Zinc supplementation for preventing mortality, morbidity, and growth failure in children aged 6 months to 12 years of age (Review)

Mayo-Wilson E, Junior JA, Imdad A, Dean S, Chan XHS, Chan ES, Jaswal A, Bhutta ZA

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2014, Issue 5

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[Intervention Review]

Zinc supplementation for preventing mortality, morbidity, and growth failure in children aged 6 months to 12 years of age

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Editorial group: Cochrane Developmental, Psychosocial and Learning Problems Group.
Publication status and date: New, published in Issue 5, 2014.
Review content assessed as up-to-date: 29 June 2013.

Citation: Mayo-Wilson E, Junior JA, Imdad A, Dean S, Chan XHS, Chan ES, Jaswal A, Bhutta ZA. Zinc supplementation for preventing mortality, morbidity, and growth failure in children aged 6 months to 12 years of age. *Cochrane Database of Systematic Reviews* 2014, Issue 5. Art. No.: CD009384. DOI: 10.1002/14651858.CD009384.pub2.

ABSTRACT

Background

Zinc deficiency is prevalent in low- and middle-income countries, and contributes to significant diarrhoea-, pneumonia-, and malaria-related morbidity and mortality among young children. Zinc deficiency also impairs growth.

Objectives

To assess the effects of zinc supplementation for preventing mortality and morbidity, and for promoting growth, in children aged six months to 12 years of age.

Search methods

Between December 2012 and January 2013, we searched CENTRAL, MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, Embase, African Index Medicus, Conference Proceedings Citation Index, Dissertation Abstracts, Global Health, IndMED, LILACS, WHOLIS, *meta*Register of Controlled Trials, and WHO ICTRP.

Selection criteria

Randomised controlled trials of preventive zinc supplementation in children aged six months to 12 years compared with no intervention, a placebo, or a waiting list control. We excluded hospitalised children and children with chronic diseases or conditions. We excluded food fortification or intake, sprinkles, and therapeutic interventions.

Data collection and analysis

Two authors screened studies, extracted data, and assessed risk of bias. We contacted trial authors for missing information.

Main results

We included 80 randomised controlled trials with 205,401 eligible participants. We did not consider that the evidence for the key analyses of morbidity and mortality outcomes were affected by risk of bias. The risk ratio (RR) for all-cause mortality was compatible with a reduction and a small increased risk of death with zinc supplementation (RR 0.95, 95% confidence interval (CI) 0.86 to 1.05, 14 studies, high-quality evidence), and also for cause-specific mortality due to diarrhoea (RR 0.95, 95% CI 0.69 to 1.31, four studies, moderate-quality evidence), lower respiratory tract infection (LRTI) (RR 0.86, 95% CI 0.64 to 1.15, three studies, moderate-quality evidence), or malaria (RR 0.90, 95% CI 0.77 to 1.06, two studies, moderate-quality evidence).

Supplementation reduced diarrhoea morbidity, including the incidence of all-cause diarrhoea (RR 0.87, 95% CI 0.85 to 0.89, 26 studies, moderate-quality evidence), but the results for LRTI and malaria were imprecise: LRTI (RR 1, 95% CI 0.94 to 1.07, 12 studies, moderate-quality evidence); malaria (RR 1.05, 95% 0.95 to 1.15, four studies, moderate-quality evidence).

There was moderate-quality evidence of a very small improvement in height with supplementation (standardised mean difference (SMD) -0.09, 95% CI -0.13 to -0.06; 50 studies), but the size of this effect might not be clinically important. There was a medium to large positive effect on zinc status.

Supplementation was associated with an increase in the number of participants with at least one vomiting episode (RR 1.29, 95% CI 1.14 to 1.46, five studies, high-quality evidence). We found no clear evidence of benefit or harm of supplementation with regard to haemoglobin or iron status. Supplementation had a negative effect on copper status.

Authors' conclusions

In our opinion, the benefits of preventive zinc supplementation outweigh the harms in areas where the risk of zinc deficiency is relatively high. Further research should determine optimal intervention characteristics such as supplement dose.

PLAIN LANGUAGE SUMMARY

Zinc supplementation for preventing death and disease, and for growth, in children aged six months to 12 years of age

Review question

This review investigated the effectiveness of zinc supplementation for preventing illness and mortality, and for promoting growth, in children between six months and 12 years of age.

Background

Zinc is an essential micronutrient and zinc deficiency is an important public health problem in low- and middle-income countries. Zinc deficiency impairs growth and contributes to numerous child deaths per year due to diarrhoea, pneumonia, and malaria. This review aimed to determine if giving children zinc supplements would help prevent child death, disease, and growth deficits.

Study characteristics

We searched a wide range of electronic databases for studies that randomly assigned children aged six months to 12 years to either zinc supplementation or a control group that did not receive zinc. Eighty randomised studies with 205,401 eligible participants were included in this review. The evidence is current to December 2012.

Key results and the quality of the evidence

Giving children zinc supplements might reduce their risk of death in general, and their risk of death due to diarrhoea, lower respiratory tract infection (LRTI), or malaria. The quality of evidence for overall mortality was high, though evidence for other critical outcomes was only moderate. Children given zinc experience less diarrhoeal disease than children not given zinc; however, zinc does not seem to reduce children's risk of respiratory infection or malaria. Zinc supplementation may have a very small effect on growth, but eating more calories would probably have a larger effect for many malnourished children. Children who take zinc supplements may experience vomiting as a side effect.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Zinc versus no zinc for preventing mortality, morbidity, and growth failure in children aged 6 months to 12 years of age

Patient or population: children aged six months to 12 years of age
Settings: Primary prevention (mostly in low- and middle-income countries)
Intervention: zinc versus no zinc

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Control	Zinc versus no zinc			
All-cause mortality Follow-up: 17 to 72 weeks	**Low**		**RR 0.95** (0.86 to 1.05)	138,302 (14 studies)	⊕⊕⊕⊕ **high**
	2400 per 1,000,000	**2280 per 1,000,000** (2064 to 2520)			
	High				
	34,900 per 1,000,000	**33,155 per 1,000,000** (30,014 to 36,645)			
Mortality due to all-cause diarrhoea Follow-up: 52 to 69 weeks	**Low**		**RR 0.95** (0.69 to 1.31)	132,321 (4 studies)	⊕⊕⊕◯ **moderate**[1]
	800 per 1,000,000	**760 per 1,000,000** (552 to 1048)			
	High				
	3000 per 1,000,000	**2850 per 1,000,000** (2070 to 3930)			
Mortality due to LRTI Follow-up: 52 to 69 weeks	**Low**		**RR 0.86** (0.64 to 1.15)	132,063 (3 studies)	⊕⊕⊕◯ **moderate**[1]

	1200 per 1,000,000	**1032 per 1,000,000** (768 to 1380)			
	High				
	3000 per 1,000,000	**2580 per 1,000,000** (1920 to 3450)			
Mortality due to malaria Follow-up: 46 to 69 weeks	**Low**		**RR 0.9** (0.77 to 1.06)	42,818 (2 studies)	⊕⊕⊕○ **moderate**[1]
	7400 per 1,000,000	**6660 per 1,000,000** (5698 to 7844)			
	High				
	14,200 per 1,000,000	**12,780 per 1,000,000** (10,934 to 15,052)			
Incidence of all-cause diarrhoea Follow-up: 12 to 72 weeks	**Low**		**RR 0.87** (0.85 to 0.89)	15,042 (26 studies)	⊕⊕⊕○ **moderate**[2]
	20,000 per 1,000,000	**17,400 per 1,000,000** (17,000 to 17,800)			
	High				
	1,770,000 per 1,000,000	**1,539,900 per 1,000,000** (1,504,500 to 1,575,300)			
Incidence of LRTI Follow-up: 12 to 52 weeks	**Low**		**RR 1** (0.94 to 1.07)	9610 (12 studies)	⊕⊕⊕⊕ **high**
	30,000 per 1,000,000	**30,000 per 1,000,000** (28,200 to 32,100)			
	High				
	370,000 per 1,000,000	**370,000 per 1,000,000** (347,800 to 395,900)			

Incidence of malaria Follow-up: 24 to 47 weeks	**Low**		**RR 1.05** (0.95 to 1.15)	2407 (4 studies)	⊕⊕⊕○ **moderate**[3]
	140,000 per 1,000,000	**147,000 per 1,000,000** (133,000 to 161,000)			
	High				
	2,950,000 per 1,000,000	**3,097,500 per 1,000,000** (2,802,500 to 3,392,500)			
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** (-0.13 to -0.06)	13,669 (50 studies)	⊕⊕⊕○ **moderate**[4]
Participants with 1 vomiting episode Follow-up: 24 to 52 weeks	**Low**		**RR 1.29** (1.14 to 1.46)	35,192 (5 studies)	⊕⊕⊕⊕ **high**
	17,500 per 1,000,000	**22,575 per 1,000,000** (19,950 to 25,550)			
	High				
	300,600 per 1,000,000	**387,774 per 1,000,000** (342,684 to 438,876)			

*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; **HAZ:** height-for-age z-score; **LRTI:** lower respiratory tract infection; **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.

[1] Few deaths observed overall.
[2] $I^2 = 88\%$.
[3] $I^2 = 44\%$.

[4] $I^2 = 86\%$.

BACKGROUND

Description of the condition

Zinc is an essential micronutrient. Regular dietary intake of zinc is necessary because the human body cannot produce zinc and does not have an adequate mechanism for storing or releasing it (Hotz 2004; Maggini 2010). Severe zinc deficiency affects numerous organ systems, including the immune, gastrointestinal, skeletal, reproductive, and central nervous systems (Tuerk 2009). Even marginal deficiency may be associated with immune system dysfunction and restricted physical development (Prasad 1963; Shankar 1998). Children are especially vulnerable to deficiency because their periods of rapid growth create increased zinc needs that may remain unmet (Gibson 2006).

In 2011, about 116,000 deaths in children under five years of age were attributable to zinc deficiency (1.7% of all mortalities in this group) (Black 2013). Intervention studies suggest that deficiency leads to deaths due to diarrhoea, pneumonia, and malaria, which are leading causes of mortality in this age group (Bryce 2005; Fischer Walker 2008; WHO 2009; Black 2010; Wazny 2013). Zinc deficiency may also impair growth and contribute to childhood stunting (Williams 1970; Hess 2009b; Prasad 2009); high stunting prevalence is used as an indicator of population-level zinc deficiency (Engle-Stone 2007; Hess 2009b).

The global prevalence of zinc deficiency is approximately 17% (Wessells 2012a), and rates of deficiency approach 73% in some regions (Caulfield 2004; Black 2008). Countries in most of South and Southeast Asia, sub-Saharan Africa, and parts of Latin America have relatively high rates of deficiency (Caulfield 2004; Hotz 2004; Black 2008).

At both national and individual levels, zinc deficiency and its consequences are linked to poverty. Firstly, foods from animal sources, which are rich in zinc, are often expensive. Particularly in low- and middle-income countries, poor individuals may primarily eat foods such as cereals, grains, and legumes (Hotz 2004). These foods have relatively low concentrations of zinc; they also have relatively high concentrations of fibre and phytate molecules, which reduce zinc absorption by the intestine (Sandstead 1991; Hotz 2004). Secondly, in resource-scarce settings, poor water and sanitation systems lead to frequent exposure to gastrointestinal pathogens and high rates of infectious disease and diarrhoea (Hotz 2004). Finally, factors such as poverty, poor nutrition and sanitation, and infectious morbidity exacerbate one another. For instance, diarrhoea can compromise intestinal function and damage the gastrointestinal tract lining, thereby causing increased zinc excretion via the intestine (Aggarwal 2007; Maggini 2010). Damage to the gastrointestinal tract lining can hinder the absorption of zinc and other nutrients (Fagundes-Neto 1984; Salazar-Lindo 2004; McKay 2010). Thus, a cycle of zinc deficiency can develop, leading to infectious morbidity, in turn leading to further zinc deficiency. Similarly, since morbidity and mortality contribute to reduced economic productivity (Behrman 2004), a cycle can develop in which poverty contributes to zinc-related morbidity and mortality, which contribute to further poverty.

Description of the intervention

Zinc supplementation is a relatively easily implemented and inexpensive intervention that could help address zinc deficiency (Shrimpton 2005). Zinc supplements come in various physical forms, including liquid solutions, syrups, pills, tablets, capsules, powders, and pastes (Hotz 2004). Supplements also come in various chemical forms, such as zinc sulfate and zinc acetate, with water soluble compounds often preferred because they may be more efficiently absorbed (Hotz 2004; Brown 2009). In addition, zinc is sometimes administered with other micronutrients such as vitamin A or iron (Brown 2009). Zinc supplements have been provided at various doses, daily and weekly, for a few weeks to over a year (Brown 2009).

Recommendations for normal zinc consumption among children range between 2 mg and 11 mg per day, depending on age and diet (Institute of Medicine 2001; Hotz 2004; WHO/FAO 2004). The World Health Organization (WHO) recommends a supplemental dose of 20 mg per day for 10 to 14 days to treat diarrhoea in children six to 59 months of age (WHO/UNICEF 2004). A dose of 10 mg per day for six months may significantly reduce stunting (Imdad 2011), and 5 mg or 10 mg per day may be appropriate for preventive supplementation among children under 14 years of age (Hotz 2004). However, there are no standard recommendations for dose, frequency, and duration of preventive zinc supplementation (Boy 2009).

How the intervention might work

Zinc is in every cell of the human body and is required for normal functioning (Fisher 1975; Fischer Walker 2004). It plays critical catalytic, structural, and regulatory roles (Cousins 1994; Tuerk 2009). Zinc enables hundreds of enzymes to function, facilitates protein synthesis and folding, and regulates processes such as gene expression and apoptosis (MacDonald 2000; Hotz 2004; Stefanidou 2006; Aggarwal 2007; Hambidge 2007; Tuerk 2009). Zinc is also important for DNA and RNA metabolism, as well as cellular replication, differentiation, and growth (MacDonald 2000; Stefanidou 2006). Zinc is involved in both non-specific and specific immune system processes, including phagocytosis, maintenance of gastrointestinal and respiratory tract linings, and development and function of T- and B-cells (Shankar 1998). Zinc is also involved in bone development, growth hormone function, taste acuity, and appetite (Salgueiro 2002). By increasing the availability of zinc for these biological processes, supplementation may improve health outcomes.

Most importantly, zinc supplementation may reduce all-cause mortality among children by reducing mortality due to diarrhoea, lower respiratory tract infection (LRTI), and malaria. Trials show that preventive supplementation may reduce the incidence of these three morbidities (Bhutta 1999; Brown 2009). Trials also show that therapeutic supplementation reduces the duration of acute and persistent diarrhoea (Lazzerini 2008). In addition, some trials indicate that zinc supplementation promotes linear growth and weight gain (Brown 2009).

However, not all trials have found zinc supplementation to be effective for certain outcomes (Brown 2009; Ramakrishnan 2009). In addition, the effects of zinc may be influenced and complicated by several factors. For example, children with more severe deficiency, such as those who are stunted, may benefit more from supplementation than children with less severe deficiency. Children with certain chronic diseases and severe protein-energy malnutrition may have different zinc requirements and growth trajectories than children without these comorbidities (Brown 2002). Supplementation might also affect children with non-chronic illnesses and healthy children differently. For instance, presence of infection generally causes zinc to be sequestered in the liver, and conditions that affect intestinal function and integrity can influence zinc homeostasis (Hotz 2004). Despite such complications, it has been proposed that short-term therapeutic zinc supplementation, such as the kind recommended by the WHO for diarrhoea, might also result in some long-term preventive effects (Haider 2009).

Another set of factors influencing the effects of zinc supplementation are interactions between zinc, iron, and copper. Iron supplementation may interfere with the absorption of zinc, and zinc may interfere with iron and copper absorption (Sandstrom 1985; Allen 1998; Sandstrom 2001; Maret 2006); however, the evidence is mixed as to whether supplemental zinc contributes to anaemia, iron deficiency, and/or copper deficiency (Fosmire 1990; Brown 2009). Other potential adverse effects of zinc occur primarily when it is given in very high doses (such as 225 mg to 450 mg) (Fosmire 1990). These adverse effects include abdominal pain, nausea, vomiting, and diarrhoea (Fosmire 1990; Larson 2008).

Why it is important to do this review

Zinc supplementation in children has been investigated in several non-Cochrane reviews, some of which have had conflicting results (Bhutta 1999; Brown 2002; Aggarwal 2007; Brown 2009; Ramakrishnan 2009; Dekker 2010; Roth 2010; Imdad 2011; Patel 2011; Yakoob 2011). For example, some reviews have found that zinc supplementation has a significant effect on height (Brown 2002; Brown 2009; Imdad 2011) and weight gain (Brown 2002; Brown 2009). However, another review found that zinc did not significantly affect these outcomes (Ramakrishnan 2009). This review seeks to resolve such discrepancies.

Zinc supplementation has also been investigated in several Cochrane Reviews. There are reviews of zinc supplementation as an adjunct to diarrhoea treatment (Lazzerini 2008), pneumonia treatment (Haider 2011), and for mental and motor development in children (Gogia 2012). There are reviews of zinc supplementation in populations with HIV (Humphreys 2010; Irlam 2010). Reviews have also focused on zinc supplementation for pregnancy and infant outcomes (Mahomed 2007), the common cold (Singh 2011), otitis media (Abba 2010), and pneumonia prevention (Lassi 2010). However, zinc supplementation may have multiple and complex effects, and no Cochrane Review has investigated its impact on all-cause mortality as well as the illnesses responsible for a plurality of child deaths worldwide.

OBJECTIVES

To assess the effects of zinc supplementation for preventing mortality and morbidity, and for promoting growth, in children aged six months to 12 years of age.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) and cluster-RCTs with a parallel-group design, in which intervention and control groups were enrolled concurrently. We excluded quasi-RCTs such as trials in which allocation was determined by alternation or date of birth.

Types of participants

Children of six months to 12 years of age (inclusive) at the baseline time point of a study.

We excluded the following:

- children less than six months of age (the WHO recommends exclusive breastfeeding for children less than six months of age, and trials assessing zinc for lactating mothers were excluded);
- hospitalised children;
- children with any of the following: severe protein-energy malnutrition; HIV; chronic diseases, such as cystic fibrosis and sickle cell disease, or conditions, such as Down syndrome, that could affect growth.

If some, but not all, of a study's participants were eligible for our review, then we asked the study authors for disaggregated data. If we were unable to obtain the appropriate disaggregated data, then we included a study if the majority (at least 51%) of its participants were eligible for our review. If we were unable to determine the

exact per cent of a study's participants who were eligible, then we included the study if its participants were eligible on average (for example, the mean participant age was less than 13 years).

Types of interventions

Intervention

Orally administered zinc given as a supplement, regardless of compound, formulation, dose, duration, or frequency.
We excluded the following:

- food fortification or intake;
- studies of mixed micronutrients that did not isolate zinc (for example, a review has already been conducted on micronutrient sprinkles (De-Regil 2011));
- trials evaluating the therapeutic effects of zinc (that is, trials in which children received zinc while they were ill with diarrhoea, LRTI, or malaria, but stopped receiving zinc after recovering from illness).

Comparisons

Placebo, no intervention, and waiting list controls. A control comparison group could have been administered a non-zinc co-intervention (such as a vitamin A supplement), as long as the intervention group to which it was being compared was administered the same co-intervention. Comparisons between two different dosages of zinc (that is a high dose and a low dose) were not eligible; nor were comparisons between different zinc compounds, durations of supplementation, or frequencies at which doses were given. To evaluate the effect of providing zinc and iron simultaneously, we also included comparisons of iron plus zinc versus zinc alone.

Types of outcome measures

We assessed the preventive effects of zinc supplementation by extracting data for the following outcomes. In studies reporting more than one measure of an outcome, we extracted measures for meta-analysis using the methods described below (see Measures of treatment effect).

Primary outcomes

1. All-cause mortality
2. Cause-specific mortality
2.1 Mortality due to all-cause diarrhoea
2.2 Mortality due to lower respiratory tract infection (LRTI, including pneumonia)
2.3 Mortality due to malaria

Secondary outcomes

3. All-cause hospitalisation
4. Diarrhoea
4.1 Incidence of all-cause diarrhoea
4.2 Prevalence of all-cause diarrhoea
4.3 Hospitalisation due to all-cause diarrhoea
4.4 Incidence of severe diarrhoea
4.5 Prevalence of severe diarrhoea
4.6 Incidence of persistent diarrhoea
4.7 Prevalence of persistent diarrhoea
4.8 Hospitalisation due to persistent diarrhoea
5. Lower respiratory tract infection (LRTI)
5.1 Incidence of LRTI (including pneumonia)
5.2 Prevalence of LRTI
5.3 Hospitalisation due to LRTI
6. Malaria
6.1 Incidence of malaria
6.2 Prevalence of malaria
6.3 Hospitalisation due to malaria
7. Growth
7.1 Height
7.2 Weight
7.3 Weight-to-height ratio
7.4 Prevalence of stunting
8. Zinc status
8.1 Serum or plasma zinc concentration
8.2 Prevalence of zinc deficiency

Adverse events

9. Side effects
9.1 Study withdrawal
9.2 Participants with one or more side effect
9.3 Vomiting episodes
9.4 Participants with one or more vomiting episode
10. Haemoglobin status
10.1 Blood haemoglobin concentration
10.2 Prevalence of anaemia
11. Iron status
11.1 Serum or plasma ferritin concentration
11.2 Prevalence of iron deficiency
12. Copper status
12.1 Serum or plasma copper concentration
12.2 Prevalence of copper deficiency

We included the following outcomes in the Summary of findings for the main comparison: all-cause mortality, mortality due to all-cause diarrhoea, mortality due to LRTI, mortality due to malaria, incidence of all-cause diarrhoea, incidence of severe diarrhoea, incidence of persistent diarrhoea, incidence of LRTI, incidence of malaria, height, and participants with one or more vomiting episode. Measures of treatment effect describes the measures reported in the 'Summary of findings for the main comparison'.

