baqui 2003	−0.00673403	0.13486419	161	157	5.9%	0.99 [0.76, 1.29]
Muller 2001	0.17162318	0.12304944	342	344	7.1%	1.19 [0.93, 1.51]
Lind 2003 (2)	−0.02898754	0.08383997	170	170	15.4%	0.97 [0.82, 1.14]
Lind 2003	−0.02739897	0.08077837	170	170	16.6%	0.97 [0.83, 1.14]
Bhandari 2002	−0.00591199	0.05834957	1241	1241	31.7%	0.99 [0.89, 1.11]
Total (95% CI)			**4824**	**4786**	**100.0%**	**1.00 [0.94, 1.07]**

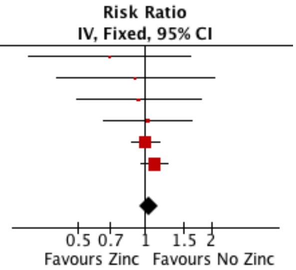
Heterogeneity: $Chi^2 = 17.16$, df = 17 (P = 0.44); $I^2 = 1\%$
Test for overall effect: Z = 0.03 (P = 0.98)



Incidence of malaria

Study or Subgroup	log[Risk Ratio]	SE	Zinc Total	No Zinc Total	Weight	Risk Ratio IV, Fixed, 95% CI
Shankar 2000	−0.37018553	0.42956235	136	138	1.3%	0.69 [0.30, 1.60]
Richard 2006 (2)	−0.09844007	0.41742355	210	208	1.3%	0.91 [0.40, 2.05]
Richard 2006	−0.06536678	0.32891813	209	209	2.1%	0.94 [0.49, 1.78]
Muller 2001	0.02817088	0.23737988	341	344	4.1%	1.03 [0.65, 1.64]
Veenemans 2011	0.00837462	0.0727393	153	153	43.9%	1.01 [0.87, 1.16]
Veenemans 2011 (2)	0.10019023	0.07006137	151	155	47.3%	1.11 [0.96, 1.27]
Total (95% CI)			**1200**	**1207**	**100.0%**	**1.05 [0.95, 1.15]**

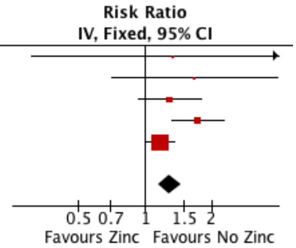
Heterogeneity: $Chi^2 = 2.04$, df = 5 (P = 0.84); $I^2 = 0\%$
Test for overall effect: Z = 0.93 (P = 0.35)



Participants with ≥1 vomiting episode

Study or Subgroup	log[Risk Ratio]	SE	Zinc Total	No Zinc Total	Weight	Risk Ratio IV, Fixed, 95% CI
Kurugöl 2006	0.28768207	0.75055535	100	100	0.7%	1.33 [0.31, 5.81]
Gupta 2007	0.51549853	0.44177764	854	858	2.0%	1.67 [0.70, 3.98]
Lind 2003	0.25343215	0.16826769	162	164	13.9%	1.29 [0.93, 1.79]
Lind 2003 (2)	0.55134234	0.14130384	161	163	19.7%	1.74 [1.32, 2.29]
Bhandari 2007	0.15688142	0.0785542	16289	16341	63.7%	1.17 [1.00, 1.36]
Total (95% CI)			**17566**	**17626**	**100.0%**	**1.29 [1.14, 1.46]**

Heterogeneity: $Chi^2 = 6.31$, df = 4 (P = 0.18); $I^2 = 37\%$
Test for overall effect: Z = 4.08 (P < 0.0001)

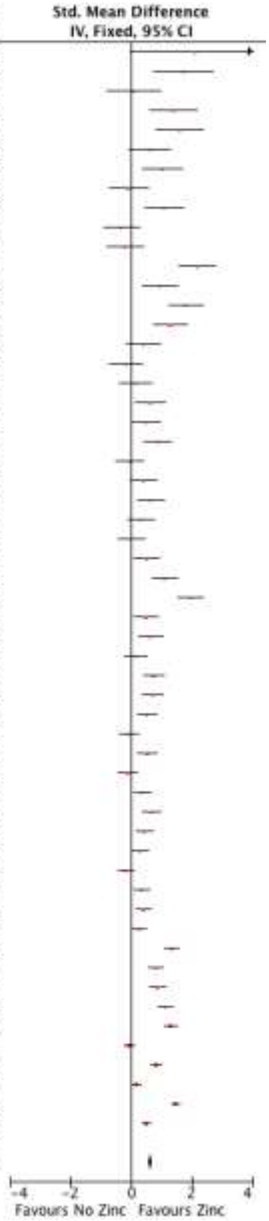


Plasma zinc

Study or Subgroup	Std. Mean Difference	SE	No Zinc Total	Zinc Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Silva 2006	2.12757492	1.10761519	30	28	0.0%	2.13 [-0.04, 4.30]
Nakamura 1993	1.7108436	0.49561271	11	10	0.2%	1.71 [0.74, 2.68]
Sayeg Porto 2000	0.07926742	0.44915102	9	9	0.2%	0.08 [-0.80, 0.96]
Rosales 2004	1.39772302	0.39918356	14	16	0.3%	1.40 [0.62, 2.18]
Rosales 2004 (2)	1.59178434	0.393349	15	18	0.3%	1.59 [0.82, 2.36]
Garcia 1998	0.61895336	0.34825576	17	16	0.4%	0.62 [-0.06, 1.30]
Smith 1999	1.02871696	0.33059672	20	20	0.4%	1.03 [0.38, 1.68]
Gibson 1989	-0.07887671	0.33058919	18	17	0.4%	-0.08 [-0.73, 0.57]
Clark 1999	1.08857292	0.32653377	19	23	0.4%	1.09 [0.45, 1.73]
Walravens 1989	-0.32044174	0.3159476	25	16	0.5%	-0.32 [-0.94, 0.30]
Walravens 1983	-0.21002838	0.31083333	20	20	0.5%	-0.21 [-0.82, 0.40]
Udomkesmalee 1992	2.16724629	0.30343932	35	33	0.5%	2.17 [1.57, 2.76]
Sempertegui 1996	0.94195962	0.30001048	25	23	0.5%	0.94 [0.35, 1.53]
Udomkesmalee 1992 (2)	1.80519359	0.29181765	33	32	0.5%	1.81 [1.23, 2.38]
Tupe 2009	1.2972891	0.28675374	40	43	0.6%	1.30 [0.74, 1.86]
Fallahi 2007	0.39627284	0.28402418	25	24	0.6%	0.40 [-0.16, 0.95]
Mahloudji 1975	-0.165458	0.2788914	25	25	0.6%	-0.17 [-0.71, 0.38]
Sandstead 2008	0.14492933	0.27877714	25	25	0.6%	0.14 [-0.40, 0.69]
Ba Lo 2011	0.62542586	0.24941159	32	34	0.7%	0.63 [0.14, 1.11]
Schultink 1997	0.47144486	0.24494512	34	33	0.8%	0.47 [-0.01, 0.95]
Hettiarachchi 2008 (2)	0.86739385	0.24267158	30	114	0.8%	0.87 [0.39, 1.34]
Ruz 1997	-0.04794779	0.23832669	33	36	0.8%	-0.05 [-0.52, 0.42]
Mazariegos 2010	0.3998476	0.23138369	40	35	0.9%	0.40 [-0.05, 0.85]
Muller 2001	0.63830688	0.22576313	40	41	0.9%	0.64 [0.20, 1.08]
Baqui 2003	0.30706347	0.22305208	38	42	0.9%	0.31 [-0.13, 0.74]
Baqui 2003 (2)	0	0.21750534	42	41	1.0%	0.00 [-0.43, 0.43]
Hettiarachchi 2008	0.51369923	0.21562749	41	100	1.0%	0.51 [0.09, 0.94]
Umeta 2000	1.09640714	0.21307062	50	50	1.0%	1.10 [0.68, 1.51]
Hong 1982	1.94421305	0.21124116	67	64	1.0%	1.94 [1.53, 2.36]
Rosado 1997	0.49001387	0.20662869	47	48	1.1%	0.49 [0.09, 0.89]
Rosado 1997 (2)	0.62774877	0.20438775	50	49	1.1%	0.63 [0.23, 1.03]
Uckardes 2009	0.14435311	0.18964639	54	56	1.3%	0.14 [-0.23, 0.52]
Penny 2004	0.73471063	0.17762983	69	65	1.4%	0.73 [0.39, 1.08]
Wuehler 2008	0.70122941	0.16887846	49	142	1.6%	0.70 [0.37, 1.03]
Cavan 1993	0.51245133	0.1679712	74	71	1.6%	0.51 [0.18, 0.84]
Rahman 2001 (2)	-0.08998801	0.16760985	70	71	1.6%	-0.09 [-0.42, 0.24]
Brown 2007	0.53520617	0.16389707	84	70	1.7%	0.54 [0.21, 0.86]
Rahman 2001	-0.11598147	0.16210648	77	74	1.7%	-0.12 [-0.43, 0.20]
Chang 2010	0.36204843	0.15223956	89	85	2.0%	0.36 [0.06, 0.66]
Richard 2006	0.67063373	0.15053466	92	93	2.0%	0.67 [0.38, 0.97]
Chen 2012	0.43585676	0.14985294	93	88	2.0%	0.44 [0.14, 0.73]
Richard 2006 (2)	0.27769813	0.14757993	90	94	2.1%	0.28 [-0.01, 0.57]
Shankar 2000	-0.18954625	0.13723333	109	103	2.4%	-0.19 [-0.46, 0.08]
Tielsch 2006	0.35339326	0.13023913	146	152	2.7%	0.35 [0.10, 0.61]
Friis 1997	0.40647134	0.1292236	121	122	2.7%	0.41 [0.15, 0.66]
Chang 2010 (2)	0.2481705	0.12815887	93	177	2.8%	0.25 [-0.00, 0.50]
Veenemans 2011	1.33657691	0.1276632	150	149	2.8%	1.34 [1.09, 1.59]
Lind 2003 (2)	0.7946871	0.12563884	136	136	2.9%	0.79 [0.55, 1.04]
Lind 2003	0.86027128	0.12535047	143	134	2.9%	0.86 [0.61, 1.11]
Veenemans 2011 (2)	1.11626145	0.12407823	151	148	3.0%	1.12 [0.87, 1.36]
Wessells 2012	1.30076381	0.11129748	146	279	3.7%	1.30 [1.08, 1.52]
Soofi 2013	-0.05814114	0.09971627	203	198	4.6%	-0.06 [-0.25, 0.14]
Sazawal 1996	0.8263088	0.08664303	292	285	6.1%	0.83 [0.66, 1.00]
DiGirolamo 2010	0.18538814	0.07877571	318	328	7.4%	0.19 [0.03, 0.34]
Bhandari 2002	1.46023697	0.07309568	499	450	8.6%	1.46 [1.32, 1.60]
Bhandari 2007	0.49031017	0.0714016	419	438	9.0%	0.49 [0.35, 0.63]
Total (95% CI)			**4717**	**5093**	**100.0%**	**0.62 [0.58, 0.67]**