Search methods for identification of studies

We conducted the initial searches in August and September 2011. The searches were updated between 29 December 2012 and 15 January 2013.

Electronic searches

We searched the following databases without date or language restrictions. Appendix 1 provides details of the search strategy for each database.

- Cochrane Central Register of Controlled Trials (CENTRAL), part of *The Cochrane Library*, searched 29 December 2012
- Ovid MEDLINE, searched 29 December 2012
- Ovid MEDLINE In-Process & Other Non-Indexed Citations, searched 29 December 2012
- Embase, searched 29 December 2012
- African Index Medicus, searched December 2012
- Global Health, searched 29 December 2012
- IndMED, searched 29 December 2012
- Latin American Caribbean Health Sciences Literature (LILACS), searched 15 January 2013
- WHO Library & Information Networks for Knowledge Database (WHOLIS), searched 15 January 2013
- *meta*Register of Controlled Trials (controlled-trials.com/mrct/), searched 15 January 2013
- WHO International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/), searched 15 January 2013
- Conference Proceedings Citation Index -Science (Web of Science), searched 15 January 2013
- ProQuest Dissertations & Theses Database, searched 29 December 2012

Searching other resources

Reference lists

We searched the reference lists of relevant review articles and included studies to identify additional studies in the published or unpublished literature.

Correspondence

We contacted the authors of included studies to identify additional studies that were ongoing or unpublished.

Data collection and analysis

Selection of studies

Two review authors (from JJ, AI, EMW, EC, AJ) independently screened the titles and abstracts of all reports yielded by the search to determine which were eligible for inclusion in the review. We then obtained and independently screened the full text of all potentially relevant studies to determine whether or not they met the inclusion criteria. If the authors disagreed about the eligibility of a study, then they discussed the disagreement between themselves and with a third author in order to reach a consensus about the study's eligibility. We sought additional information from study authors to help clarify any uncertainties about eligibility. During the study selection process, we were not blinded to study authors, institutions, journal of publication, or results.

Data extraction and management

We drafted a data extraction form to capture the following characteristics of each study.

General

- Year of study
- Country
- Setting (that is urban or rural, specific region or city if provided)
- Unit of analysis (for example, individual or cluster randomisation)

Participants

- Total number of study participants and clusters
- Number of study participants and clusters randomised to each included group
- Age
- Gender
- Inclusion and exclusion criteria
- Comorbidities

For each intervention or comparison group of interest

- Dose of zinc supplement
- Duration of zinc supplementation
- Frequency of zinc supplementation
- Co-interventions (if any)

For each outcome of interest

- Time points (i) collected and (ii) reported
- Missing data (exclusion of participants, attrition)

For each study, we also rated risk of bias (see Assessment of risk of bias in included studies).

Two review authors (JJ and SD) independently piloted the data extraction form on several studies included in the review and revised the form (with EMW and AI). Two authors (from JJ, EMW, AI, SD, XHSC, AJ) used the revised form to independently extract data from the rest of the studies. If a disagreement arose about the data extracted, then they discussed the disagreement between themselves and with a third author in order to reach a consensus. Details of the data extracted for each study are provided in a Characteristics of included studies table.

Assessment of risk of bias in included studies

Two authors (EMW or JJ and either SD, AI, XHSC, or AJ) coded each included study using The Cochrane Collaboration's tool for assessing risk of bias (Higgins 2011). We used this tool to judge whether each study was at low, high, or unclear risk of bias relating to sequence generation, allocation concealment, blinding of study participants, blinding of personnel, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias. If a disagreement arose concerning a 'Risk of bias' assessment, then the authors discussed the disagreement between themselves and with another author (EMW or JJ) in order to reach a consensus. We were not blinded to study authors, institutions, journal of publication, or results. Details are provided in a 'Risk of bias' table.

Measures of treatment effect

Multiple outcomes

Studies often report outcomes using multiple definitions and outcome measures. When studies reported outcomes, we did the following:

Diarrhoea

If a trial presented data on diarrhoea overall, undifferentiated by severity level, then we included these data in meta-analyses for all-cause diarrhoea outcomes. We did the same for outcomes that trial authors defined as acute diarrhoea. We defined persistent diarrhoea as lasting 14 or more days. We defined diarrhoea as severe if it was defined this way by trial authors.

LRTI

Several systematic reviews have found that LRTI is often defined inconsistently across studies (Bhutta 1999; Imdad 2010; Roth 2010). To deal with this inconsistency, we only included LRTI data from a study if the study's LRTI definition matched any of the following definitions. The first two of these definitions could have been diagnosed by someone who was not a medical professional (for example, a field worker). The third definition must have been diagnosed by a medical professional (for example, a physician).

- Difficulty breathing or rapid breathing, or both.
- Difficulty breathing or cough, along with one or more of the following: age-specific rapid breathing rates, lower chest wall indrawing, chest auscultation signs of pneumonia (decreased breath sounds, bronchial breath sounds, crackles, abnormal voice resonance, pleural rub), nasal flaring, grunting, fever, central cyanosis, inability to breastfeed or drink, vomiting everything, convulsions, lethargy, unconsciousness, or severe respiratory distress (for example, head nodding) (WHO 2000; WHO/UNICEF 2005).
- Clinical evidence of LRTI based on chest auscultation (decreased breath sounds, bronchial breath sounds, crackles, abnormal voice resonance, pleural rub) or chest radiograph.

We gave preference to more severe or rigorously diagnosed LRTI outcome data. For example, if a study provided LRTI data based on rapid breathing and LRTI data based on both rapid breathing and symptoms such as chest indrawing, then we extracted the latter. If a study provided data from caregivers of children and from study field workers, then we extracted the latter. If a study provided fieldworker-reported and physician-reported data, we extracted the latter. If a trial reported LRTI outcomes and pneumonia outcomes separately, then we used the LRTI outcomes. We did not include upper respiratory tract infection data.

Malaria

As with LRTI, we gave preference to more virulent forms of malaria (for example, preference was given to *Plasmodium falciparum* rather than *Plasmodium vivax*) if it was not possible to extract all forms.

Growth

Height data could be described in terms of raw lengths (for example, in units of centimetre (cm)), or in terms of height-for-age z-scores. Z-scores describe a child's height as a standard deviation score in a height distribution from a reference population of children of similar ages. If a study reported height outcomes as both raw lengths and height-for-age z-scores, then we preferentially extracted the height-for-age z-scores. However, if a study only reported raw lengths, then we extracted these. We did the same for raw weights and weight-for-age z-scores.

Zinc and other micronutrient status and adverse events

We included measures of zinc deficiency, anaemia, iron deficiency, or copper deficiency, as defined by trial authors. If authors reported more than one measure for a particular outcome, then we gave preference to the one defined as most severe.

Multiple outcome measures

To avoid review author bias, we predetermined the order of preference for extracting outcomes when data were available in several formats.

For studies that randomised individuals, we gave preference to data that required the least manipulation by authors or inference by review authors. We extracted raw values (for example, means and standard deviations) rather than calculated effect sizes (for example, Cohen's d). If outcomes were reported as both final values and changes from baseline, then we preferentially extracted the final values. In the case of cluster-RCTs, we (i) used adjusted estimates reported by the authors, or (ii) used raw data and inflated the standard error (SE) using the procedures described below.

For mortality data, we gave preference to denominators in the following order: number with definite outcome known (or imputed, as described in Dealing with missing data), number randomised, and child-years. For other dichotomous outcomes to which both survivors and non-survivors may have contributed data, we gave preference to child-years, number with definite outcome known, and number randomised.

Summary measures

Whenever possible, we used a risk ratio (RR) as the effect measure for each outcome for which there was dichotomous data. For incidence data, we combined risk ratios (events per child) and rate ratios (events per child year), because these ratios used the same scale and could be interpreted in the same way for these studies. Since we expected the duration of studies to be short, we did not anticipate interaction between the intervention and time at risk. We estimated time at risk if appropriate, as when authors reported incidence rate, study duration, and number of children in a group. We used Hedges' (adjusted) *g* (a standardised mean difference) for each outcome for which there was continuous data. We report all outcomes with a 95% confidence interval.

Unit of analysis issues

Cluster-randomised trials

Cluster-randomised trials randomise groups of people rather than individuals. For each cluster-randomised trial, we first determined whether or not its data incorporated sufficient controls for clustering (such as robust standard errors or hierarchical linear models). If the data did not have proper controls, then we attempted to obtain an appropriate estimate of the data's intracluster correlation coefficient (ICC). If we could not find an estimate in the report of the trial, then we requested an estimate from the trial report authors. If the authors did not provide an estimate, then we obtained one from a similar study and conducted a sensitivity analysis to determine if the results were robust when different values were imputed. We used the ICC estimate to control the trial's data for clustering, according to procedures described in Higgins 2011.

Cross-over trials

For cross-over trials, we extracted and analysed data from the first period only.

Studies with multiple treatment groups

For factorial studies, we included all comparisons that differed only in the presence or absence of zinc. For example, in a 2 x 2 factorial study of zinc and vitamin A supplementation, we included two comparisons: (1) zinc versus placebo and (2) zinc and vitamin A versus vitamin A alone. For other studies, multiple eligible intervention groups were combined.

Outcomes measured at multiple time points

For outcomes measured at multiple time points, we only included the time point that occurred the most days after randomisation in our meta-analyses.

Dealing with missing data

Missing data, and methods for imputing such data, may affect the magnitude and direction of a point estimate and its standard error. For all analyses, we attempted to include all randomised study participants. When analyses were reported for completers as well as controlling for dropout (for example, imputed using regression methods), we extracted the latter. If data were missing for some cases, or if reasons for dropout were not reported, then we contacted study authors to request missing data and further information on dropouts.

For the primary outcome, data were likely to be missing at random. Secondary outcome data may have been missing for reasons related to group assignment (for example, early mortality in the comparison group). We reported reasons for missing data, including reasons for dropout and number of dropouts. The potential impact of missing data on review findings is discussed below.

Assessment of heterogeneity

We discussed the similarities and differences between included studies in terms of their participants, interventions, outcomes, and methods. For each meta-analysis, we used three methods to identify statistical heterogeneity: visually inspecting forest plots to see if the confidence intervals of individual studies have poor overlap - a rough indication of statistical heterogeneity, conducting a Chi^2 test, and calculating an I^2 statistic. We deemed a meta-analysis to have substantial heterogeneity if its Chi^2 P value is less than 0.10 and its I^2 statistic is greater than 50%.

Assessment of reporting biases

We created a funnel plot for each meta-analysis that included 10 or more studies and looked to see if any funnel plot appeared asymmetrical. We judged a meta-analysis with an asymmetrical funnel plot to be potentially biased by small-study effects or reporting bias.

Data synthesis

We used Review Manager (RevMan) Version 5.2 software (Review Manager 2013) to conduct all meta-analyses. We used Mantel-Haenszel methods to meta-analyse dichotomous data that could be combined directly in RevMan. If studies reported dichotomous data in multiple formats that could not be combined in RevMan, we used Comprehensive Meta-Analysis Version 2 software (Borenstein 2005) to calculate log risk ratios and standard errors for the data, enter these log risk ratios and standard errors

into RevMan, and then meta-analyse these using inverse-variance methods. We also used the inverse-variance method to meta-analyse continuous data. We used fixed-effect methods for all meta-analyses. Although there may have been some differences across trials (for example, dose and population), the biological mechanism should have been similar across trials. However, we conducted a sensitivity analysis in which random-effects methods were used (see Sensitivity analysis).

Subgroup analysis and investigation of heterogeneity

We planned to conduct the following subgroup analyses for outcomes with at least 10 studies measuring the relevant characteristic. We report a Chi^2 test for each analysis to determine whether or not the effects of zinc are statistically significantly different for different subgroups.

1. Country income level: low- and middle-income countries versus high-income countries, as defined by the World Bank's country income classification system (World Bank 2011).
2. Age: children six months to under one year, versus one to under five years, versus five years to under 13 years.
3. Stunting: children with a height-for-age z-score of < -2 versus children with a height-for-age z-score ≥ -2.
4. Dose: daily dose equivalent less than 5 mg per day, versus 5 mg to under 10 mg, versus 10 mg to under 15 mg, versus 15 mg to under 20 mg, versus 20 mg or more per day.
5. Duration: supplementation lasting zero to five months, versus six to 11 months, versus 12 months or more.
6. Iron co-interventions: iron + zinc versus iron alone, zinc versus no supplementation.
7. Formulation: solution versus pill and/or tablet versus capsule versus powder.

Sensitivity analysis

We had planned to conduct the following sensitivity analyses to examine whether or not our findings were robust to certain decisions we made while conducting the review; however, only the first of these was possible.

1. We repeated the analyses using random-effects methods.
2. We had planned to repeat the primary meta-analysis excluding studies at high risk of bias due to incomplete outcome data.
3. We had planned to repeat the primary meta-analysis if it included one or more cluster-randomised trials for which we had to impute the ICC. We planned to repeat the meta-analysis using an ICC value at least as large as the largest observed ICC.

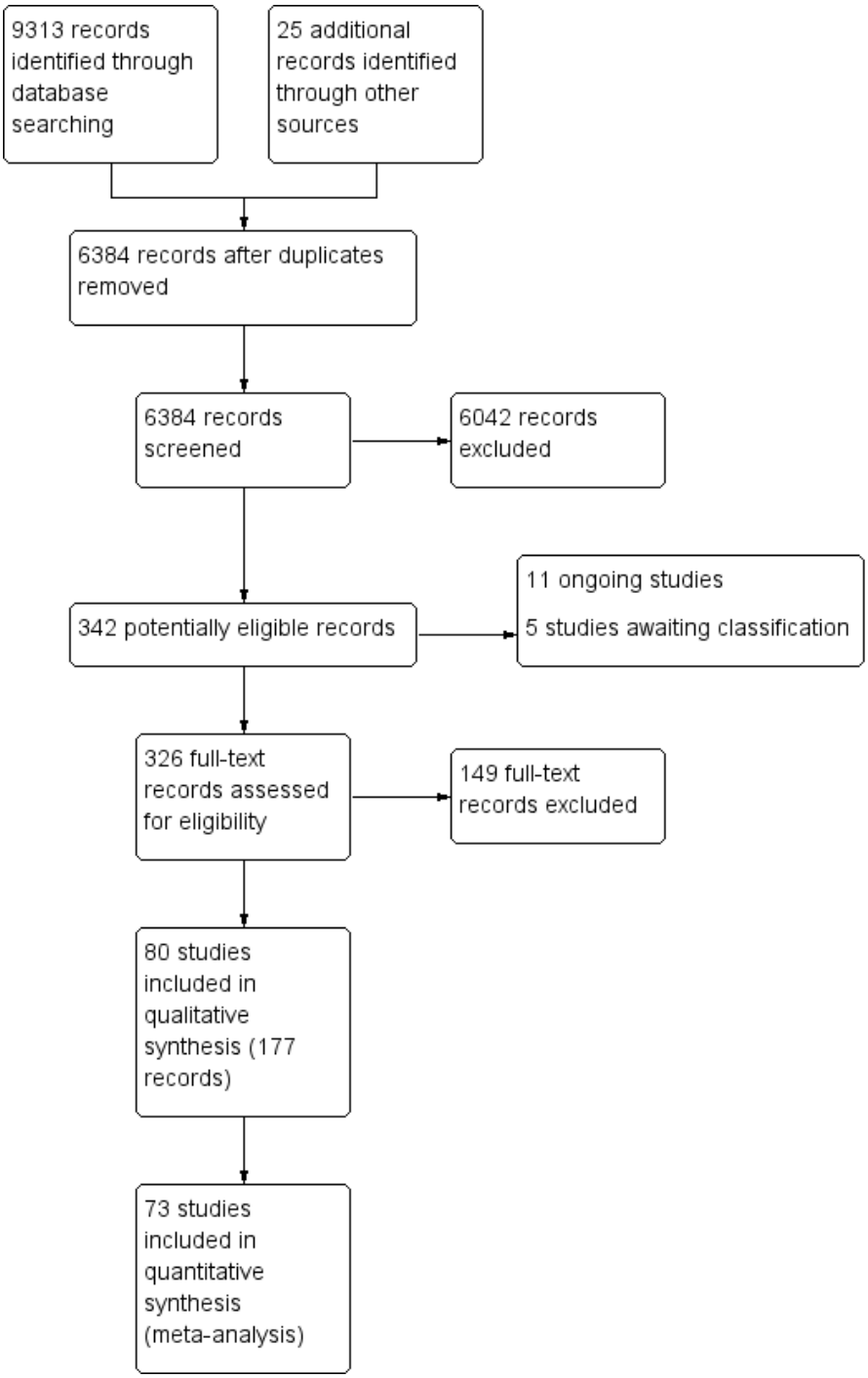
RESULTS

Description of studies

Results of the search

We screened 6384 records and 326 full-text trial reports (Figure 1).

Figure 1. Study flow diagram.



Included studies

Eighty eligible studies, reported in 177 trial reports, compared zinc versus placebo or zinc with a co-intervention versus the co-intervention alone. Thirty-six studies were reported in more than one publication or paper. Five studies were published in non-English languages: two studies written in Spanish, one in Chinese, and two in Portuguese. Seven studies did not contribute to any meta-analysis because they did not report any outcomes of interest to this review or because they did not report sufficient data (Sanjur 1990; Marinho 1991; Sandstead 1998; Castillo-Durán 2002; Ahmed 2009a; Vakili 2009; Shah 2011). A Characteristics of included studies table describes each included study in greater detail.

Design

There were two cross-over trials, for which data from the first period only were analysed (Hong 1982; Garcia 1998).
Nine studies were cluster-RCTs (Sandstead 1998; Sazawal 2006; Tielsch 2006; Bhandari 2007; Gupta 2007; Hettiarachchi 2008; Tupe 2009; Chen 2012; Soofi 2013). Sazawal 2006 and Bhandari 2007 randomised households and had average cluster sizes of fewer than two children. The other meta-analysed cluster-RCTs randomised by school class or community health worker surveillance area, and had cluster sizes ranging from approximately eight to 116 individuals. Sazawal 2006 and Tielsch 2006 reported design effects, and unpublished ICCs were obtained for the Bhandari 2007 and Tupe 2009 studies. An ICC was calculated based on the design effect from Tielsch 2006. ICCs from Tielsch 2006 and Tupe 2009 were then averaged, and the average (0.014) was used to adjust data from Gupta 2007 and Hettiarachchi 2008 for clustering. Results of the meta-analyses of which Gupta 2007 and Hettiarachchi 2008 were a part were robust regardless of whether an ICC of 0.014, 0, or 1 was assumed from these studies.

Sample sizes

This review includes approximately 205,923 eligible participants from the 80 included studies. The 73 studies (91%) that contributed to at least one meta-analysis had approximately 205,401 participants (more than 99% of those randomised). Sample sizes of included studies ranged from 21 to 72,438 eligible participants, with a median sample size of 200. The three largest studies in this review accounted for 88% of the eligible participants (Sazawal 2006; Tielsch 2006; Bhandari 2007). Participants were approximately evenly split between zinc and control groups.

Setting

Thirty-two countries are represented amongst the studies included in this review. Seventy-three studies (91%) were conducted in low- or middle-income countries: 37 in Asia, 26 in Latin America and the Caribbean, and 10 in sub-Saharan Africa. Seven were conducted in North America or Europe. The countries where the most studies were conducted were Bangladesh and India, with seven and eight studies, respectively. The three largest trials took place in India, Nepal, and Zanzibar (a semi-autonomous region of Tanzania). Among the 72 studies that described their setting, 46 were conducted in urban or peri-urban areas, 21 in rural areas, and five in both urban and rural areas.

Participants

Sixty-one studies reported mean participant age at baseline. The median of these mean ages was 28 months. Most participants in this review were under five years of age. Of the 76 trials that could be classified in an age subgroup, only 24 were in the five to 13 years of age category. The gender of participants was reported in 73 studies, which was usually equally divided.
Forty-eight studies reported the mean height-for-age z-score of their participants at baseline. The median of these mean scores was -1.6, with scores ranging from -2.9 to 0.10. Both stunted and non-stunted children were included in 42 studies; five included only stunted children, five included only non-stunted children, and 28 did not specify whether or not their participants were stunted.
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.