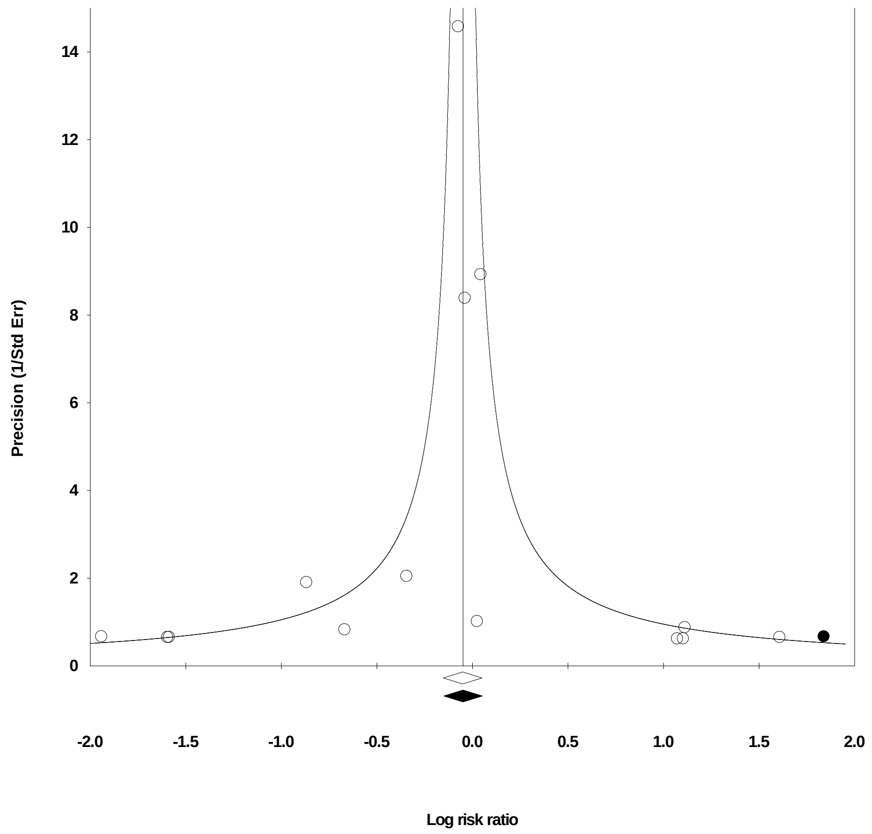
Heterogeneity: $Chi^2 = 582.45$, $df = 55$ ($P < 0.00001$); $I^2 = 91\%$

Test for overall effect: $Z = 29.16$ ($P < 0.00001$)