Interventions

Studies reporting the formulation of their zinc supplements provided zinc as a solution or syrup (46), pill or tablet (17), capsule (6), or powder (2). One trial provided zinc as a syrup to one study group and as a tablet to another study group (Wessells 2012b).
Studies reporting the chemical compound of their zinc supplements provided zinc as sulfate (45), gluconate (12), acetate (six), and other compounds (eight).
Studies provided zinc for less than two months (eight), two to less than six months (22), six to less than 12 months (33), and 11 months or more (16). Twenty-five studies provided zinc for six months and 11 provided zinc for 12 months. Studies reporting the frequency of zinc supplementation had frequencies ranging from daily to weekly. Zinc was provided daily in 48 studies and 11 provided zinc weekly. Studies that could be classified based on zinc dose administered daily dose equivalents of less than 5 mg

(five), 5 mg to less than 10 mg (19), 10 mg to less than 15 mg (30), 15 mg to less than 20 mg (eight), and 20 mg or more (12). Twenty trials were factorial. Among both factorial and non-factorial trials in this review, there were 100 eligible comparisons. Of these eligible comparisons, 51 (49%) included a co-intervention that both the zinc and the control groups received. Common co-interventions were iron, vitamin A, or multivitamin supplements.

Duration

Outcomes were observed at a median time period of 26 weeks after randomisation, with follow-up periods ranging between two and 80 weeks.

Excluded studies

We excluded 149 full-text records, including 28 studies that came close to meeting this review's inclusion criteria but were ultimately excluded (see Characteristics of excluded studies table).

Ongoing studies

Eleven likely eligible ongoing or completed studies were identified (CTRI/2010/091/001417; NCT00133406; NCT00228254; NCT00374023; NCT00421668; NCT00589264; NCT00944359; NCT00967551; NCT00980421; NCT01306097; NCT01616693). We contacted the authors and asked them to supply data. These studies are described in a Characteristics of ongoing studies table.

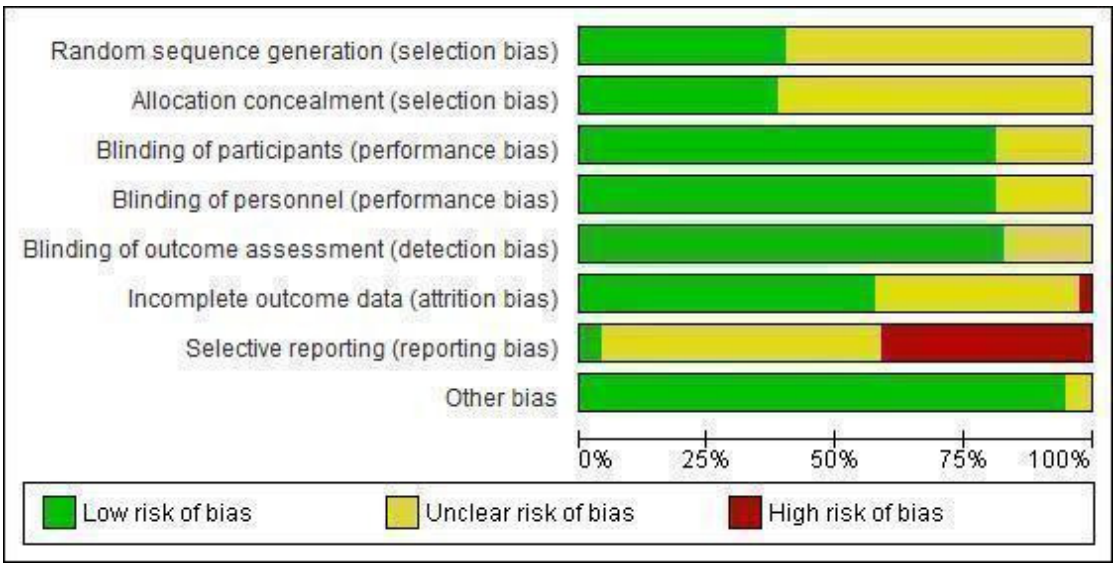
Studies awaiting classification

Five potentially eligible studies could not be definitively classified as eligible or ineligible (Smith 1985; Jimenez 2000; Chicourel 2001; Mitter 2009; Arabaci 2010). For these studies, no full-text trial records could be obtained, or records obtained did not report sufficient information concerning inclusion criteria such as participant age. These studies are described in a Characteristics of studies awaiting classification table.

Risk of bias in included studies

We used The Cochrane Collaboration's tool for assessing risk of bias (Higgins 2011) to judge each included study as being at low, high, or unclear risk of bias in five domains. These judgements are summarised in Figure 2 and detailed justifications for each judgement are listed in the Characteristics of included studies table.

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

Random sequence generation

For the random sequence generation domain, 34 studies were at low risk of bias and 46 were at unclear risk. Of the 34 studies at low risk of bias, 18 used a computer random number generator to randomise participants, eight used a random number table, three used drawing of lots, and one tossed a coin. Four of these 34 studies did not refer explicitly to any of these sequence generation methods, but did report the use of permuted blocks.

Allocation concealment

For allocation concealment, 32 studies were at low risk of bias and 48 were at unclear risk. Among studies at low risk, methods such as central randomisation (that is randomisation by someone not involved with enrolling participants) were used to conceal allocation. Furthermore, though allocation concealment and blinding are distinct bias domains, some have argued that "blinded trials of drugs are very likely to be concealed" (Devereaux 2004; Guyatt 2011b). In this review, risk of bias related to blinding did not seem substantial, nor did risk of bias related to allocation concealment.

Blinding

For blinding of participants and for blinding of personnel, 63 studies were at low risk of bias and 15 were at unclear risk. For blinding of outcome assessment, 65 studies were at low risk of bias and 15 were at unclear risk. To ensure blinding, trials used strategies such as providing the control group a placebo of identical appearance and taste to that of zinc. Strategies such as these make blinding an intervention, such as zinc supplementation, easier than blinding more complex, interactive interventions. Furthermore, the primary outcome of this review is mortality and this outcome is less vulnerable to bias related to blinding than other, more subjective, outcomes (Altman 2001).

Incomplete outcome data

For incomplete outcome data, 47 studies were at low risk of bias, 31 were at unclear risk, and two were at high risk. For 70 studies, it was possible to calculate an approximate percentage of study participants with missing data for non-mortality outcomes. Of these, 35 studies had less than 10% missing data, 23 had 10% to less than 20% missing data, and 12 had at least 20% missing data. Amounts of and reasons for missing data were generally balanced between groups.

Selective reporting

For selective reporting, three studies were at low risk of bias, 44 were at unclear risk, and 32 were at high risk. For 31 of the studies at unclear risk, a trial protocol could not be obtained and it was not possible to confirm whether their outcomes were reported as planned in their protocols. Among many studies at high risk of bias, trial reports stated that certain outcomes were measured but no numerical data disaggregated by study group were reported for these outcomes, or insufficient data were reported to include them in a meta-analysis. Many missing outcomes were biochemical, growth, and side effect outcomes.

Other potential sources of bias

Other potential sources of bias appeared to be minimal and unlikely to impact the results of this review.

Effects of interventions

See: **Summary of findings for the main comparison** Zinc versus no zinc for preventing mortality, morbidity, and growth failure in children aged 6 months to 12 years of age

This section describes the results of the meta-analysis of each outcome in this review. Results are presented as the pooled effect estimate followed by the lower and upper limits of its 95% confidence interval (CI) in brackets. For all analyses, smaller or more negative effect estimates (risk ratio (RR) < 1; standardised mean difference (SMD) < 0) favour intervention. Within forest plots, outcome data for each eligible comparison are in a separate row. For instance, in a factorial trial, the zinc versus placebo comparison would be in one row of a forest plot, and the zinc and vitamin A versus vitamin A comparison would be in another row. Within the Data and analyses tables, each eligible comparison is counted as a separate study.

No studies reported the prevalence of severe diarrhoea or hospitalisation due to malaria, so these outcomes do not appear below. As per the protocol, we did not conduct subgroup analyses for analyses with fewer than 10 comparisons. Specifically, we did not conduct analyses for country income for outcomes that did not include any studies conducted in high-income countries. We did not conduct stunting subgroup analyses for outcomes when no study reported separate data on that outcome for stunted or non-stunted children. When country income and stunting subgroup analyses were conducted, one group often contained few studies. In some subgroup analyses, one or more subgroups contained no study data and effects are reported for all subgroups except those without data.

One sensitivity analysis was to repeat the primary meta-analysis excluding studies at high risk of bias due to incomplete outcome data. We did not undertake this analysis because only two studies were at high risk of bias due to incomplete outcome data and these studies did not report any of the primary outcomes for this review (Gupta 2007; Ba Lo 2011). Another sensitivity analysis was to repeat the primary meta-analysis to test if the results from it were robust to assumptions about imputed intracluster correlation co-

efficients (ICCs) for cluster-randomised controlled trials (RCTs). We did not undertake this analysis because neither of the two studies for which ICCs were imputed reported any of the primary outcomes for this review. Finally, we conducted a random-effects sensitivity analysis for all meta-analyses. We report the pooled estimate from the random-effects model when heterogeneity is potentially important (that is I^2 > 25%).

Comparison 1: Zinc versus no zinc

Primary outcomes

(1) All-cause mortality

Thirteen studies, one of which included two comparisons (total number of comparisons = 14), comprising 138,302 participants (67% of participants in the review), were included in the analysis of all-cause mortality (see Analysis 1.1). Other studies included no deaths in either group. Zinc supplementation did not have a statistically significant effect on all-cause mortality (RR 0.95, 95% CI 0.86 to 1.05) and there was no statistical heterogeneity (Chi² = 10.57, df = 13 (P value = 0.65); I² = 0%), but the results were consistent with a small reduction in mortality.

A funnel plot, which we created to explore the possibility of small-study effects or reporting bias further, appeared symmetrical.

Subgroup analyses

Effects did not differ significantly among age (P value = 0.11), dose (P value = 0.45), duration (P value = 0.55), iron co-intervention (P value = 0.25), or formulation (P value = 0.91) subgroups.

(2) Cause-specific mortality

(2.1) Mortality due to all-cause diarrhoea

Four studies, involving 132,321 participants (64% of participants in the review), reported no significant effect on mortality due to diarrhoea (RR 0.95, 95% CI 0.69 to 1.31) (see Analysis 1.2) and no heterogeneity (Chi² = 0.82, df = 3 (P value = 0.84); I² = 0%).

(2.2) Mortality due to lower respiratory tract infection (LRTI)

In three studies including 132,063 participants (64% of participants in the review), zinc supplementation did not have a statistically significant effect on mortality due to LRTI (RR 0.86, 95% CI 0.64 to 1.15) and there was no heterogeneity (Chi² = 0.07, df = 2 (P value = 0.96); I² = 0%) (see Analysis 1.3).

(2.3) Mortality due to malaria

Two studies (Shankar 2000; Sazawal 2006), including 42,818 participants (21% of participants in the review), reported mortality due to malaria (see Analysis 1.4). Zinc supplementation did not have a statistically significant effect (RR 0.90, 95% CI 0.77 to 1.06) and there was no heterogeneity (Chi² = 0.01, df = 1 (P value = 0.94); I² = 0%).

Secondary outcomes

(3) All-cause hospitalisation

Seven trials, two of which contributed two comparisons (total number of comparisons = nine), included 92,872 participants (45% of participants in the review) and reported no overall effect on all-cause hospitalisation (RR 1.04, 95% CI 0.97 to 1.11); heterogeneity was moderate (Chi² = 14.41, df = 8 (P value = 0.07); I² = 44%) (Analysis 1.5).

Three studies reported hospitalisation data as the number of participants ever hospitalised rather than as the number of hospitalisations (Meeks Gardner 1998; Bhandari 2002; Chhagan 2009). Excluding these from the analysis did not change the result (RR 1.04, 95% CI 0.97 to 1.12). The result also remained insignificant when calculated using a random-effects model (RR 0.98, 95% CI 0.83 to 1.14).

(4) Diarrhoea

(4.1) Incidence of all-cause diarrhoea

In 26 studies (nine of which included two comparisons; total number of comparisons = 35) involving 15,042 participants (7% of participants in the review), there was a combined 13% reduction in the incidence of all-cause diarrhoea (RR 0.87, 95% CI 0.85 to 0.89), though heterogeneity was substantial (Chi² = 295.56, df = 34 (P < 0.00001); I² = 88%) (Analysis 1.6). Three studies in this meta-analysis reported data as medians, but excluding these from the analysis did not change the result (RR 0.87, 95% CI 0.86 to 0.89) (Ruel 1997; Meeks Gardner 1998; Meeks Gardner 2005).

There was some evidence of funnel plot asymmetry, with several smaller studies reporting unusually large reductions in all-cause diarrhoea incidence. However, the result of this meta-analysis was similar when we used a random-effects model (RR 0.84, 95% CI 0.78 to 0.91), which suggests that the result was not strongly influenced by small-study effects.

Subgroup analyses

Effects did not differ significantly by duration of supplementation (P value = 0.56) or age (P value = 0.85).

Dose subgroups were significantly different (P < 0.00001), but there did not appear to be a coherent pattern of increasing or decreasing effect across doses: 0 mg to 5 mg (RR 0.95, 95% CI 0.89 to 1.01); 5 mg to 10 mg (RR 0.73, 95% CI 0.64 to 0.83); 10 mg to 15 mg (RR 0.96, 95% CI 0.92 to 0.99); 15 mg to 20 mg (RR 0.61, 95% CI 0.58 to 0.65); 20 mg or more (RR 0.90, 95% CI 0.87 to 0.94).

Formulation subgroups were significantly different (P < 0.00001), but most studies used a solution and effects generally favoured

intervention for solution (RR 0.84, 95% CI 0.82 to 0.86), pill and/or tablet (RR 0.90, 95% CI 0.81 to 0.99), and capsule (RR 0.78, 95% CI 0.60 to 1.01); there was no significant effect in two studies using micronutrient powder (RR 1.04, 95% CI 0.98 to 1.09).

Iron co-intervention subgroups were significantly different (P < 0.00001), with no benefit for the group that received iron (RR 1.00, 95% CI 0.96 to 1.05) and a significant benefit for the group that did not receive iron (RR 0.82, 95% CI 0.80 to 0.84).

(4.2) Prevalence of all-cause diarrhoea

In 13 studies (two of which included two comparisons; total number of comparisons = 15) including 8519 participants (4% of participants in the review), there was a 12% reduction in the prevalence all-cause diarrhoea (RR 0.88, 95% CI 0.86 to 0.90), though heterogeneity was considerable (Chi^2 = 118.88, df = 14 (P < 0.00001); I^2 = 88%) (Analysis 1.7). Two studies in this meta-analysis reported data as medians, but excluding these from the analysis had no effect on the result (RR 0.88, 95% CI 0.87 to 0.90) (Ruel 1997; Chhagan 2009). The result was robust when we used random-effects (RR 0.87, 95% CI 0.81 to 0.93). We created a funnel plot, which appeared symmetrical.

Subgroup analyses

Age subgroups were significantly different (P < 0.00001), with greater benefit in the older age group, but both effects favoured intervention: between six and 12 months (RR 0.96, 95% CI 0.93 to 1.00); between one and five years (RR 0.85, 95% CI 0.83 to 0.87).

Dose subgroups were significantly different (P < 0.0001), with potentially larger effects at higher doses: 0 mg to 5 mg (RR 1.00, 95% CI 0.92 to 1.08); 5 mg to 10 mg (RR 1.17, 95% CI 0.60 to 2.28); 10 mg to 15 mg (RR 0.93, 95% CI 0.90 to 0.96); 15 mg to 20 mg (RR 0.61, 95% CI 0.54 to 069), 20 mg or more (RR 0.85, 95% CI 0.82 to 0.87).

Duration subgroups were significantly different (P value = 0.00009), but there did not appear to be a coherent pattern of results: between zero and six months (RR 0.85, 95% CI 0.82 to 0.87); between six and 12 months (RR 0.92, 95% CI 0.89 to 0.95); 12 months or more (RR 0.88, 95% CI 0.74 to 1.03).

Formulation subgroups were significantly different (P value = 0.00009), but most studies used a solution and effects generally favoured intervention for solution (RR 0.88, 95% CI 0.85 to 0.90) and pill and/or tablet (RR 0.86, 95% CI 0.81 to 0.92); there was no significant effect in one study using micronutrient powder (RR 1.03, 95% CI 0.95 to 1.12). The solution and tablet groups were consistent when the powder study was removed from the analysis.

Iron co-intervention subgroups were significantly different (P value = 0.05), with no clear benefit for the group that received iron (RR 0.96, 95% CI 0.88 to 1.05) and a significant benefit for the group that did not receive iron (RR 0.88, 95% CI 0.86 to 0.90), but only three studies contributed to the first group.

(4.3) Hospitalisation due to all-cause diarrhoea

Four trials, one of which reported two comparisons (total number of comparisons = five), including 74,039 participants (36% of participants in the review) found no significant combined effect on hospitalisation due to all-cause diarrhoea (RR 1.03, 95% CI 0.87 to 1.22), but there was moderate heterogeneity (Chi^2 = 6.91, df = 4 (P value = 0.14); I^2 = 42%) (Analysis 1.8). Excluding data from one study that reported hospitalisation data as the number of participants ever hospitalised (Chhagan 2009) did not change the result (RR 1.03, 95% CI 0.87 to 1.22), but the effect changed when calculated using random-effects (RR 0.90, 95% CI 0.65 to 1.24).

(4.4) Incidence of severe diarrhoea

Six trials, one of which reported two comparisons (total number of comparisons = seven), included 4982 participants (2% of participants in the review) and found a significant combined effect on incidence of severe diarrhoea (RR 0.89, 95% CI 0.84 to 0.95). However, heterogeneity was substantial (Chi^2 = 13.54, df = 6 (P value = 0.04); I^2 = 56%) (Analysis 1.9). The estimated effect was not importantly different, though it was no longer significant when calculated using random-effects (RR 0.92, 95% CI 0.82 to 1.03).

(4.5) Incidence of persistent diarrhoea

Seven trials, two of which reported two comparisons each (total number of comparisons = nine), including 6216 participants (3% of participants in the review), found that zinc supplementation was associated with a 27% decrease in the incidence of persistent diarrhoea (RR 0.73, 95% CI 0.62 to 0.85), with substantial heterogeneity (Chi^2 = 20.47, df = 8 (P value = 0.009); I^2 = 61%) (Analysis 1.10). The estimated effect was not importantly different when calculated using random-effects (RR 0.72, 95% CI 0.54 to 0.96).

(4.6) Prevalence of persistent diarrhoea

Only one trial, which made two comparisons (Rahman 2001/ Rahman 2001 (2); total number of comparisons = two), with 665 participants (< 1% of participants in this review), reported a 30% reduction in the prevalence of persistent diarrhoea (RR 0.70, 95% CI 0.64 to 0.76) (Analysis 1.11).

(5) LRTI

(5.1) Incidence of LRTI

One trial reported no LRTI in either group (Sempertegui 1996). Twelve trials, six of which made two comparisons (total number of comparisons = 18), contributed 9610 participants (5% of participants in this review) to a meta-analysis that found no effect on LRTI incidence (RR 1.00, 95% CI 0.94 to 1.07) and had no im-

portant heterogeneity (Chi² = 17.16, df = 17 (P value = 0.44); I² = 1%) (Analysis 1.12). A funnel plot did not appear asymmetrical.

Subgroup analyses

Effects were not significantly heterogeneous across different age (P value = 0.47), dose (P value = 0.74), duration (P value = 0.67), iron co-intervention (P value = 0.80), or formulation (P value = 0.29) subgroups.

(5.2) Prevalence of LRTI

Three trials, one reporting two comparisons (total number of comparisons = four), included 1955 participants (1% of participants in the review) and found that zinc supplementation was associated with a 20% increase in the prevalence of LRTI (RR 1.20, 95% CI 1.10 to 1.30), though heterogeneity was considerable (Chi² = 89.87, df = 3 (P < 0.00001); I² = 97%) (Analysis 1.13).

This increase in prevalence was not significant when a random-effects model was used (RR 1.13, 95% CI 0.71 to 1.81). However, given that the three studies in this meta-analysis had sample sizes of 603, 666, and 686, it seems unlikely that small-study effects influenced the results. LRTI outcome criteria were similar across these studies, so LRTI criteria would not likely explain the difference between the random-effects and fixed-effect models. One possible explanation for this difference is that baseline population characteristics were different among the studies included in this meta-analysis, and some results were the result of chance. For example, Rahman 2001/Rahman 2001 (2) had a lower average baseline height-for-age z-score (-2.41) than that of Muller 2001 (-1.6). Baseline risk of LRTI was different across the studies: Sazawal 1996 (2.11 days per child-year), Muller 2001 (1.56 days per child-year), Rahman 2001 (2.94 days per child-year), Rahman 2001 (2) (3.58 days per child-year).

(5.3) Hospitalisation due to LRTI

Three trials, one making two comparisons (total number of comparisons = four) (Bhandari 2007; Chang 2010/Chang 2010 (2); Soofi 2013), included 74,743 participants (36% of participants in this review) and found no statistically significant effect on hospitalisation due to LRTI (RR 1.10, 95% CI 0.93 to 1.30). There was no heterogeneity (Chi² = 0.35, df = 3 (P value = 0.95); I² = 0%) (Analysis 1.14).

(6) Malaria

(6.1) Incidence of malaria

Four trials, two of which made two comparisons (total number of comparisons = six), included 2407 participants (1% of participants in this review) and found no statistically significant effect on malaria incidence (RR 1.05, 95% CI 0.95 to 1.15); heterogeneity was not significant (Chi² = 2.04, df = 5 (P value = 0.84); I² = 0%) (Analysis 1.15). The effect was not importantly different when analysed using random-effects (RR 0.99, 95% CI 0.83 to 1.18).

(6.2) Prevalence of malaria

One study (Muller 2001) with 661 participants (< 1% of participants in this review) reported no significant effect on malaria prevalence (RR 0.88, 95% CI, 0.47 to 1.64) (Analysis 1.16).

(7) Growth

(7.1) Height

Fifty studies, nine of which made two comparisons (total number of comparisons = 59), reported height for 13,669 participants (7% of participants in this review) (see Analysis 1.17). As explained in Measures of treatment effect, some studies measured height in units of cm; other studies measured height as height-for-age z-scores. We combined these height measures for this analysis. In all but one study (Sazawal 2006/Sazawal 2006 (2)), height was measured at, or after, the end of the supplementation period. Zinc supplementation was associated with a small, but significant, increase in height (SMD -0.09, 95% CI -0.13 to -0.06), but heterogeneity was considerable (Chi² = 407.92, df = 58 (P < 0.00001); I² = 86%). The result was not importantly different when analysed using random-effects (SMD -0.10, 95% CI -0.20 to -0.00). A funnel plot appeared generally symmetrical.

Subgroup analyses

Studies were not significantly different in the subgroup analyses for country income level (P value = 0.50) or stunting (P value = 0.32).

Age subgroups were significantly heterogeneous (P < 0.00001), with greater benefit in older age groups: between six and 12 months (SMD 0.26, 95% CI 0.19 to 0.33); between one and five years (SMD -0.09, 95% CI -0.14 to -0.04); between five and 13 years (SMD -0.25, 95% CI -0.32 to -0.18).

Dose subgroups were significantly different (P < 0.00001). There did not appear to be a coherent pattern of increasing or decreasing effect across increasing doses: 0 mg to 5 mg (SMD -0.02, 95% CI -0.13 to 0.10); 5 mg to 10 mg (SMD -0.29, 95% CI -0.37 to -0.22); 10 mg to 15 mg (SMD -0.06, 95% CI -0.12 to -0.00); 15 mg to 20 mg (SMD 0.01, 95% CI -0.24 to 0.26); 20 mg or more (SMD 0.01, 95% CI -0.05 to 0.07).

Duration subgroups were significantly different (P < 0.0001). There did not appear to be a coherent pattern of increasing or decreasing effect across increasing durations: between zero and six months (SMD 0.01, 95% CI -0.04 to 0.07); between six and 12 months (SMD -0.17, 95% CI -0.22 to -0.12); 12 months or more (SMD -0.10, 95% CI -0.17 to -0.02).

Iron co-intervention subgroups were significantly different (P value = 0.01), with a significant benefit in the group without iron (SMD -0.12, 95% CI -0.16 to -0.08) and no difference in the group with iron (SMD -0.01, 95% CI -0.08 to 0.07).

Formulation subgroups were significantly different (P value = 0.02). There were larger benefits in the solution and capsule sub-

groups than the pill/tablet subgroup: solution (SMD -0.12, 95% CI -0.16 to -0.07); pill and/or tablet (SMD -0.02, 95% CI -0.09 to 0.04); capsule (SMD -0.31, 95% CI -0.59 to -0.03).

(7.2) Weight

Forty-four trials, eight of which reported two comparisons (total number of comparisons = 52), included 12,305 participants (6% of participants in this review) and found that zinc was associated with a small increase in weight (SMD -0.10, 95% CI -0.14 to -0.07), but heterogeneity was substantial (Chi^2 = 216.64, df = 51 (P < 0.00001); I^2 = 76%) (Analysis 1.18). The result was not different when analysed using random-effects (SMD -0.10, 95% CI -0.18 to -0.02). However, there was some visual asymmetry in the funnel plot for this analysis, suggesting that small-study effects or reporting bias might have influenced the result.

Subgroup analyses

Effects did not differ significantly among country income level (P value = 0.62), stunting (P value = 0.13), or iron co-intervention (P value = 0.22) subgroups.

Age subgroups were significantly heterogeneous (P < 0.00001), with greater benefit in older age groups: between six and 12 months (SMD 0.31, 95% CI 0.25 to 0.38); between one and five years (SMD -0.06, 95% CI -0.11 to -0.01); between five and 13 years (SMD -0.28, 95% CI -0.36 to -0.20). The apparent harmful effect in the youngest subgroup is explained by the result of a subgroup analysis from one study (Bhandari 2002).

Dose subgroups were significantly different (P < 0.00001), but there did not appear to be a coherent pattern of increasing or decreasing effect across increasing doses: 0 mg to 5 mg (SMD -0.00, 95% CI -0.12 to 0.11); 5 mg to 10 mg (SMD -0.27, 95% CI -0.35 to -0.20); 10 mg to 15 mg (SMD -0.11, 95% CI -0.17 to -0.04); 15 mg to 20 mg (SMD 0.20, 95% CI -0.06 to 0.45); 20 mg or more (SMD -0.01, 95% CI -0.08 to 0.05).

Duration subgroups were significantly different (P < 0.00001), but there did not appear to be a coherent pattern of increasing or decreasing effect across increasing durations: between zero and six months (SMD -0.05, 95% CI -0.11 to 0.00); between six and 12 months (SMD -0.20, 95% CI -0.26 to -0.15); 12 months or more (SMD 0.01, 95% CI -0.07 to 0.09).

Formulation subgroups were significantly different (P value = 0.0004). There were statistically significant benefits in the solution and capsule subgroups and no statistically significant effect in the pill/tablet subgroup: solution (SMD -0.14, 95% CI -0.19 to -0.10); pill and/or tablet (SMD -0.01, 95% CI -0.08 to 0.06); capsule (SMD -0.41, 95% CI -0.71 to -0.12).

(7.3) Weight-to-height ratio

Twenty-four trials, five of which reported two comparisons (total number of comparisons = 29), included 7901 participants (4% of participants in this review) and found that zinc supplementation was associated with a small increase in weight-to-height ratio (SMD -0.05, 95% CI -0.10 to -0.01). There was no heterogeneity (Chi^2 = 34.96, df = 28 (P value = 0.17); I^2 = 20%) (Analysis 1.19). The funnel plot appeared symmetrical.

Subgroup analyses

Studies were not significantly different in the subgroup analyses for country income level (P value = 0.66), age (P value = 0.75), dose (P value = 0.34), duration (P value = 0.29), iron co-interventions (P value = 0.06), or formulation (P value = 0.16).

(7.4) Prevalence of stunting

Six trials, three of which included two comparisons (total number of comparisons = nine), included 3838 participants (2% of participants in this review) and found no significant effect on the prevalence of stunting (RR 0.94, 95% CI, 0.86 to 1.02), but heterogeneity was substantial (Chi^2 = 19.43, df = 8 (P value = 0.01); I^2 = 59%) (Analysis 1.20). The average effect was not importantly different when calculated using random-effects (RR 0.90, 95% CI 0.72 to 1.12).

(8) Zinc status

(8.1) Serum or plasma zinc concentration

Forty-six studies, 10 of which made two comparisons (total number of comparisons = 56), included 9810 participants (5% of participants randomised) and found that zinc supplementation was associated with a medium to large increase in zinc concentration (SMD -0.62, 95% CI -0.67 to -0.58), though heterogeneity was considerable (Chi^2 = 582.45, df = 55 (P < 0.00001); I^2 = 91%) (Analysis 1.21). The result was not different when analysed using random-effects (SMD -0.62, 95% CI -0.77 to -0.48). The funnel plot did not appear to have any substantive asymmetry.

Subgroup analyses

Age subgroups were significantly heterogeneous (P < 0.0001) with the greatest benefit in the one to five year age group: between six and 12 months (SMD -0.46, 95% CI -0.55 to -0.37); between one and five years (SMD -0.75, 95% CI -0.81 to -0.69); between five and 13 years (SMD -0.47, 95% CI -0.55 to -0.38).

Country income level subgroups were significantly different (P value = 0.003), with statistically significant benefit only in the low- and middle-income subgroups (SMD -0.63, 95% CI -0.68 to -0.59), which contained most of the data, and no difference in the high-income subgroup (SMD -0.23, 95% CI, -0.49 to 0.03).

Dose subgroups were significantly different (P < 0.00001) with larger doses associated with larger increases in zinc concentration: 0 mg to 5 mg (SMD -0.35, 95% CI -0.49 to -0.21); 5 mg to 10 mg (SMD -0.49, 95% CI -0.59 to -0.40); 10 mg to 15 mg (SMD -0.62, 95% CI -0.68 to -0.56); 15 mg to 20 mg (SMD -0.76, 95% CI -0.94 to -0.58); 20 mg or more (SMD -0.88, 95% CI -0.98 to -0.78).

Duration subgroups were significantly different (P < 0.0001). Shorter durations were associated with larger increases in zinc concentration: between zero and six months (SMD -0.81, 95% CI -0.88 to -0.73); between six and 12 months (SMD -0.52, 95% CI -0.58 to -0.46); 12 months or more (SMD -0.59, 95% CI -0.67 to -0.50).
Formulation subgroups were significantly different (P < 0.00001), with greatest benefit in the capsule subgroup (SMD -1.07, 95% CI -1.21 to -0.94), then the solution group (SMD -0.78, 95% CI -0.84 to -0.72), and least benefit in the pill and/or tablet subgroup (SMD -0.42, 95% CI -0.49 to -0.35).
Iron co-intervention subgroups were significantly different (P < 0.00001), with greater benefit in the subgroup not given iron: no iron (SMD -0.70, 95% CI -0.75 to -0.65); iron (SMD -0.47, 95% CI -0.54 to -0.39).

(8.2) Prevalence of zinc deficiency

Fifteen trials, six of which reported two comparisons each (total number of comparisons = 21), included 5434 participants (3% of participants in this review) and found that zinc supplementation was associated with a 51% reduction in the prevalence of zinc deficiency (RR 0.49, 95% CI 0.45 to 0.53), but heterogeneity was substantial (Chi^2 = 144.77, df = 20 (P < 0.00001); I^2 = 86%) (Analysis 1.22). There was a larger effect when calculated using random-effects (RR 0.36, 95% CI 0.27 to 0.48) and the funnel plot appeared to be skewed.

Subgroup analyses

Age subgroups were significantly different (P < 0.00001), with greater benefit in older age groups: between six and 12 months (RR 0.62, 95% CI 0.54 to 0.70); between one and five years (RR 0.41, 95% CI 0.37 to 0.47); between five and 13 years (RR 0.31, 95% CI 0.20 to 0.49).
Dose subgroups were significantly different (P < 0.00001). There did not appear to be a coherent pattern of increasing or decreasing effect across increasing doses: 5 mg to 10 mg (RR 0.34, 95% CI 0.27 to 0.44); 10 mg to 15 mg (RR 0.57, 95% CI 0.52 to 0.63); 15 mg to 20 mg (RR 0.46, 95% CI 0.24 to 0.89); 20 mg or more (RR 0.14, 95% CI 0.10 to 0.19).
Duration subgroups were significantly different (P < 0.00001). There did not appear to be a coherent pattern of increasing or decreasing effect across increasing durations: between zero and six months (RR 0.22, 95% CI 0.18 to 0.27); between six and 12 months (RR 0.59, 95% CI 0.53 to 0.67); 12 months or more (RR 0.55, 95% CI 0.48 to 0.64).
Iron co-intervention subgroups were significantly different (P < 0.00001), with greater benefit in the subgroup not given iron (RR 0.37, 95% CI 0.33 to 0.42) compared with the group given iron (RR 0.62, 95% CI 0.55, 0.69).
Formulation subgroups were significantly different (P < 0.0001), with greatest benefit in the capsule subgroup (RR 0.29, 95% CI 0.23 to 0.37), then the solution group (RR 0.49, 95% CI 0.44 to 0.54), and then the pill and/or tablet group (RR 0.59, 95% CI 0.50 to 0.68).

Adverse events

(9) Side effects

Two trials (Alarcon 2004; Mazariegos 2010) reported no adverse events, including vomiting, in either group.

(9.1) Study withdrawal

Six trials, which included data for 4263 participants (1% of participants in this review), found no significant effect on study withdrawal (RR 1.75, 95% CI 0.93 to 3.32) and heterogeneity was not significant (Chi^2 = 5.07, df = 4 (P value = 0.28); I^2 = 21%) (Analysis 1.23). There were only 37 events in total.
This meta-analysis included 3437 participants in five trials. There was no significant effect on study withdrawal.

(9.2) Participants with more than one side effect

Three trials, including data for 850 participants (< 1% of participants in this review), found some evidence of increased side effects (RR 1.13, 95% CI 1.00 to 1.27) with no heterogeneity (Chi^2 = 0.49, df = 2 (P value = 0.78); I^2 = 0%) (Analysis 1.24).

(9.3) Vomiting episodes

Five trials, one of which made two comparisons (total number of comparisons = six), included 4095 participants (2% of participants in this review) and suggest that zinc supplementation was associated with an increase in vomiting episodes (RR 1.68, 95% CI 1.61 to 1.75), though heterogeneity was considerable (Chi^2 = 34.28, df = 5 (P < 0.00001); I^2 = 85%) (Analysis 1.25). This effect appears to be slightly larger when analysed using random-effects (RR 1.85, 95% CI 1.30 to 2.63).

(9.4) Participants with more than one vomiting episode

Five trials, including data for 35,192 participants (< 17% of participants in this review) found some evidence of increased vomiting associated with supplementation (RR 1.29, 95% CI 1.14 to 1.46), with some heterogeneity (Chi^2 = 6.31, df = 4 (P value = 0.18); I^2 = 37%) (see Analysis 1.26).

(10) Haemoglobin status

(10.1) Blood haemoglobin concentration

Twenty-six trials, 10 of which made two comparisons (total number of comparisons = 36), included 6024 participants (3% of participants in the review) and reported a very small difference in blood haemoglobin concentration (SMD 0.05, 95% CI -0.00 to 0.10); heterogeneity was moderate (Chi^2 = 63.96, df = 35 (P < 0.002); I^2 = 45%) (Analysis 1.27). This effect estimate remained

trivial when estimated using random-effects (SMD 0.05, 95% CI -0.03 to 0.12). The funnel plot was generally symmetrical.

Subgroup analyses

Studies did not differ significantly in the subgroup analyses for age (P value = 0.46), dose (P value = 0.71), duration (P value = 0.12), iron co-interventions (P value = 0.40), or formulation (P value = 0.71).

(10.2) Prevalence of anaemia

Thirteen trials, six of which made two comparisons (total number of comparisons = 19), included 4287 participants (2% of participants in this review) and found no overall effect on the prevalence of anaemia (RR 1.00, 95% CI 0.95 to 1.06); heterogeneity was moderate (Chi^2 = 28.52, df = 18 (P value = 0.05); I^2 = 37%) (Analysis 1.28). The estimate was not importantly different when estimated using random-effects methods (RR 0.98, 95% CI 0.89 to 1.07), but there was evidence of some funnel plot asymmetry.

Subgroup analyses

Effects were not significantly different across age (P value = 0.34), iron co-intervention (P value = 0.93), or formulation (P value = 0.36) subgroups.

Dose subgroups were significantly different (P value = 0.01), though this was explained by one high-dose study that reported a large effect (Alarcon 2004). There did not appear to be a coherent pattern otherwise: 0 mg to 5 mg (RR 1.01, 95% CI 0.94 to 1.09); 5 mg to 10 mg (RR 0.94, 95% CI 0.47 to 1.87); 10 mg to 15 mg (RR 1.01, 95% CI 0.92 to 1.11); 15 mg to 20 mg (RR 0.76, 95% CI 0.40 to 1.46); 20 mg or more (RR 0.17, 95% CI 0.06 to 0.46).

Duration subgroups were significantly different (P value = 0.003), but this was also a consequence of one trial (Alarcon 2004): between zero and six months (RR 0.18, 95% CI 0.06 to 0.48); between six and 12 months (RR 1.01, 95% CI 0.94 to 1.08); 12 months or more (RR 1.00, 95% CI 0.90 to 1.12).

(11) Iron status

(11.1) Serum or plasma ferritin concentration

Twenty studies, five of which made two comparisons (total number of comparisons = 25), included 4474 participants (2% of participants in this review) and found that zinc supplementation was associated with a small increase in ferritin concentration (SMD -0.07, 95% CI -0.13 to -0.00), though heterogeneity was considerable (Chi^2 = 480.50, df = 24 (P < 0.00001); I^2 = 95%) (Analysis 1.29). One study in this meta-analysis reported data as medians, but excluding this study from the analysis did not affect the result importantly (SMD -0.11, 95% CI -0.17 to 0.04) (Tielsch 2006 (2)). The average effect was not importantly different when calculated using random-effects (SMD -0.13, 95% CI -0.42 to 0.15), but there was evidence of some funnel plot asymmetry.

Subgroup analyses

Studies did not differ significantly in the subgroup analyses for age (P value = 0.60).

Country income level subgroups were significantly different (P value = 0.01), but only one trial in a high-income country reported the outcome (Sandstead 2008), and it was inconsistent with the others (SMD 0.88, 95% CI 0.29 to 1.47).

Dose subgroups were significantly different (P value = 0.00009). There did not appear to be a coherent pattern of results: 0 mg to 5 mg (SMD 0.07, 95% CI -0.14 to 0.28); 5 mg to 10 mg (SMD 0.15, 95% CI -0.34 to 0.63); 10 mg to 15 mg (SMD 0.20, 95% CI 0.13 to 0.28); 15 mg to 20 mg (SMD 0.14, 95% CI -0.08 to 0.36); 20 mg or more (SMD -0.17, 95% CI -0.33 to -0.02).

Duration subgroups were significantly different (P < 0.00001), with some evidence of harm at increasing doses: between zero and six months (SMD -0.06, 95% CI -0.20 to 0.07); between six and 12 months (SMD 0.07, 95% CI -0.03 to 0.17); 12 months or more (SMD 0.34, 95% CI 0.24 to 0.45).

Iron co-intervention subgroups were significantly different (P value = 0.0009). There was statistically significant harm in the subgroup without iron (SMD 0.27, 95% CI 0.17 to 0.38) and no statistically significant effect in the subgroup with iron (SMD 0.05, 95% CI -0.02 to 0.13).

Formulation subgroups were significantly different (P < 0.00001) due to the inclusion of one outlier in the capsule group (Veenemans 2011; Veenemans 2011 (2))

(11.2) Prevalence of iron deficiency

Ten trials (comprising a total of 15 comparisons) included 3149 participants (2% of those included in the review) and found that there was no significant effect on the prevalence of iron deficiency (RR 0.99, 95% CI 0.89 to 1.10), with no significant heterogeneity (Chi^2 = 16.44, df = 14 (P value = 0.29); I^2 = 15%) (Analysis 1.30). The funnel plot appeared generally symmetrical.

Subgroup analyses

Effects were not significantly different across age (P value = 0.17), dose (P value = 0.12), duration (P value = 0.13), iron co-intervention (P value = 0.48), or formulation (P value = 0.39) subgroups.

(12) Copper status

(12.1) Serum or plasma copper concentration

Eleven trials (comprising a total of 13 comparisons), reported data for 3071 participants (1% of participants in this review) and suggested that zinc supplementation was associated with a small decrease in copper concentration (SMD 0.22, 95% CI 0.14 to 0.29), though there was substantial heterogeneity (Chi^2 = 37.47, df = 12

(P value = 0.0002); I^2 = 68%) (Analysis 1.31). This estimate was reduced when calculated using random-effects (SMD 0.11, 95% CI -0.03 to 0.25) and there was evidence of funnel plot asymmetry.

Subgroup analyses

Effects did not differ significantly among country income level (P value = 0.06), age (P value = 0.06), or iron co-intervention (P value = 0.09) subgroups.

Dose subgroups were significantly heterogeneous (P < 0.00001), but there was not a coherent pattern of results: 0 mg to 5 mg (SMD 0.08, 95% CI -0.12 to 0.27); 5 mg to 10 mg (SMD 0.31, 95% CI 0.13 to 0.49); 10 mg to 15 mg (SMD 0.01, 95% CI -0.10 to 0.12); 20 mg or more (SMD 0.46, 95% CI 0.33 to 0.59).

Duration subgroups were significantly heterogeneous (P < 0.00001). There was statistically significant harm when zinc was given for between zero and six months, and no statistically significant effect when zinc was given for longer durations: between zero and six months (SMD 0.44, 95% CI 0.33 to 0.55); between six and 12 months (SMD 0.08, 95% CI -0.04 to 0.20); 12 months or more (SMD -0.06, 95% CI -0.24 to 0.11). However, few studies were included in each group.

Formulation subgroups were significantly different (P < 0.00001), with greater harm in the pill/tablet subgroup: solution (SMD 0.37, 95% CI 0.29 to 0.46); pill and/or tablet (SMD 0.83, 95% CI 0.65 to 1.01).

(12.2) Prevalence of copper deficiency

Three trials including 1337 participants (1% of participants in this review) reported that zinc supplementation was associated with an increase in the prevalence of copper deficiency (RR 2.64, 95% CI 1.28 to 5.42), though heterogeneity was substantial (Chi^2 = 4.94, df = 2 (P value = 0.08); I^2 = 59%) (Analysis 1.32). The estimate was not significant when analysed using random-effects (RR 2.72, 95% CI 0.73 to 10.18).