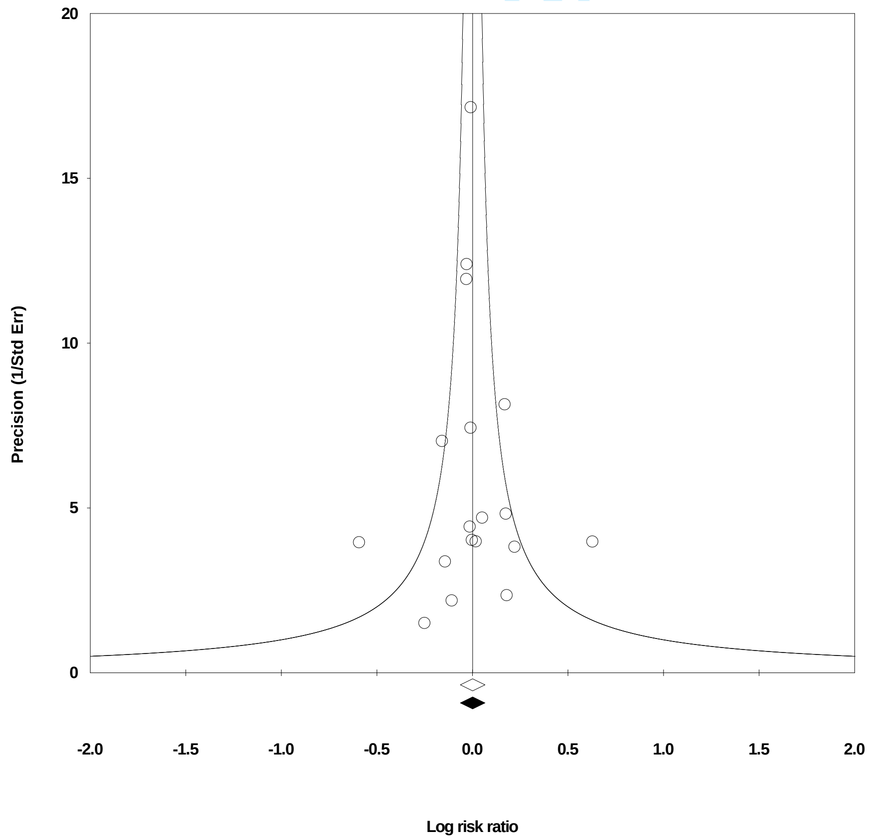


Appendix 8: Tests for reporting bias

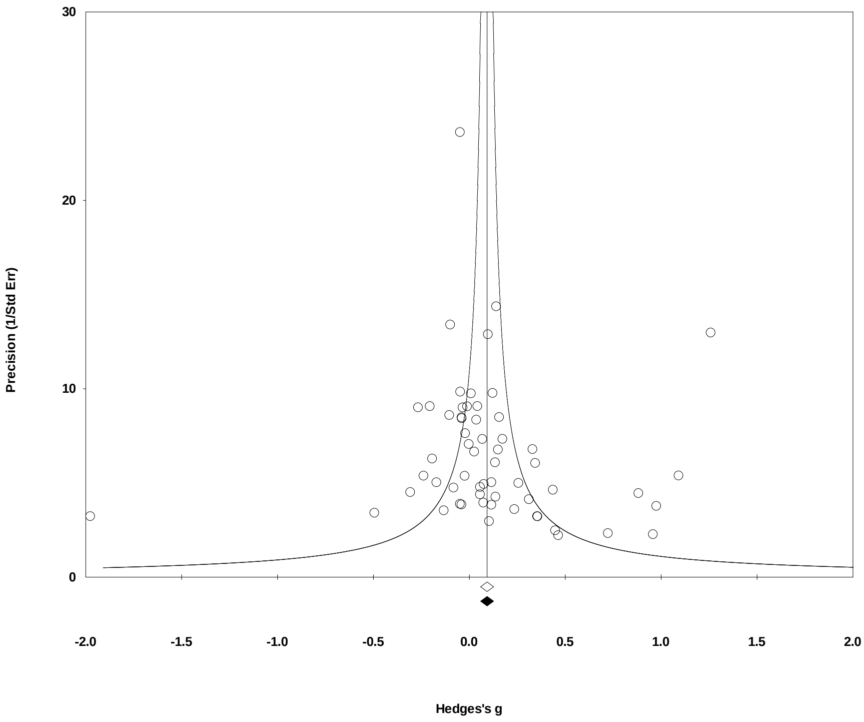
All cause mortality funnel plot (observed and imputed studies)



Incidence of LRTI (observed and imputed studies)



Height (observed and imputed studies)



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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3, App 1
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	App 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	3
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	3
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	3, 5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	3
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	3

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	4
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	3, 5-6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	4, Fig 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	App 4
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	App 5
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Fig 3 to 5, App 7
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	4-5, Table 2-3
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	4, Fig 2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	5-6, Table 4, App 6 and 8
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	6-7
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	6-7
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	7
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	2

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