Comparison 2: Zinc plus iron versus zinc alone

In addition to comparing zinc to no intervention, several trials compared zinc with iron versus zinc alone. Post hoc, we conducted additional analyses of key outcomes to test the hypothesis that delivering zinc with iron would reduce the effect of zinc.

Primary outcomes

(1) All-cause mortality

One trial reported all-cause mortality for 323 participants and the difference was not significant (RR 0.33, 95% CI 0.01 to 8.39) (Analysis 2.1).

Secondary outcomes

(2) Hospitalisation

One trial reported all-cause hospitalisation for 399 participants and the difference was not significant (RR 0.92, 95% CI 0.45 to 1.89) (Analysis 2.2).

(3) Diarrhoea

(3.1) Incidence of all-cause diarrhoea

Five trials reported the incidence of all-cause diarrhoea for 1530 participants and the difference favoured zinc alone (RR 1.10, 95% CI 1.03 to 1.18), but there was considerable heterogeneity (Chi^2 = 16.92, df = 4 (P value = 0.002); I^2 = 76%) (Analysis 2.3), and there was no difference between groups when analysed using random-effects (RR 1.07, 95% CI 0.91 to 1.25).

(3.2) Prevalence of all-cause diarrhoea

One trial reported the prevalence of all-cause diarrhoea for 399 participants and the difference was not significant (RR 0.90, 95% CI 0.76 to 1.06) (Analysis 2.4).

(3.3) Incidence of severe diarrhoea

One trial reported the incidence of severe diarrhoea for 323 participants and the difference was not significant (RR 0.78, 95% CI 0.59 to 1.04) (Analysis 2.5).

(3.4) Hospitalisation due to all-cause diarrhoea

One trial reported hospitalisation due to diarrhoea for 399 participants and the difference was not significant (RR 0.99, 95% CI 0.25 to 3.88) (Analysis 2.6).

(4) Incidence of LRTI

Three trials reported the prevalence of all-cause diarrhoea for 1065 participants and the difference was not significant (RR 0.93, CI 0.83 to 1.04), with no important heterogeneity (Chi^2 = 2.52, df = 2 (P value = 0.28); I^2 = 21%) (Analysis 2.7).

(5) Incidence of malaria

One trial reported the incidence of malaria for 419 participants and the difference was not significant (RR 0.86, 95% CI 0.59 to 1.24) (Analysis 2.8).

(6) Growth

(6.1) Height

Five trials reported height for 1517 participants and the difference was not significant (SMD 0.06, 95% CI -0.04 to 0.16), with no heterogeneity (Chi^2 = 3.54, df = 4 (P value = 0.47); I^2 = 0%) (Analysis 2.9).

(6.2) Weight

Four trials reported weight for 910 participants and the difference was not significant (SMD 0.12, 95% CI -0.01 to 0.25), with no important heterogeneity (Chi² = 2.29, df = 3 (P value = 0.51); I² = 0%) (Analysis 2.10).

(6.3) Weight-to-height ratio

Four trials reported weight-to-height ratio for 933 participants and the difference was not significant (SMD 0.06, 95% CI -0.07 to 0.19), with no heterogeneity (Chi² = 1.36, df = 3 (P value = 0.71); I² = 0%) (Analysis 2.11).

(6.4) Prevalence of stunting

Two trials reported stunting for 462 participants (RR 0.92, 95% CI 0.85 to 0.99) but the studies appeared to be inconsistent (Chi² = 1.82, df = 1 (P value = 0.18); I² = 45%) (Analysis 2.12).

(7) Zinc status

(7.1) Serum or plasma zinc concentration

Eight trials reported serum zinc concentration for 1337 participants and the difference favoured zinc alone (SMD 0.16, 95% CI 0.05 to 0.27), but there was considerable heterogeneity (Chi² = 17.84, df = 7 (P value = 0.01); I² = 61%) (Analysis 2.13), and the difference between groups was no longer significant when analysed using random-effects (SMD 0.14, 95% CI -0.05 to 0.33).

(7.2) Prevalence of zinc deficiency

Three trials reported the prevalence of zinc deficiency for 350 participants and the difference was not significant (RR 1.42, 95% CI 0.75 to 2.68) (Analysis 2.14).

Adverse events

(8) Study withdrawal

Two trials reported study withdrawal for 557 participants and the difference was not significant (RR 1.41, 95% CI 0.91 to 2.18) (Analysis 2.15).

(9) Haemoglobin status

Eight trials reported blood haemoglobin concentration for 1341 participants and the difference favoured zinc with iron (SMD -0.23, 95% CI -0.34 to -0.12), but there was considerable heterogeneity (Chi² = 33.53, df = 7 (P < 0.00001); I² = 79%) (Analysis 2.16), and the difference between groups was no longer significant when analysed using random-effects (SMD -0.21, 95% CI -0.47 to 0.05).

(10) Iron status

(10.1) Serum or plasma ferritin concentration

Six trials reported serum ferritin concentration for 945 participants and the difference favoured zinc with iron (SMD -1.78, 95% CI -1.99 to -1.56); there was considerable heterogeneity (Chi² = 927.92, df = 5 (P < 0.00001); I² = 99%) (Analysis 2.17), and the range of possible effects appears wider (less certain) when analysed using random-effects (SMD -3.28, 95% CI -6.27 to -0.30).

(10.2) Prevalence of iron deficiency

Two trials reported the prevalence of iron deficiency for 248 participants and the difference favoured zinc with iron (RR 0.12, 95% CI 0.04 to 0.32) (Analysis 2.18).

(11) Copper status

Two trials reported serum copper concentration for 353 participants and the difference was not significant (SMD 0.06, 95% CI -0.15 to 0.27), with no heterogeneity (Chi² = 0.11, df = 1 (P value = 0.74); I² = 0%) (Analysis 2.20).

DISCUSSION

Summary of main results

See Summary of findings for the main comparison for an overview of the main results and quality of the evidence.

Primary outcomes

The effect of preventive zinc supplementation on all-cause mortality was not statistically significant, but these results are consistent with a small reduction in mortality. Cause-specific mortality due to diarrhoea, lower respiratory tract infection (LRTI), and malaria are thought to be key pathways through which zinc deficiency leads to increased overall mortality. This review's pooled estimates for mortality due to diarrhoea, LRTI, and malaria were not statistically significant; however, all of these estimates were consistent with a previous review suggesting that there are small benefits of zinc supplementation (Black 2013). To change the conclusions of this review, additional studies would need to be extremely large and very precise. It seems unlikely that further research will affect the primary outcome.

Secondary outcomes

Zinc supplementation was associated with significant reductions in diarrhoea incidence and prevalence. Supplementation resulted in very small, but statistically significant, improvements in most growth-related outcomes; however, these may be too small to be clinically significant. Zinc status also reflects significant, medium to large improvements as a result of supplementation. Supplementation did not significantly affect reported hospitalisation outcomes. There were no significant effects on LRTI, and malaria incidence and prevalence.

Adverse events

Supplementation may be associated with increased vomiting. Supplementation had no important effect on haemoglobin or iron status, but it may have a negative effect on copper status. Most studies provided supplements as zinc sulfate and it is unclear if the chemical formulation may relate to side effects.

Overall completeness and applicability of evidence

Overall, the external validity of this review is strong. This review included 80 studies conducted in a large number of countries. Almost all outcomes of interest were reported in multiple trials and almost all meta-analyses included over 1000 participants. Non-stunted and stunted children of both genders and all eligible ages were represented in the included trials and numerous types of preventive zinc supplementation characteristics are represented. Clinical outcomes were investigated, as well as side effects and biochemical outcomes (such as zinc status). Furthermore, there was no important heterogeneity among studies for the primary outcomes of this review. Given these strengths, there may be no need for further placebo-controlled trials of the effects of preventive zinc supplementation for the population and outcomes of this review.

Setting

Most of the studies in this review were conducted in low- or middle-income countries, and a wide range of such countries are represented. The evidence of this review may not be as applicable in high-income countries, as the risk of zinc deficiency is a greater problem in low- and middle-income countries.

Among low- and middle-income countries, there is inter- and intra-country variation. For instance, zinc supplementation may be more effective in settings with relatively low levels of meat intake, high levels of undernutrition, and high population-level risk of zinc deficiency. The impact of supplementation may also vary with varying levels of fibre and phytate consumption.

The effectiveness of zinc might also be influenced by differing disease prevalence and pathogen profiles among low- and middle-income countries. For instance, particular micronutrient supplementation interventions may have differing levels of benefit or harm when delivered in malaria endemic versus non-endemic areas (Sazawal 2006). The impact of supplementation might also be influenced by the particular infectious, disease-causing pathogens in a given area (Patel 2011).

Participant characteristics

The full range of eligible ages was represented among participants in this review. However, the majority of studies - including the largest three trials - did not include children over five years of age. Most of the age subgroup analyses, including the analysis for all-cause mortality, did not indicate that the effects of zinc supplementation were significantly different for different age groups. However, of those that did indicate a difference, supplementation was generally more effective in the one to five years age group than the six to 12 months group. This possible association must be interpreted with caution; trials may be more likely to report disaggregated data for participant subgroups when these groups are significantly different, and subgroup analyses in systematic reviews often yield false positive results (Guyatt 2008; Guyatt 2011a).

Stunted children were also represented in this review, as illustrated by the number of studies that included stunted children and the median baseline height-for-age z-scores across trials. Most stunting subgroup analyses indicated that the effects of supplementation for stunted children were similar to those for non-stunted children. However, due to a lack of data reported separately for stunted versus non-stunted children, this review might have been underpowered to detect any meaningful effect modification by stunting status.

Intervention implementation

The evidence from this review seems applicable to preventive zinc supplementation programmes with a variety of doses, durations, co-interventions, and formulations. Furthermore, there was not strong evidence of meaningful effect modification based on dose, duration, presence or absence of an iron co-intervention, or formulation. Significant subgroup differences were generally inconsistent across outcomes, heterogeneity was often high even within individual subgroups, and subgroup differences often lacked a coherent directionality (for example, higher doses leading to greater effects).

For many subgroup analyses, a few studies contributed most of the weight and the tests for subgroup differences were underpowered. Furthermore, certain types of effect modification, such as a gradient of effectiveness based on dose, might be more conducive to meta-regression analysis than categorical subgroup analysis. There could have been a relationship between effect estimates and dose or effect estimates and duration that the subgroup analyses in this review were unable to detect.

Furthermore, though we analysed studies of zinc with an iron co-intervention versus those without an iron co-intervention, this review was not primarily designed to explore this relationship fully. It has been shown previously that co-supplementation of iron and zinc may reduce the efficacy of zinc for growth (Imdad 2011). This aspect is very important as there are existing programmes of iron supplementation for prevention of anaemia using multiple micronutrients or additional zinc and co-supplementation with iron might decrease the desired preventive effect of zinc supplementation. Our subgroup analyses identified few statistically significant differences between subgroups receiving an iron co-intervention versus subgroups not receiving an iron co-intervention; however, there were relatively few studies in most analyses. Within trials

that made multiple comparisons, effects for groups receiving an iron co-intervention were not consistently different from effects for groups without an iron co-intervention (Comparison 2: Zinc versus zinc plus iron).

Quality of the evidence

This review included 80 studies with approximately 205,923 children, who were evaluated for mortality, morbidity, growth, and adverse event outcomes. We used the GRADE framework to assess the quality of evidence for outcomes in this review based on the following factors: indirectness of evidence, unexplained heterogeneity, publication bias, risk of bias due to study design limitations, and imprecision of results (Balshem 2011).

The meta-analysis of all-cause mortality included outcomes for 138,302 participants in 14 studies. For all-cause and cause-specific mortality outcomes, the quality of evidence was moderate to high. Thus, there may be no need for further placebo-controlled trials analysing the effects of preventive zinc supplementation on mortality in the population of this review. As discussed above, indirectness of evidence did not seem to be a significant problem for this review, because it did not have to use proxies for its populations, interventions, and outcomes of interest. There was no significant heterogeneity among studies in the mortality meta-analyses. Though it is difficult to evaluate the probability of publication bias accurately, no such bias was detected for the primary outcomes through funnel plot inspections.

The three largest studies in this review, which accounted for almost all of the effects in each mortality meta-analysis, were at low risk of bias for sequence generation, allocation concealment, blinding, and incomplete outcome data. Many studies in this review were at high risk of bias due to selective outcome reporting. However, it seems unlikely that selective reporting substantially biased the results of the mortality meta-analyses given that the three largest studies in this review all reported mortality outcomes. Thus, even if mortality outcome data were selectively withheld from the trial reports of certain studies, these studies would not likely be numerous or large enough to influence the results of the primary analysis. In terms of imprecision, the 95% confidence interval for all-cause mortality suggests that the intervention is highly unlikely to cause appreciable harm. The confidence intervals for mortality due to diarrhoea or LRTI included the possibility of harm and there were also few cause-specific deaths observed due to diarrhoea, LRTI, or malaria. We thus downgraded the latter outcomes and considered them to be moderate rather than high-quality evidence.

Compared to the primary outcomes of this review, the quality of evidence for the secondary outcomes and adverse events was more mixed. Heterogeneity was significant for some of these outcomes and this heterogeneity remained largely unexplained even after subgroup analyses were undertaken. Due to unexplained heterogeneity, we downgraded incidence of all-cause diarrhoea, incidence of malaria, and height from high to moderate quality. Selective reporting was also more likely to influence secondary outcomes with meta-analyses involving relatively small numbers of participants.

Inverse variance methods may give biased results for rare events, but the overall effects are small and many are not significant; small biases in the methods may have minimal consequences for the results and interpretation.

Potential biases in the review process

This review had several strengths in terms of preventing bias. Its search was comprehensive and yielded both unpublished and non-English language trial reports. Two independent review authors extracted data to reduce the possibility of errors and bias being introduced by a single extractor. Numerous trials presented at least some baseline, outcome, or risk of bias data that were unclear, incomplete, discrepant, or reported for some trial participants outside of the age range of this review. Whenever the relevant contact information could be obtained, we contacted the authors of such trials at least twice to obtain clarification or disaggregated data (or both). This comprehensive process of contacting authors improved the completeness of data in this review.

However, as with any systematic review, subjective judgements and decisions had to be made during the research process. We made attempts to be transparent about any such judgement calls in the text of this review, and in the Characteristics of included studies and Characteristics of excluded studies tables.

In areas of research with less evidence or areas with rapid publication, our searches could be considered outdated. However, large trials are unlikely to change the main conclusions of this review, so it may not be necessary to update the searches and analyses for several years.

Agreements and disagreements with other studies or reviews

The results of this review were generally consistent with those of past systematic reviews of zinc supplementation. This was true of mortality outcomes (previously investigated by Brown 2009, Patel 2011 and Yakoob 2011) and diarrhoea morbidity outcomes (previously investigated by Bhutta 1999, Aggarwal 2007, Brown 2009, Patel 2011 and Yakoob 2011).

Previously, reviews have generally found a beneficial impact of zinc supplementation on LRTI (Bhutta 1999; Aggarwal 2007; Brown 2009; Lassi 2010; Roth 2010; Yakoob 2011). The results of this review do not support this finding. However, this discrepancy might be due to slightly differing inclusion criteria and eligible LRTI outcome definitions. For example, Lassi 2010 included studies with children infected with HIV, while we excluded them. Similarly, Brown 2009 included studies with children younger than six months of age while we excluded them; however, differing age criteria did not seem to account for all of the differences in results.

Zinc supplementation may be more beneficial for severe LRTI or LRTI that meets more specifically defined clinical criteria (Roth 2010). While this review indicates a slight, statistically insignificant harm in terms of malaria incidence, one other review indicated a statistically insignificant benefit (Yakoob 2011).

Previously reviews have disagreed on whether supplementation has a significant positive effect on growth outcomes (Brown 2002; Brown 2009; Imdad 2011) or not (Ramakrishnan 2009). Though this review does not fully explain this disagreement, it does support the hypothesis that supplementation may have a very small but positive effect on growth. As shown by the age subgroup analysis for height and weight, zinc may be more effective at improving growth outcomes in the five to 13 years of age subgroup. Thus, one potential reason for the disagreement between previous reviews is the fact that Brown 2002 and Brown 2009 included participants older than five years of age and Ramakrishnan 2009 did not.

The results of this review are also generally consistent with past investigations of zinc (Brown 2002; Brown 2009), haemoglobin (Brown 2009; Dekker 2010), and iron status (Brown 2009). However, while this review indicates that supplementation has a negative effect on copper status, one past review indicated no effect (Brown 2009).

Finally, previous reviews have attempted to explain heterogeneity related to the impact of zinc supplementation. Two reviews have suggested that age may modify the impact of supplementation, with benefits limited to children one year of age or older (Brown 2009; Patel 2011). Subgroup analyses for some outcomes in this review were consistent with this hypothesis. However, this potential association could be spurious; indeed, Patel 2011 notes that studies in their review with higher age groups also appeared to be at higher risk of bias.

AUTHORS' CONCLUSIONS

Implications for practice

The benefits, harms, and costs of preventive zinc supplementation should be carefully considered when deciding whether or not to use this intervention. On the one hand, supplementation positively impacted zinc status and diarrhoea morbidity. There were statistically significant effects for growth outcomes, but these may not be clinically important. Supplementation may have had a small positive impact on all-cause mortality, though the effects of zinc on this outcome, and on most hospitalisation, lower respiratory tract infection (LRTI), and malaria outcomes, were not statistically significant. On the other hand, supplementation was associated with increased vomiting and worsened copper status, though it was not associated with any important effect on haemoglobin or iron status. Balancing these factors, the benefits of zinc supplementation would outweigh the harms in low- and middle-income countries where the risk of zinc deficiency is relatively high.

It has been argued that zinc supplementation, as part of a package of interventions to reduce undernutrition among preschoolers, is among the most cost-effective interventions for advancing human welfare (Horton 2009).

However, preventive zinc supplementation is not a sufficient or long-term solution to the nutrition and health challenges facing children in resource-scarce settings. Children ultimately need well-balanced diets, and poverty is often a risk factor for undernutrition and pathogen exposure. Unfortunately, until these issues are effectively addressed, zinc deficiency (and the mortality, morbidity, and growth deficits associated with it) will likely remain. The evidence suggests that preventive zinc supplementation offers a short-term intervention to help alleviate these problems in resource-scarce settings. It may also be pragmatic and effective to deliver zinc supplementation along with other public health interventions such as growth monitoring. Furthermore, fortification may be beneficial in areas where food production and processing systems could enrich foods with zinc (Hotz 2004; Hess 2009a).

On the basis of our review findings, policymakers may wish to consider preventive zinc supplementation as one of the public health and nutrition interventions offered to children at risk in low- and middle-income countries. Where zinc supplements are locally available, clinicians in such settings could provide them to children under their care who likely lack sufficient dietary zinc intake. However, the evidence also suggests that monitoring for side effects, such as vomiting, may be required. Finally, families can be encouraged to recognise the importance of adequate dietary zinc for their children.

Implications for research

Populations

Finding ways to improve the delivery of zinc to hard to reach populations (for example, the poorest of the poor) is one of the most important priorities to reduce mortality and morbidity due to childhood diarrhoeal disease (Wazny 2013).

Children with severe protein-energy malnutrition were excluded from this review, as well as children with chronic diseases such as cystic fibrosis and sickle cell disease. The effects of zinc in populations with co-morbidities such as these could be examined in future systematic reviews. As mentioned above, two Cochrane reviews have already addressed the effects of zinc supplementation in populations with HIV (Humphreys 2010; Irlam 2010).

Interventions

Although zinc is an apparently simple intervention, a large study of vitamin A supplementation (Awasthi 2013), which is inconsistent with a large body of previous research (Mayo-Wilson 2011), demonstrates that interventions with proven effectiveness may fail

to scale-up if they are not implemented with fidelity. Further research is needed to determine the best way to ensure the effective delivery of zinc supplementation on a large scale (Wazny 2013). This review has not confirmed the optimal range of doses, durations, frequencies, or formulations necessary for zinc supplementation to achieve clinically meaningful improvements in mortality, morbidity, or growth outcomes. Future studies could try to specify these optimal intervention characteristics better. In addition, the timing of when preventive supplementation should be initiated in children could be further investigated. For instance, a few studies in this review started several months of preventive supplementation immediately after participants received therapeutic supplementation for an episode of diarrhoea (Sazawal 1996; Larson 2010). In addition, future studies could further evaluate fortification and dietary change interventions as alternative means of addressing zinc deficiency. These could be compared to a zinc supplementation intervention.

Outcomes

Overall, this review presents strong evidence for the effectiveness of preventive zinc supplementation on most of the outcomes analysed. Many of the conclusions of this review would be robust to the results of further preventive zinc supplementation trials. Further updates of this review are unlikely to come to different conclusions in the absence of extremely large trials with importantly different results.

ACKNOWLEDGEMENTS

We thank the Cochrane Developmental Psychosocial and Learning Problems Group (especially Margaret Anderson, Laura MacDonald, and Geraldine Macdonald) for help with the preparation of the protocol and review, the Cochrane Methods Group for statistical advice and assistance, and anonymous peer reviewers for their feedback. Chris Champion generously extracted one study in Portuguese. We would also like to thank Dr Jai Das, who helped with double data extraction for additional analysis of zinc plus iron.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Ahmed 2009a

Methods	CRCT?: IRCT; Cross-over?: non-cross-over
Participants	Country: Bangladesh; Setting: Mirpur, a slum area in Dhaka; Urbanicity: urban Inclusion criteria: healthy Exclusion criteria: history of gastrointestinal disorder; suffered from any diarrhoeal disease in the past 2 weeks; febrile illness in the preceding week; received antibiotic treatment at least 7 days prior to enrolment; ≤ 2 SD (weight/length as NCHS); stool that was positive for common enteric pathogens *Baseline characteristics* Avg age (mo): 14; Min age (mo): 10; Max age (mo): 18; % Female: 53 Avg HAZ: N/A; Stunting: unclear; Avg height (cm): 74.3; Avg zinc concentration (μg/dL): 73 Total N: 40; Group 1 N: 20; Group 2 N: 20
Interventions	*Group 1:* zinc Formulation: solution; Compound: acetate; Frequency: daily; Duration (mo): 1.5; Dose (mg): 20; Co-intervention(s): oral inactivated cholera vaccine *Group 2*: no zinc Placebo not given; Co-intervention(s): oral inactivated cholera vaccine
Outcomes	No outcomes of interest reported in a way that can be meta-analysed
Notes	- In addition to the study groups mentioned in this table, there was a group of participants who received zinc only; but there was no placebo group to which this zinc group could be compared in this review. So, baseline characteristics reported in this table are weighted averages of all groups except this zinc group, since this group is not included in any meta-analyses in this review - The trial authors might have meant to report "≤ -2 SD (weight/length as NCHS)" rather than "≤ 2 SD (weight/length as NCHS)" as part of this study's exclusion criteria

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The children were randomly assigned…" Comment: insufficient details available to make a judgement as to whether or not an allocation sequence was generated using a truly random method
Allocation concealment (selection bias)	Unclear risk	Quote: N/A Comment: insufficient details available to make a judgement

Blinding of participants (performance bias) All outcomes	Unclear risk	Quote: "...no zinc placebo was administered…" Comment: given that no placebo was provided, it seems likely that people involved with the study were aware of which study group participants were in. It is unclear how measured outcomes might be influenced by this lack of blinding
Blinding of personnel (performance bias) All outcomes	Unclear risk	Quote: "...no zinc placebo was administered…" Comment: given that no placebo was provided, it seems likely that people involved with the study were aware of which study group participants were in. It is unclear how measured outcomes might be influenced by this lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "...no zinc placebo was administered…" Comment: given that no placebo was provided, it seems likely that people involved with the study were aware of which study group participants were in. It is unclear how measured outcomes might be influenced by this lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	% Missing: 5 Reasons/details: N/A Comment: 5% of the randomised participants eligible for our review had data missing; this 5% missing figure includes all groups except the zinc group, since this group is not included in any meta-analyses in this review. 2 children, both in the vaccine + zinc group, did not complete the study. Reasons for missing data were not given. However, the amount of missing data seems too minimal to impact results
Selective reporting (reporting bias)	Unclear risk	Comment: no trial protocol referenced by the study
Other bias	Low risk	Comment: appears to be free of other bias

Akramuzzaman 1994

Methods	CRCT?: IRCT; Cross-over?: non-cross-over
Participants	Country: Bangladesh; Setting: N/A; Urbanicity: peri-urban Inclusion criteria: undernourished Exclusion criteria: N/A *Baseline characteristics* Avg age (mo): 34.8; Min age (mo): N/A; Max age (mo): N/A; % Female: N/A Avg HAZ: N/A; Stunting: both - separate data not given; Avg height (cm): N/A; Avg zinc concentration (μg/dL): N/A Total N: 256; Group 1 N: N/A; Group 2 N: N/A
Interventions	*Group 1:* zinc Formulation: solution; Compound: acetate; Frequency: daily; Duration (mo): 15; Dose (mg): 20; Co-intervention(s): Vitamins A, D, and C *Group 2*: no zinc Placebo given; Co-intervention(s): Vitamins A, D, and C
Outcomes	Height, weight Time point (wk): 60
Notes	Though "both baseline and final measurements of weight and height were available in 197 (93 and 104 in zinc and placebo groups respectively) children", the numbers of children initially randomised to each group is not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "…randomized clinical trial…" Comment: insufficient details available to make a judgement as to whether or not an allocation sequence was generated using a truly random method
Allocation concealment (selection bias)	Unclear risk	Quote: N/A Comment: insufficient details available to make a judgement
Blinding of participants (performance bias) All outcomes	Unclear risk	Quote: "...double blind…clinical trial..." Comment: insufficient details available to make a judgement
Blinding of personnel (performance bias) All outcomes	Unclear risk	Quote: "...double blind…clinical trial..." Comment: insufficient details available to make a judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "...double blind…clinical trial..." Comment: insufficient details available to make a judgement

Akramuzzaman 1994 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	% Missing: N/A Reasons/details: N/A Comment: "Of 256 children, both baseline and final measurements of weight and height were available in 197 (93 and 104 in zinc and placebo groups respectively) children." So, no more than 59 participants (23% of the original 256 randomised) were missing. However, the number randomised to each study group was not reported; nor was the exact number of participants missing in the zinc group, the exact number of participants missing in the placebo group, or reasons for missing data
Selective reporting (reporting bias)	Unclear risk	Comment: no trial protocol referenced by the study
Other bias	Low risk	Comment: appears to be free of other bias

Alarcon 2004

Methods	CRCT?: IRCT; Cross-over?: non-cross-over
Participants	Country: Peru; Setting: Collique, a shanty town of Lima, Peru; Urbanicity: peri-urban Inclusion criteria: moderately anaemic (haemoglobin concentration between 70 and 99.9 g/L) Exclusion criteria: severe anaemia (haemoglobin < 70.0 g/L); mild anaemia (haemoglobin 100.0 to 109.9 g/L); chronic disease; any dietary restrictions; received treatment with one of the micronutrients in the study in the previous 6 mo; measles; received a measles vaccine in the preceding 2 mo; severe malnutrition (defined as weight-for-height < -3 SDs, height-for-age < -3 SDs, or both) *Baseline characteristics* Avg age (mo): 17.4; Min age (mo): 6; Max age (mo): 35; % Female: N/A Avg HAZ: -1.04; Stunting: unclear; Avg height (cm): 76.8; Avg zinc concentration (μg/dL): N/A Total N: 223; Group 1 N: 112; Group 2 N: 111
Interventions	*Group 1:* zinc Formulation: solution; Compound: sulfate; Frequency: 6 days/wk; Duration (mo): 4.5; Dose (mg): 3 mg/kg; Co-intervention(s): 3 mg/kg iron *Group 2*: no zinc Placebo given; Co-intervention(s): 3 mg/kg iron
Outcomes	Incidence of all-cause diarrhoea, prevalence of all-cause diarrhoea, height, weight, weight-to-height ratio, study withdrawal, participants with $\geq$ 1 side effect, blood haemoglobin concentration, prevalence of anaemia, serum or plasma ferritin concentration, prevalence of iron deficiency

	Time point (wk): 18	
Notes	In addition to the study groups mentioned in this table, there was a group of 112 participants who received zinc, iron, and vitamin A. Baseline characteristics reported in this table are weighted averages of all groups except the group that received zinc, iron, and vitamin A, since this group is not included in any meta-analyses in this review	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "The children were...allocated by block randomization…" Comment: insufficient details available to make a judgement as to whether or not an allocation sequence was generated using a truly random method
Allocation concealment (selection bias)	Unclear risk	Quote: N/A Comment: insufficient details available to make a judgement
Blinding of participants (performance bias) All outcomes	Low risk	Quote: "This was a...double-blind trial…Supplements, prepared as syrup, were individually bottled and coded according to treatment group. The code was known only to the pharmacist and was not broken until the data analyses were completed. The placebos were tested before the study started, and no visual or organoleptic differences in the preparations could be detected." Comment: sufficient blinding seems likely
Blinding of personnel (performance bias) All outcomes	Low risk	Quote: "This was a...double-blind trial…Supplements, prepared as syrup, were individually bottled and coded according to treatment group. The code was known only to the pharmacist and was not broken until the data analyses were completed. The placebos were tested before the study started, and no visual or organoleptic differences in the preparations could be detected." Comment: sufficient blinding seems likely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "This was a...double-blind trial…Supplements, prepared as syrup, were individually bottled and coded

		according to treatment group. The code was known only to the pharmacist and was not broken until the data analyses were completed. The placebos were tested before the study started, and no visual or organoleptic differences in the preparations could be detected." Comment: sufficient blinding seems likely
Incomplete outcome data (attrition bias) All outcomes	Low risk	% Missing: 4 Reasons/details: in the zinc + iron group: 2 "moved", and 1 withdrew because their mothers "believed after 5-7 wk of treatment that their children were 'healthy' and refused further treatment." In the iron group: 2 "moved", 2 withdrew because their mothers "believed after 5-7 wk of treatment that their children were 'healthy' and refused further treatment", 1 was "absent at last sampling", and 2 "stopped treatment for perceived side effects (constipation, stomachaches, and staining of the teeth)." Comment: 4% of the randomised participants eligible for our review had data missing; this 4% missing figure includes all groups except the group that received zinc, iron, and vitamin A, since this group is not included in any meta-analyses in this review. Missing data seem too minimal to impact results
Selective reporting (reporting bias)	Unclear risk	Comment: no trial protocol referenced by the study
Other bias	Low risk	Comment: appears to be free of other bias

Albert 2003

Methods	CRCT?: IRCT; Cross-over?: non-cross-over
Participants	Country: Bangladesh; Setting: Dhaka; Urbanicity: urban Inclusion criteria: vitamin A deficiency (serum retinol level < 20 μg/dL; determined by testing of a blood sample obtained for pre-enrolment screening); nutritional status corresponding to a weight-for-age score that was ≥ 61% of the median National Center for Health Standards standard Exclusion criteria: received vitamin A supplementation during the preceding 6 months; history of night blindness or sickness due to underlying illnesses such as diarrhoea, respiratory tract infections, or other infections

Albert 2003 (*Continued*)

	Baseline characteristics Avg age (mo): N/A; Min age (mo): 24; Max age (mo): 60; % Female: N/A Avg HAZ: N/A; Stunting: unclear; Avg height (cm): N/A; Avg zinc concentration (μg/dL): 62 Total N: 256; Group 1 N: N/A; Group 2 N: N/A; Group 3 N: N/A; Group 4 N: N/A
Interventions	*Group 1:* zinc Formulation: solution; Compound: acetate; Frequency: daily; Duration (mo): 1.5; Dose (mg): 20; Co-intervention(s): killed oral cholera vaccine *Group 2*: no zinc Placebo given; Co-intervention(s): killed oral cholera vaccine *Group 3:* zinc Co-intervention(s): killed oral cholera vaccine; 200,000 IU vitamin A syrup 2 weeks after the start of zinc supplementation *Group 4*: no zinc Placebo given; Co-intervention(s): killed oral cholera vaccine; 200,000 IU vitamin A syrup 2 weeks after the start of zinc supplementation
Outcomes	Prevalence of zinc deficiency Time point (wk): 6
Notes	- At the end of the study, 61, 63, 62, and 63 children remained in the vitamin A, zinc, vitamin A + zinc, and placebo groups, respectively; however, the number of children randomised to each study group is not reported - Though the percentage of trial participants who were female is approximately 44%, the reported ratio of boys to girls did not add up in the zinc group - Though the unit of baseline zinc concentration was reported to be mg/dL, it seems that the unit should be mg/L. Assuming that the intended unit of zinc concentration was actually mg/L, then the average baseline zinc concentration was 62 μg/dL

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "…children were randomly assigned…The randomization code…" Comment: Though a "randomization code" was used, there are insufficient details available to make a judgement as to whether or not an allocation sequence was generated using a truly random method
Allocation concealment (selection bias)	Low risk	Quote: "The randomization code was broken after completion of the study. Bottles of syrup were serially numbered according to the randomization list, and this numbering corresponded to the study serial numbers. Enrolled children were assigned numbered bottles in the order in which they were re-

Albert 2003 (*Continued*)

		cruited." Comment: indicates sequentially numbered drug containers of identical appearance to conceal allocation
Blinding of participants (performance bias) All outcomes	Low risk	Quote: "...double-blind trial…" "The zinc syrup and its placebo syrup looked very similar…The randomization code was broken after completion of the study. " Comment: sufficient blinding seems likely
Blinding of personnel (performance bias) All outcomes	Low risk	Quote: "...double-blind trial…" "The zinc syrup and its placebo syrup looked very similar…The randomization code was broken after completion of the study. " Comment: sufficient blinding seems likely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "...double-blind trial…" "The zinc syrup and its placebo syrup looked very similar…The randomization code was broken after completion of the study. " Comment: sufficient blinding seems likely
Incomplete outcome data (attrition bias) All outcomes	Low risk	% Missing: 3 Reasons/details: N/A Comment: missing data seem too minimal to impact results
Selective reporting (reporting bias)	High risk	Comment: serum zinc concentration was measured, but is not reported in a way that can be meta-analysed
Other bias	Low risk	Comment: appears to be free of other bias

Albert 2003 (2)

Methods	
Participants	
Interventions	
Outcomes	Prevalence of zinc deficiency
Notes	As Albert 2003 above

Ba Lo 2011

Methods	CRCT?: IRCT; Cross-over?: non-cross-over
Participants	Country: Senegal; Setting: neighbourhood of Dakar; Urbanicity: urban Inclusion criteria: length-for-age z score (LAZ) and weight-for-length z score (WLZ) > -2.0 with respect to the World Health Organization growth standard; haemoglobin concentration > 80 g/L; no consumption of zinc-fortified foods or zinc-containing vitamin-mineral supplements; no symptomatic infections within the preceding 2 wk Exclusion criteria: N/A *Baseline characteristics* Avg age (mo): 13.2; Min age (mo): 9; Max age (mo): 17; % Female: 52.6 Avg HAZ: -0.44; Stunting: non-stunted; Avg height (cm): 75; Avg zinc concentration (μg/dL): 63.3 Total N: 97; Group 1 N: 50; Group 2 N: 47
Interventions	*Group 1:* zinc Formulation: solution; Compound: sulfate; Frequency: daily; Duration (mo): 0.5; Dose (mg): 6; Co-intervention(s): 200 mg albendazole as a single oral dose at enrolment; 30 g dry weight iron-fortified cereal porridge; a liquid multivitamin supplement *Group 2*: no zinc Placebo given; Co-intervention(s): 200 mg albendazole as a single oral dose at enrolment; 30 g dry weight iron-fortified cereal porridge; a liquid multivitamin supplement
Outcomes	Serum or plasma zinc concentration Time point (wk): 2
Notes	In addition to the study groups mentioned in this table, there was a group of 40 participants who received 30 g dry weight iron-fortified cereal porridge with added zinc to provide 6 mg zinc per 25 g dry weight of porridge, but who did not receive any zinc supplement. Baseline characteristics reported in this table are weighted averages of all groups except this "ZnFort group", since this group is not included in any meta-analyses in this review

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Eligible children were randomly assigned to 1 of 3 treatment groups for a 15-d period by using a computer-generated block randomization scheme, with a varied block length of 3, 6, or 9 (www.randomization.com)." Comment: N/A
Allocation concealment (selection bias)	Unclear risk	Quote: N/A Comment: insufficient details available to make a judgement

Blinding of participants (performance bias) All outcomes	Low risk	Quote: "A double-blind intervention trial…Group assignments remained masked until all biochemical and statistical analyses were completed." Comment: sufficient blinding seems likely
Blinding of personnel (performance bias) All outcomes	Low risk	Quote: "A double-blind intervention trial…Group assignments remained masked until all biochemical and statistical analyses were completed." Comment: sufficient blinding seems likely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "A double-blind intervention trial…Group assignments remained masked until all biochemical and statistical analyses were completed." Comment: sufficient blinding seems likely
Incomplete outcome data (attrition bias) All outcomes	High risk	% Missing: 32 Reasons/details: in the zinc group: 2 participants were missing due to illness, 6 due to travel, 7 due to "insufficient consumption of porridge", and 1 due to withdrawn consent. In the control group: 1 participant was missing due to illness, 6 due to travel, 5 due to "insufficient consumption of porridge", and 3 due to withdrawn consent Comment: 32% of the randomised participants eligible for our review had data missing; this 32% missing figure includes all groups except the "ZnFort group", since the ZnFort group is not included in any meta-analyses in this review. A large proportion of data is missing. Different proportions of each study group were missing due to "insufficient consumption of porridge" and withdrawn consent. Those who were randomised, but not analysed also had slightly different anthropometric data at baseline
Selective reporting (reporting bias)	Low risk	Comment: length, weight, and haemoglobin concentration were measured at baseline and at the end of the supplementation period, but are not reported as post-intervention outcomes. Diarrhoea prevalence was measured, but is not reported in a way that can be meta-analysed. All of these outcomes were pre-specified in the protocol

		for this study. However, the authors of this study explained that there was probably not sufficient time to allow for detectable differences in morbidity or growth, and that these outcomes were included in the measurements simply to control for any baseline differences or possible confounding Protocol identifier: NCT0094398
Other bias	Low risk	Comment: appears to be free of other bias

Baqui 2003

Methods	CRCT?: IRCT; Cross-over?: non-cross-over
Participants	Country: Bangladesh; Setting: Matlab subdistrict; Urbanicity: rural Inclusion criteria: N/A Exclusion criteria: fed infant formula; severe malnutrition (mid-upper arm circumference (MUAC) < 110 mm); severe anaemia (haemoglobin concentration < 90 g/L); signs of neurological disorders, physical disability, or chronic illness that might affect feeding, activity, and cognitive development; family not planning to stay in the trial area for 6 mo *Baseline characteristics* Avg age (mo): 6; Min age (mo): 6; Max age (mo): 6; % Female: 47.2 Avg HAZ: -1.2; Stunting: both - separate data not given; Avg height (cm): 64.1; Avg zinc concentration (μg/dL): 67.6 Total N: 645; Group 1 N: 161; Group 2 N: 157; Group 3 N: 162; Group 4 N: 165
Interventions	*Group 1:* zinc Formulation: solution; Compound: acetate; Frequency: weekly; Duration (mo): 6; Dose (mg): 20; Co-intervention(s): 1 mg riboflavin *Group 2*: no zinc Placebo given; Co-intervention(s): 1 mg riboflavin *Group 3:* zinc Co-intervention(s): 20 mg iron, 1 mg riboflavin *Group 4*: no zinc Placebo given; Co-intervention(s): 20 mg iron, 1 mg riboflavin
Outcomes	All-cause mortality, incidence of all-cause diarrhoea, incidence of severe diarrhoea, incidence of LRTI, height, weight, weight-to-height ratio, serum or plasma zinc concentration, blood haemoglobin concentration, serum or plasma ferritin concentration, serum or plasma copper concentration Time point (wk): 24
Notes	- In addition to the 645 participants mentioned in this table, there was a group of 154 participants who received a micronutrient mix (MM). Baseline characteristics reported in this table were obtained from the Baqui 2003 trial report and are weighted averages of all groups except the MM group, because the MM group is not included in any meta-

	analyses in this review - Though vitamin A was not directly provided in this study, "Because vitamin A supplementation is a national program in Bangladesh, infants in all groups received 100,000 IU of vitamin A...at the beginning of the study."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Block randomization was done within strata to ensure equivalent enrollment…" Comment: insufficient details available to make a judgement as to whether or not an allocation sequence was generated using a truly random method
Allocation concealment (selection bias)	Unclear risk	Quote: N/A Comment: insufficient details available to make a judgement
Blinding of participants (performance bias) All outcomes	Low risk	Quote: "...double-blind, randomized, controlled community trial...Each study infant received a weekly dose of the assigned supplement, which was presented in the same type of capsules and labeled in such a way that the various types of supplements could not be differentiated." "The supplements were prepared as capsules, which were mixed with flavored syrup and fed to the infants. The mixtures were similar in taste and appearance." Comment: sufficient blinding seems likely
Blinding of personnel (performance bias) All outcomes	Low risk	Quote: "...double-blind, randomized, controlled community trial...Each study infant received a weekly dose of the assigned supplement, which was presented in the same type of capsules and labeled in such a way that the various types of supplements could not be differentiated." "The supplements were prepared as capsules, which were mixed with flavored syrup and fed to the infants. The mixtures were similar in taste and appearance." Comment: sufficient blinding seems likely

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "...double-blind, randomized, controlled community trial...Each study infant received a weekly dose of the assigned supplement, which was presented in the same type of capsules and labeled in such a way that the various types of supplements could not be differentiated." "The supplements were prepared as capsules, which were mixed with flavored syrup and fed to the infants. The mixtures were similar in taste and appearance." Comment: sufficient blinding seems likely
Incomplete outcome data (attrition bias) All outcomes	Low risk	% Missing: 12 Reasons/details: 14, 19, 30, and 12 participants "refused continued participation" in the iron, zinc, iron-zinc, and control group, respectively; in the zinc group, 2 migrated out and 1 died; in the control group, 1 migrated out. "6% in the iron + zinc group dropped out due to vomiting. In contrast, 0-2% of the infants in other groups dropped out due to vomiting", though it is unclear whether or not these participants who dropped out due to vomiting are included in the number of participants who "refused continued participation." For the sub-set of participants contributing zinc, haemoglobin, ferritin, and copper concentration data, "It was not possible to obtain 2 blood samples from all children and some samples were found to be hemolyzed or insufficient in quantity." For the sub-set of participants contributing height, weight, and height-to-rate ratio data, "Staff availability, transportation, and inclement weather were the primary reasons for missing data." Comment: 12% of the 645 randomised participants eligible for our review had data missing for diarrhoea and LRTI outcomes; this 12% missing figure includes all groups except the micronutrient mix (MM) group, since the MM group is not included in any meta-analyses in this review. "The baseline characteristics of the children who were excluded or lost to follow up were comparable to those of the children who continued in

Baqui 2003 (*Continued*)

		the study", and missing data seem unlikely to bias results
Selective reporting (reporting bias)	High risk	Comment: number of participants who dropped out due to vomiting was measured, but is not reported in a way that can be meta-analysed
Other bias	Low risk	Comment: appears to be free of other bias

Baqui 2003 (2)

Methods	
Participants	
Interventions	
Outcomes	All-cause mortality, incidence of all-cause diarrhoea, incidence of severe diarrhoea, incidence of LRTI, height, weight, weight-to-height ratio, serum or plasma zinc concentration, blood haemoglobin concentration, serum or plasma ferritin concentration, serum or plasma copper concentration
Notes	As Baqui 2003 above

Bhandari 2002

Methods	CRCT?: IRCT; Cross-over?: non-cross-over
Participants	Country: India; Setting: the urban slum of Dakshinpuri, New Deli; Urbanicity: urban Inclusion criteria: in family that did not intend to emigrate Exclusion criteria: likely to move out of the study area within the next 4 months; required urgent hospitalisation on the scheduled enrolment day; received massive dose of vitamin A (100,000 IU (30 mg) for infants and 200,000 IU (60 mg) for older children) within the last 2 months *Baseline characteristics* Avg age (mo): 15.3; Min age (mo): 6; Max age (mo): 30; % Female: 47.7 Avg HAZ: -1.82; Stunting: both - separate data not given; Avg height (cm): 72.7; Avg zinc concentration (μg/dL): 62 Total N: 2482; Group 1 N: 1241; Group 2 N: 1241
Interventions	*Group 1:* zinc Formulation: solution; Compound: gluconate; Frequency: daily; Duration (mo): 4; Dose (mg): 10 mg to children 6 to 12 months of age, 20 mg to children 12 to 30 months of age; Co-intervention(s): 100,000 IU vitamin A at enrolment for infants, 200,000 IU vitamin A at enrolment for older children *Group 2*: no zinc Placebo given; Co-intervention(s): 100,000 IU vitamin A at enrolment for infants, 200,000 IU vitamin A at enrolment for older children

Outcomes	All-cause mortality, all-cause hospitalisation, incidence of all-cause diarrhoea, prevalence of all-cause diarrhoea, incidence of severe diarrhoea, incidence of persistent diarrhoea, incidence of LRTI, height, weight, weight-to-height ratio, serum or plasma zinc concentration, prevalence of zinc deficiency, study withdrawal, vomiting episodes, serum or plasma ferritin concentration, serum or plasma copper concentration, prevalence of copper deficiency Time point (wk): 16 to 17
Notes	"…all included subjects were given a massive dose of vitamin A...at enrollment in addition to zinc or placebo as required by the national program policy."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A simple randomization scheme in blocks of 8 was generated...using the SAS software…" Comment: N/A
Allocation concealment (selection bias)	Low risk	Quote: "A simple randomization scheme... was generated by a person at Statens Serum Institut, who was not involved in the field work or the data analysis…The zinc and placebo syrups were prepared and packaged in unbreakable bottles by GK Pharma ApS (Køge, Denmark), which also labeled the bottles with unique identification numbers according to the randomization code. The zinc and placebo syrups were similar in... packaging." Comment: indicates central randomisation (i.e. randomisation by someone not involved with enrolling patients) and sequentially numbered drug containers of identical appearance to conceal allocation
Blinding of participants (performance bias) All outcomes	Low risk	Quote: "A double-blind, randomized, placebo-controlled trial was conducted... The zinc and placebo syrups were similar in appearance, taste, and packaging." Comment: sufficient blinding seems likely
Blinding of personnel (performance bias) All outcomes	Low risk	Quote: "A double-blind, randomized, placebo-controlled trial was conducted... The zinc and placebo syrups were similar in appearance, taste, and packaging." Comment: sufficient blinding seems likely

Bhandari 2002 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "A double-blind, randomized, placebo-controlled trial was conducted... The zinc and placebo syrups were similar in appearance, taste, and packaging." Comment: sufficient blinding seems likely
Incomplete outcome data (attrition bias) All outcomes	Low risk	% Missing: 10 Reasons/details: in the zinc group, 13 participants "refused further participation on the first weekly visit", 35 "refused further participation" after the first weekly visit, and 100 moved. In the placebo group, 5 participants "refused further participation on the first weekly visit", 16 "refused further participation" after the first weekly visit, and 84 moved. "Eight children in the zinc group and none in the placebo group discontinued the intervention because of vomiting." It seems that these 8 children are probably included among those who refused further participation. "Three children, all in the placebo group, died." Comment: reasons for missing data were similar between study groups. Migration was the most common reason for missing data, and this reason is unlikely to bias results
Selective reporting (reporting bias)	High risk	Comment: plasma ferritin was measured, but is not reported. Plasma ferritin was not pre-specified in the protocol for this study. All-cause hospitalisation was reported, but was not pre-specified in the protocol for this study Protocol identifier: NCT00272116
Other bias	Low risk	Comment: appears to be free of other bias

Bhandari 2007

Methods	CRCT?: CRCT; Cross-over?: non-cross-over
Participants	Country: India; Setting: north and northwest New Delhi; Urbanicity: urban Inclusion criteria: local residents; unlikely to move away over the next 6 months; unlikely to be absent from the study area for 3 months or more over the subsequent year Exclusion criteria: major congenital anomalies, severe malnutrition, or any serious condition that affected the ability of the child to consume the supplement. Children with visible severe wasting were enrolled after rehabilitation. Children with illnesses requiring

	hospitalisation were excluded temporarily and screened again after recovery *Baseline characteristics* Avg age (mo): 14.88; Min age (mo): 6; Max age (mo): 23; % Female: 47.1 Avg HAZ: -1.95; Stunting: both - separate data not given; Avg height (cm): 72.35; Avg zinc concentration (μg/dL): 64.27 Total N: 72,438; Group 1 N: 36,293; Group 2 N: 36,145 Total clusters: 68,146; Group 1 clusters: 34,201; Group 2 clusters: 33,945
Interventions	*Group 1:* zinc Formulation: pill/tablet; Compound: sulfate; Frequency: daily; Duration (mo): 12; Dose (mg): 10; Co-intervention(s): 12.5 mg iron, 50 µg folic acid *Group 2*: no zinc Placebo given; Co-intervention(s): 12.5 mg iron, 50 µg folic acid
Outcomes	All-cause mortality, mortality due to all-cause diarrhoea, mortality due to LRTI, all-cause hospitalisation, hospitalisation due to all-cause diarrhoea, hospitalisation due to LRTI, height, weight, prevalence of stunting, serum or plasma zinc concentration, prevalence of zinc deficiency, participants with $\geq$ 1 vomiting episode, serum or plasma ferritin concentration, prevalence of iron deficiency, serum or plasma copper concentration Time point (wk): 52
Notes	All baseline and outcome data from this study included in this review apply only to the subset of this study's participants who were at least 6 months of age at baseline

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Two randomization lists were computer generated (one for each stratum) ...Each list had permuted blocks of 16 participants randomly allocated to 16 letter codes. Half of the 16 letter codes were randomly assigned to the zinc and IFA group and the other half to the IFA group." Comment: N/A
Allocation concealment (selection bias)	Low risk	Quote: "…randomization lists were computer generated...by a staff member of the World Health Organization (WHO)." Participants were "randomly allocated to 16 letter codes. Half of the 16 letter codes were randomly assigned to the zinc and IFA group and the other half to the IFA group. This code was only available with the WHO and the company that prepared and packaged the supplement...Randomization lists containing only serial numbers (that represented household numbers) and

		respective letter codes were made available to the investigators, but they did not know which of the 16 letter codes represented the 2 study groups." Comment: indicates central randomisation (i.e. randomisation by someone not involved with enrolling patients) to conceal allocation
Blinding of participants (performance bias) All outcomes	Low risk	Quote: "...double blind cluster-randomized controlled trial…The control group tablets were similar in appearance and taste except they contained a placebo for zinc." Comment: sufficient blinding seems likely
Blinding of personnel (performance bias) All outcomes	Low risk	Quote: "...double blind cluster-randomized controlled trial…The control group tablets were similar in appearance and taste except they contained a placebo for zinc." Comment: sufficient blinding seems likely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "...double blind cluster-randomized controlled trial…The control group tablets were similar in appearance and taste except they contained a placebo for zinc." Comment: sufficient blinding seems likely
Incomplete outcome data (attrition bias) All outcomes	Low risk	% Missing: 4 Reasons/details: in the zinc + iron + folic acid group: 173 participants died, 31 participants "refused further participation", and 1394 "moved away before completing 12 mo follow-up." In the iron + folic acid group: 165 participants died, 17 participants "refused further participation", and 1369 "moved away before completing 12 mo follow-up." Comment: reasons for missing data were similar between study groups. Migration was the most common reason for missing data, and this reason is unlikely to bias results. Missing data seem too minimal to impact results
Selective reporting (reporting bias)	High risk	Comment: prevalence of stunting and mean plasma copper concentration were pre-specified as secondary outcomes in the protocol for this study, but are not reported. Height and weight were measured,

		but were not pre-specified in the protocol for this study and are not reported. Plasma zinc concentration, prevalence of iron deficiency, hospitalisation due to any cause, mortality due to diarrhoea, and mortality due to LRTI were reported, but were not pre-specified in the protocol for this study; though related outcomes, such as prevalence of zinc deficiency, plasma ferritin concentration, hospitalisations due to diarrhoea and pneumonia, and all-cause mortality, were pre-specified in the protocol for this study Protocol identifier: NCT00269542
Other bias	Low risk	Comment: appears to be free of other bias

Brown 2007

Methods	CRCT?: IRCT; Cross-over?: non-cross-over
Participants	Country: Peru; Setting: Trujillo, a city on the northern coast of Peru; Urbanicity: peri-urban Inclusion criteria: length-for-age z score (LAZ) < -0.5; weight-for-length z score > -3 (to exclude those with acute malnutrition, who were referred for treatment); haemoglobin > 8.0 g/dL Exclusion criteria: congenital abnormalities or chronic diseases affecting growth; use of infant formula providing > 1 mg Zn/d ≥ 5 times/wk; a twin enrolled in the study; families that were not planning to remain in the study community for the next 7 mo *Baseline characteristics* Avg age (mo): 7.5; Min age (mo): 6; Max age (mo): 8; % Female: 51.5 Avg HAZ: -1.19; Stunting: both - separate data not given; Avg height (cm): 65.4; Avg zinc concentration (μg/dL): 77.6 Total N: 200; Group 1 N: 101; Group 2 N: 99
Interventions	*Group 1:* zinc Formulation: solution; Compound: sulfate; Frequency: daily; Duration (mo): 6; Dose (mg): 3; Co-intervention(s): 30 g dry weight of an iron-fortified cereal porridge; an aqueous multivitamin (MV) supplement *Group 2*: no zinc Placebo given; Co-intervention(s): 30 g dry weight of an iron-fortified cereal porridge; an aqueous multivitamin (MV) supplement
Outcomes	Prevalence of all-cause diarrhoea, incidence of severe diarrhoea, incidence of LRTI, height, weight, weight-to-height ratio, serum or plasma zinc concentration, blood haemoglobin concentration, prevalence of anaemia, serum or plasma ferritin concentration, prevalence of iron deficiency, serum or plasma copper concentration Time point (wk): 24

Notes	In addition to the study groups mentioned in this table, there was a group of 102 participants who received 30 g dry weight of an iron- and zinc-fortified cereal porridge along with the aqueous multivitamin (MV) supplement. Baseline characteristics reported in this table are weighted averages of all groups except this zinc-fortified group, since this group is not included in any meta-analyses in this review

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: participants "were randomly assigned to...treatment groups by using a block randomization scheme, with a varied block length of 3 or 6." "We used the random number generator within SAS to randomly shuffle the treatments within each block." Comment: N/A
Allocation concealment (selection bias)	Low risk	Quote: in response to the question, "Could you describe how you ensured that participants, and investigators enrolling participants, could not tell which group a new participant would be assigned to?" an author of this study replied as follows: "One of the study investigators (Mary Penny) was responsible for coding and treatment assignment. She was not involved with the implementation of the study at the field site and the rest of the investigators, study personnel, and of course participants, were not aware of the coding and treatment assignment. The trial was conducted in a city 600 km north of Lima. Dr. Penny kept the code in Lima and every month sent coded porridge and supplements to the field site." Comment: sufficient allocation concealment seems likely
Blinding of participants (performance bias) All outcomes	Low risk	Quote: "Zinc supplements were delivered in coded bottles undistinguishable from placebo. A lab technician in Lima prepared zinc supplements and placebos and placed this in the coded bottles. Zinc supplements and placebo had the same appearance, taste, etc." Comment: sufficient blinding seems likely

Blinding of personnel (performance bias) All outcomes	Low risk	Quote: "Zinc supplements were delivered in coded bottles undistinguishable from placebo. A lab technician in Lima prepared zinc supplements and placebos and placed this in the coded bottles. Zinc supplements and placebo had the same appearance, taste, etc." Comment: sufficient blinding seems likely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Zinc supplements were delivered in coded bottles undistinguishable from placebo. A lab technician in Lima prepared zinc supplements and placebos and placed this in the coded bottles. Zinc supplements and placebo had the same appearance, taste, etc." Comment: sufficient blinding seems likely
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	% Missing: 11 Reasons/details: N/A Comment: 11% of the randomised participants eligible for our review had data missing; this 11% missing figure includes all groups except the zinc-fortified group, since this group is not included in any meta-analyses in this review. No information was reported on reasons for dropout. Furthermore, the authors reported that, "One possible limitation of our study was the disproportionate number of dropouts from the 2 groups that received additional zinc and the fact that those who left the study early differed slightly with regard to their initial rates of breastfeeding, anthropometric indicators of nutritional status, and prevalence of diarrhea...Nevertheless... the overall attrition rate was relatively small, as were the differences between the children who left the study early and those who completed the study, so these should not have exerted any major effect on the results. "
Selective reporting (reporting bias)	Low risk	Comment: in response to an inquiry concerning the protocol for this study, an author replied as follows: "This trial was conducted, if I am not mistaken, before trial registry was implemented. Unfortunately, I cannot share the protocol with you given

		we do not share these with external investigators. Nevertheless, I can tell you that all reported outcomes in the article were prespecified before the start of the trial." Furthermore, based on the trial reports for this study, there were no outcomes of interest to this review that were: (a) measured, but (b) not reported in a way that can be meta-analysed
Other bias	Low risk	Comment: appears to be free of other bias

Castillo-Durán 1994

Methods	CRCT?: IRCT; Cross-over?: non-cross-over
Participants	Country: Chile; Setting: slums of Santiago; Urbanicity: peri-urban Inclusion criteria: in the low-income group, defined by the Graffar scale; short stature, defined as length measurements less than the 5th percentile for age according to WHO/NCHS standards Exclusion criteria: chronic diseases (e.g. celiac disease, fetal alcohol syndrome, cardiac or chronic renal disease, genetic disorders) *Baseline characteristics* Avg age (mo): 127.4; Min age (mo): 72; Max age (mo): 168; % Female: 48 Avg HAZ: N/A; Stunting: stunted; Avg height (cm): N/A; Avg zinc concentration (μg/dL): N/A Total N: 114 or 113; Group 1 N: N/A; Group 2 N: N/A
Interventions	*Group 1:* zinc Formulation: capsule; Compound: sulfate; Frequency: daily; Duration (mo): 12; Dose (mg): 10; Co-intervention(s): N/A *Group 2*: no zinc Placebo given; Co-intervention(s): N/A
Outcomes	Height, weight Time point (wk): 52
Notes	- It is unclear whether 114 or 113 participants were randomised. The number of participants randomised to the zinc group was not reported; nor was the number of participants randomised to the placebo group - The HAZ outcome in this study was calculated, in part, based on the assumption that some height data reported in "F for difference between changes" format had a pre post correlation of 0.5; however assuming a pre post correlation of 0.2 or 0.8 did not change the calculated result for this outcome

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Castillo-Durán 1994 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were assigned randomly…" Comment: insufficient details available to make a judgement as to whether or not an allocation sequence was generated using a truly random method
Allocation concealment (selection bias)	Unclear risk	Quote: N/A Comment: insufficient details available to make a judgement
Blinding of participants (performance bias) All outcomes	Low risk	Quote: "For each age and gender group, children were assigned randomly to a supplement (S) or placebo (P) group in a double-blind fashion." Participants were "followed up for 12 months using a double-blind design." Comment: sufficient blinding seems likely
Blinding of personnel (performance bias) All outcomes	Low risk	Quote: "For each age and gender group, children were assigned randomly to a supplement (S) or placebo (P) group in a double-blind fashion." Participants were "followed up for 12 months using a double-blind design." Comment: sufficient blinding seems likely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "For each age and gender group, children were assigned randomly to a supplement (S) or placebo (P) group in a double-blind fashion." Participants were "followed up for 12 months using a double-blind design." Comment: sufficient blinding seems likely
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	% Missing: 30 Reasons/details: "Thirty-four other subjects were left out during the initial 3 months of the study because of poor compliance with ingestion of the supplemental capsule…" Comment: a large proportion of data is missing. The number of participants randomised to the zinc group was not reported; nor was the number of participants randomised to the placebo group. Thus, it is difficult to tell whether amounts of missing data were similar between study groups

Castillo-Durán 1994 (*Continued*)

Selective reporting (reporting bias)	High risk	Comment: height (for pre-adolescent females), weight (for all participants except pre-adolescent males), and weight-for-height were measured, but are not reported in a way that can be meta-analysed. It is unclear whether the plasma zinc concentration reported was measured at baseline or after supplementation as a post-intervention outcome
Other bias	Low risk	Comment: appears to be free of other bias

Castillo-Durán 2002

Methods	CRCT?: IRCT; Cross-over?: non-cross-over
Participants	Country: Chile; Setting: Santiago; Urbanicity: urban Inclusion criteria: normal weight and length; free from chronic diseases; literate mothers able to understand and sign written consent Exclusion criteria: N/A *Baseline characteristics* Avg age (mo): N/A; Min age (mo): 17; Max age (mo): 19; % Female: 0 Avg HAZ: N/A; Stunting: non-stunted; Avg height (cm): N/A; Avg zinc concentration (μg/dL): N/A Total N: 42; Group 1 N: 21; Group 2 N: 21
Interventions	*Group 1:* zinc Formulation: solution; Compound: sulfate; Frequency: daily; Duration (mo): 12; Dose (mg): 5; Co-intervention(s): N/A *Group 2*: no zinc Placebo given; Co-intervention(s): N/A
Outcomes	No outcomes of interest reported in a way that can be meta-analysed
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Children were randomized…" Comment: insufficient details available to make a judgement as to whether or not an allocation sequence was generated using a truly random method

Castillo-Durán 2002 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Quote: N/A Comment: insufficient details available to make a judgement
Blinding of participants (performance bias) All outcomes	Unclear risk	Quote: "...double blind trial…" Comment: insufficient details available to make a judgement
Blinding of personnel (performance bias) All outcomes	Unclear risk	Quote: "...double blind trial…" Comment: insufficient details available to make a judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "...double blind trial…" Comment: insufficient details available to make a judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	% Missing: 19 Reasons/details: "Eight children were excluded due to non compliance with daily administration of syrup or to change of address limiting home visits." Comment: a fairly large proportion of data is missing, and neither reasons for, nor amounts of, missing data were reported separately for the zinc group versus the placebo group
Selective reporting (reporting bias)	High risk	Comment: plasma zinc concentration, weight, and length were measured, but are not reported in a way that can be meta-analysed. "Morbidity outcomes" were measured, but the exact types of morbidity outcomes measured were not defined; so, other outcomes, such as diarrhoea or LRTI, might have been measured but not reported
Other bias	Low risk	Comment: appears to be free of other bias

Cavan 1993

Methods	CRCT?: IRCT; Cross-over?: non-cross-over
Participants	Country: Guatemala; Setting: Guatemala City; Urbanicity: peri-urban Inclusion criteria: N/A Exclusion criteria: receiving vitamin and/or mineral supplementation at home in the last 2 mo *Baseline characteristics* Avg age (mo): 81.5; Min age (mo): 68; Max age (mo): 96; % Female: 45

	Avg HAZ: -1.51; Stunting: both - separate data not given; Avg height (cm): 112.2; Avg zinc concentration (μg/dL): 93.5 Total N: 162; Group 1 N: 80; Group 2 N: 82
Interventions	*Group 1:* zinc Formulation: pill/tablet; Compound: amino acid chelate; Frequency: "…each school day…"; Duration (mo): 6.25; Dose (mg): 10; Co-intervention(s): vitamin-mineral supplement that contained multiple micronutrients (including iron) *Group 2*: no zinc Placebo given; Co-intervention(s): vitamin-mineral supplement that contained multiple micronutrients (including iron)
Outcomes	Height, weight, weight-to-height ratio, serum or plasma zinc concentration Time point (wk): 25
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Children were pair matched by sex and age to constitute two groups: thereafter, a coin toss was used to assign the groups to one or the other coded treatment." Comment: N/A
Allocation concealment (selection bias)	Low risk	Quote: "...a coin toss was used to assign the groups to one or the other coded treatment. ..only the color varied between the two supplements...Only the company (Jamieson Co, Windsor, Ontario), which manufactured the supplements, was familiar with the color code; the code was broken only on completion of the project." Comment: sufficient allocation concealment seems likely
Blinding of participants (performance bias) All outcomes	Low risk	Quote: "…a double-blind zinc-supplementation study…The zinc and placebo supplements were indistinguishable in taste and size; only the color varied between the two supplements...Only the company (Jamieson Co, Windsor, Ontario), which manufactured the supplements, was familiar with the color code; the code was broken only on completion of the project." Comment: sufficient blinding seems likely

Cavan 1993 (*Continued*)

Blinding of personnel (performance bias) All outcomes	Low risk	Quote: "…a double-blind zinc-supplementation study…The zinc and placebo supplements were indistinguishable in taste and size; only the color varied between the two supplements...Only the company (Jamieson Co, Windsor, Ontario), which manufactured the supplements, was familiar with the color code; the code was broken only on completion of the project." Comment: sufficient blinding seems likely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "…a double-blind zinc-supplementation study…The zinc and placebo supplements were indistinguishable in taste and size; only the color varied between the two supplements...Only the company (Jamieson Co, Windsor, Ontario), which manufactured the supplements, was familiar with the color code; the code was broken only on completion of the project." Comment: sufficient blinding seems likely
Incomplete outcome data (attrition bias) All outcomes	Low risk	% Missing: 3.7 Reasons/details: N/A Comment: though no reasons for missing data were given, missing data seem too minimal to impact results
Selective reporting (reporting bias)	High risk	Comment: plasma copper concentration was measured as an outcome, but is not reported as an outcome
Other bias	Low risk	Comment: appears to be free of other bias

Chang 2010

Methods	CRCT?: IRCT; Cross-over?: non-cross-over
Participants	Country: Bangladesh; Setting: Mirzapur, a sub-district (thana) north of Dhaka; Urbanicity: rural Inclusion criteria: permanent resident of the selected villages Exclusion criteria: severe malnutrition (weight-for-height z-score < -3 SD); severe anaemia (haemoglobin < 70 g/l); chronic illnesses that would impair feeding ability; planned move during the study period; active fever > 38.5 °C; a sibling enrolled in the study *Baseline characteristics* Avg age (mo): 11; Min age (mo): 6; Max age (mo): 18; % Female: 48.4 Avg HAZ: -1.3; Stunting: both - separate data not given; Avg height (cm): N/A; Avg

	zinc concentration (μg/dL): 65.3 Total N: 1000; Group 1 N: 198; Group 2 N: 201; Group 3 N: 400; Group 4 N: 201
Interventions	*Group 1:* zinc Formulation: pill/tablet; Compound: sulfate; Frequency: every other day; Duration (mo) : 6; Dose (mg): 5 mg to children aged younger than 12 months; 10 to children aged 12 months or older; Co-intervention(s): N/A *Group 2*: no zinc Placebo given; Co-intervention(s): N/A *Group 3:* zinc Co-intervention(s): for children aged younger than 12 months: 6.25 mg iron every other day; 25 IU folic acid every other day. For children aged 12 months or older: 12.5 mg iron every other day; 50 IU folic acid every other day *Group 4*: no zinc Placebo given; Co-intervention(s): for children aged younger than 12 months: 6.25 mg iron every other day; 25 IU folic acid every other day. For children aged 12 months or older: 12.5 mg iron every other day; 50 IU folic acid every other day
Outcomes	All-cause mortality, all-cause hospitalisation, incidence of all-cause diarrhoea, prevalence of all-cause diarrhoea, hospitalisation due to all-cause diarrhoea, hospitalisation due to LRTI, serum or plasma zinc concentration, vomiting episodes, blood haemoglobin concentration, prevalence of anaemia Time point (wk): 26
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Block randomization in groups of 10 were computer generated." Comment: N/A
Allocation concealment (selection bias)	Low risk	Quote: "Sealed envelopes concealing supplement group allocation were opened sequentially only after complete determination of enrollment eligibility." Comment: sufficient allocation concealment seems likely
Blinding of participants (performance bias) All outcomes	Low risk	Quote: "...double blind, placebo-controlled factorial community trial…Placebo was identical in color, shape, taste...The manufacturer provided supplements with blinded designation. The principal investigator alone stored the code in a remote location from the study site. The code was not revealed until the time of manuscript

		preparation." Comment: sufficient blinding seems likely
Blinding of personnel (performance bias) All outcomes	Low risk	Quote: "...double blind, placebo-controlled factorial community trial…Placebo was identical in color, shape, taste...The manufacturer provided supplements with blinded designation. The principal investigator alone stored the code in a remote location from the study site. Analyses were performed in a blinded manner. The code was not revealed until the time of manuscript preparation." Comment: sufficient blinding seems likely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "...double blind, placebo-controlled factorial community trial…Placebo was identical in color, shape, taste...The manufacturer provided supplements with blinded designation. The principal investigator alone stored the code in a remote location from the study site. Analyses were performed in a blinded manner. The code was not revealed until the time of manuscript preparation." Comment: sufficient blinding seems likely
Incomplete outcome data (attrition bias) All outcomes	Low risk	% Missing: 0.3 Reasons/details: For diarrhoea and hospitalisation outcomes: in the placebo group, 2 participants died; in the zinc + iron group, 1 withdrew. For zinc, haemoglobin, and anaemia outcomes: In the zinc group, 2 participants were lost to follow-up (LTFU) and 10 refused to have their blood drawn; in the placebo group 2 were LTFU and 10 refused to have their blood drawn; in the zinc + iron group, 7 were LTFU and 16 refused to have their blood drawn; and in the iron group, 2 were LTFU and 7 refused to have their blood drawn Comment: reasons for, and amount of, missing data were similar between study groups. Missing data seem too minimal to impact results
Selective reporting (reporting bias)	Unclear risk	Comment: all-cause hospitalisations, hospitalisations due to diarrhoea, hospitalisation due to pneumonia, and incidence of

Chang 2010 (*Continued*)

		vomiting as a side effect were reported, but were not pre-specified in the protocol for this study. However, these were not reported as primary outcomes Protocol identifier: NCT00470158
Other bias	Low risk	Comment: appears to be free of other bias

Chang 2010 (2)

Methods	
Participants	
Interventions	
Outcomes	All-cause mortality, all-cause hospitalisation, incidence of all-cause diarrhoea, prevalence of all-cause diarrhoea, hospitalisation due to all-cause diarrhoea, hospitalisation due to LRTI, serum or plasma zinc concentration, vomiting episodes, blood haemoglobin concentration, prevalence of anaemia
Notes	As Chang 2010 above

Chen 2012

Methods	CRCT?: CRCT; Cross-over?: non-cross-over
Participants	Country: China; Setting: Banan District, a suburb of Chongqing; Urbanicity: peri-urban Inclusion criteria: 1) not having any chronic infectious diseases; 2) haemoglobin concentration 360 g/L; 3) C-reaction protein (CRP) < 5 mg/L; 4) parental/guardian agreement to avoid additional supplementing vitamin and mineral during the investigation Exclusion criteria: evidence of recent acute or chronic illnesses and/or haemoglobin concentration < 60 g/L *Baseline characteristics* Avg age (mo): 51.60; Min age (mo): 36; Max age (mo): 72; % Female: 44 Avg HAZ: -0.26; Stunting: unclear; Avg height (cm): 102; Avg zinc concentration (μg/dL): 25.6% of participants had zinc serum level < 10.7 Total N: 361; Group 1 N: 122; Group 2 N: 119
Interventions	*Group 1:* zinc Formulation: pill/tablet; Compound: gluconate; Frequency: 5 days/wk; Duration (mo) : 6; Dose (mg): 10; Co-intervention(s): vitamin A *Group 2*: no zinc Placebo not given; Co-intervention(s): vitamin A
Outcomes	Height, weight, weight-to-height ratio, serum zinc, blood haemoglobin Time point (wk): 26
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Three kindergartens were randomly selected out of 7 in this region; and 3 classes were chosen from each of them…The selected classes in each kindergarten were randomly assigned to receive vitamin A (A group), vitamin A plus zinc (AZ group), or vitamin A combined with multiple micronutrients (contain vitamins B-1, B-2, B-6, B-12, C, D, folate, niacinamide, and calcium)."
Allocation concealment (selection bias)	Unclear risk	Quote: N/A
Blinding of participants (performance bias) All outcomes	High risk	No placebo
Blinding of personnel (performance bias) All outcomes	High risk	Intervention was continued at the weekends by sending parents a supply of sachets with instructions (doesn't state whether these sachets also had the contents on the packet, if so risk of to the blinding status of the participants)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No placebo
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: 22% intervention and 28% control missing
Selective reporting (reporting bias)	Unclear risk	Trial not registered. Authors say "We cannot share our protocol with you. It's not a public file."
Other bias	Low risk	Comment: appears to be free of other bias

Chhagan 2009

Methods	CRCT?: IRCT; Cross-over?: non-cross-over
Participants	Country: South Africa; Setting: Northern KwaZulu-Natal Province; Urbanicity: rural Inclusion criteria: N/A Exclusion criteria: less than 60% of median weight-for-age using United States National Center for Health Statistics standards; nutritional oedema; received vitamin or micronutrient supplements in the previous month; diarrhoea for more than 7 days at the time of study enrolment; enrolled in another study of a clinical intervention *Baseline characteristics* Avg age (mo): 6; Min age (mo): 6; Max age (mo): 6; % Female: 48 Avg HAZ: -0.45; Stunting: both - separate data given; Avg height (cm): N/A; Avg zinc concentration (μg/dL): N/A Total N: 227; Group 1 N: 112; Group 2 N: 115
Interventions	*Group 1:* zinc Formulation: pill/tablet; Compound: gluconate; Frequency: daily; Duration (mo): 18; Dose (mg): 10; Co-intervention(s): 1250 IU vitamin A *Group 2*: no zinc Placebo given; Co-intervention(s): 1250 IU vitamin A
Outcomes	All-cause mortality, all-cause hospitalisation, incidence of all-cause diarrhoea, prevalence of all-cause diarrhoea, hospitalisation due to all-cause diarrhoea, incidence of severe diarrhoea, incidence of persistent diarrhoea, vomiting episodes, blood haemoglobin concentration, prevalence of anaemia Time point (wk): 52 (biochemical outcomes), 72 (morbidity and mortality outcomes)
Notes	- In addition to the study groups mentioned in this table, there was a group of participants who received zinc along with multiple micronutrients. Baseline characteristics reported in this table are weighted averages of all groups except this zinc and multiple micronutrient group, since this group is not included in any meta-analyses in this review - HIV-positive children are not eligible for this review, so the baseline characteristics and most outcome data that are reported in this review only apply to this trial's HIV-uninfected child participants. (For a few outcomes, separate data were not reported for HIV-uninfected participants; however, HIV-uninfected participants comprise the majority of participants in analyses of these outcomes.) - 28 participants in the vitamin A group and 26 participants in the vitamin A + zinc groups "were found to have hemoglobin below 10 g/dL during the routine testing performed on all study participants" and "were given therapeutic iron as per South Africa Department of Health guidelines…." However, "Use of any other micronutrient supplements during the study was rare." - "All supplements were given daily at home from entry into the study until 24 months of age…The median duration of enrollment in the study was 447 days and did not differ significantly between groups."

Risk of bias

Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Low risk	Quote: "An allocation list was prepared using computer-generated random numbers and a block size of six." Comment: N/A
Allocation concealment (selection bias)	Low risk	Quote: "The manufacturer prepared numbered packs of tablets corresponding to the allocation list. Children enrolled in the study were assigned by a study physician to one of the three study cohorts after results of the HIV tests became available. The physician then allocated the next pack of tablets from the blocks assigned to that cohort to the participant." Comment: sufficient allocation concealment seems likely
Blinding of participants (performance bias) All outcomes	Low risk	Quote: "...double-blind, controlled trial... All three formulations were similar in color, taste, appearance and size…participants were blind to the treatment assignments." Comment: sufficient blinding seems likely
Blinding of personnel (performance bias) All outcomes	Low risk	Quote: "...double-blind, controlled trial... All three formulations were similar in color, taste, appearance and size…study staff... were blind to the treatment assignments." Comment: sufficient blinding seems likely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "...double-blind, controlled trial... All three formulations were similar in color, taste, appearance and size…Investigators... were blind to the treatment assignments." Comment: sufficient blinding seems likely
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	% Missing: 37 Reasons/details: among all 373 enrolled trial participants, including HIV-positive participants and participants in the multiple micronutrient group: "Thirty-seven children withdrew and one died before any home visits took place...Twelve (3.6%) of the 335 children with at least one home visit died during the study...An additional 88 (26.2%) of the 335 children who had at least one home visit did not complete the study...Fifty-seven children moved out of the area during the study. Reasons given

		for withdrawal in the other 31 children included lack of time by parent to participate (2 children), the child not liking the taste of the tablets (3 children), objections from grandparent or father (2 children) and unspecified reasons in 24 children." Comment: a large proportion of the data is missing, and reasons for missing data were not reported separately for each study group
Selective reporting (reporting bias)	High risk	Comment: weight and growth were prespecified as outcomes in the protocol for this study; however, weight-for-age z-score was measured but not reported, and height-for-age z-score was measured but not reported in a way that can be meta-analysed. All-cause hospitalisations, incidence of LRTI, haemoglobin concentration, and prevalence of anaemia were reported, but were not pre-specified in the protocol for this study Protocol identifier: NCT00133419; ISRCTN39226623
Other bias	Unclear risk	Comment: "Because of a delay in shipment, 243 children enrolled in the study did not receive supplements for 11 weeks. .." This lack of supplement receipt could have influenced the outcomes, if the zinc + vitamin A group had a significantly different proportion of children who did not receive supplements than the vitamin A group

Clark 1999

Methods	CRCT?: IRCT; Cross-over?: non-cross-over
Participants	Country: United Kingdom; Setting: Sheffield; Urbanicity: urban Inclusion criteria: healthy Exclusion criteria: history of metabolic disease; taking any medication known to influence bone metabolism or zinc status *Baseline characteristics* Avg age (mo): 146.4; Min age (mo): N/A; Max age (mo): N/A; % Female: 100 Avg HAZ: N/A; Stunting: non-stunted; Avg height (cm): 154; Avg zinc concentration (μg/dL): 80.3 Total N: 47; Group 1 N: N/A; Group 2 N: N/A

Interventions	*Group 1:* zinc Formulation: unclear; Compound: citrate; Frequency: daily; Duration (mo): 1.5; Dose (mg): 15; Co-intervention(s): N/A *Group 2*: no zinc Placebo given; Co-intervention(s): N/A
Outcomes	Height, weight, serum or plasma zinc concentration Time point (wk): 10
Notes	- The number of participants randomised to each study group is not explicitly reported. However, given the numbers of participants analysed in the zinc and placebo groups for baseline and final outcome measures, there were at least 25 participants in the zinc group and at least 21 participants in the placebo group - For all outcomes, "Baseline to final measure was 10 weeks; supplementation took place over the last 6 weeks."

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "These girls…were randomised…" Comment: insufficient details available to make a judgement as to whether or not an allocation sequence was generated using a truly random method
Allocation concealment (selection bias)	Unclear risk	Quote: N/A Comment: insufficient details available to make a judgement
Blinding of participants (performance bias) All outcomes	Low risk	Quote: "...double-blind controlled trial…identical placebo..." Comment: sufficient blinding seems likely
Blinding of personnel (performance bias) All outcomes	Low risk	Quote: "...double-blind controlled trial…identical placebo..." Comment: sufficient blinding seems likely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "...double-blind controlled trial…identical placebo..." Comment: sufficient blinding seems likely
Incomplete outcome data (attrition bias) All outcomes	Low risk	% Missing: N/A Reasons/details: N/A Comment: the exact number of participants missing for each study group was not explicitly reported, nor were reasons for missing data. However, for outcomes of in-

		terest to this review, between 42 and 46 participants were analysed. So, between 2% and 11% of data are missing for outcomes of interest to this review. Missing data seem too minimal to impact results
Selective reporting (reporting bias)	Unclear risk	Comment: no trial protocol referenced by the study
Other bias	Low risk	Comment: appears to be free of other bias

Cole 2012

Methods	CRCT?: IRCT; Cross-over?: non-cross-over
Participants	Country: Brazil; Setting: Salvador-Bahia; Urbanicity: Not reported Inclusion criteria: healthy children attending day care. ("Institutionalized"?) Exclusion criteria: chronic medical problems including sickle cell disease, congenital heart disease *Baseline characteristics* Avg age (mo): 25.63; Min age (mo): 6; Max age (mo): 48; % Female: 0.42 Avg HAZ: N/A; Stunting: N/A; Avg height (cm): N/A; Avg zinc concentration (μg/dL) : N/A Total N: 143; Group 1 N: 75; Group 2 N: 68
Interventions	*Group 1:* zinc Formulation: powder/paste; Compound: gluconate; Frequency: daily; Duration (mo): 3; Dose (mg): 5; Co-intervention(s): sprinkles (including vitamin A and iron) *Group 2*: no zinc Placebo given; Co-intervention(s): sprinkles (including vitamin A and iron)
Outcomes	Incidence of all-cause diarrhoea Time point (wk): 13
Notes	Monitoring was undertaken to make sure plates were not swapped, that children ate the food, and it was recorded if they did not eat the meal, or only ate half

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "A randomização foi feita por berçários e salas, de acordo com sequência gerada por computador." - randomisation was done by nursery and classroom, according to a computer generated sequence. "The kids were randomized based on the classes that they were put in the daycare

		since that would make delivery of the micronutrient sprinkle package easy." (Personal communication) Comment: not clear how participants were clustered and how this was included in the analysis
Allocation concealment (selection bias)	Unclear risk	Quote: N/A
Blinding of participants (performance bias) All outcomes	Low risk	Quote: "duplo cego" - double blind
Blinding of personnel (performance bias) All outcomes	High risk	Quote: "Os suplementos apenas eram abertos e adicionados às refeições no momento de servir, por nutricionistas não cegas para o estudo, já que os sachês estavam identificados quanto à presença de zinco" - the supplements were only opened and added to the meals at the moment of serving, by nutritionists who were not blinded to the study, since the sachets were marked as to whether they included zinc or not Comment: intervention was continued at the weekends by sending parents a supply of sachets with instructions (does not state whether these sachets also had the contents on the packet; if so a risk to the blinding status of the participants)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Todos os médicos envolvidos estavam cegos para o estudo" - all medics involved were blinded to the study Comment: this relates to those people undertaking outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Todas completaram o estudo." - all participants completed the study
Selective reporting (reporting bias)	Unclear risk	Comment: protocol registration NCT00967551. Primary outcome reported, but unclear what other outcomes were measured
Other bias	Low risk	Comment: appears to be free of other bias

De Fonseca 2002

Methods	CRCT?: IRCT; Cross-over?: non-cross-over
Participants	Country: Brazil; Setting: Vila Mariana, São Paulo; Urbanicity: urban Inclusion criteria: N/A Exclusion criteria: any organic or genetic condition that was correlated with growth retardation *Baseline characteristics* Avg age (mo): 91.72; Min age (mo): 72; Max age (mo): 120; % Female: 47.5 Avg HAZ: N/A; Stunting: both - separate data given; Avg height (cm): N/A; Avg zinc concentration (μg/dL): N/A Total N: 199; Group 1 N: 99; Group 2 N: 100
Interventions	*Group 1:* zinc Formulation: solution; Compound: amino acid chelate; Frequency: weekly; Duration (mo): 3; Dose (mg): 30; Co-intervention(s): N/A *Group 2*: no zinc Placebo given; Co-intervention(s): N/A
Outcomes	Height, weight, weight-to-height ratio Time point (wk): 24
Notes	Quotes for this study are translated from Portuguese

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "...Randomized…Trial…With the help of the computer program Epi Info 6.02…children were randomized through the Statcalc sub-routine." Comment: N/A
Allocation concealment (selection bias)	Unclear risk	Quote: N/A Comment: insufficient details available to make a judgement
Blinding of participants (performance bias) All outcomes	Low risk	Quote: "…Double-Blind Trial…Each container contained the name and number of the child…properly labeled by a person not part of the research, who was the only one to know who was receiving medication or placebo." Comment: sufficient blinding seems likely
Blinding of personnel (performance bias) All outcomes	Low risk	Quote: "…Double-Blind Trial…Each container contained the name and number of the child…properly labeled by a person not part of the research, who was the only

		one to know who was receiving medication or placebo." Comment: sufficient blinding seems likely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "…Double-Blind Trial…Each container contained the name and number of the child…properly labeled by a person not part of the research, who was the only one to know who was receiving medication or placebo." Comment: sufficient blinding seems likely
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	% Missing: 50 Reasons/details: during the period of supplementation, 29 children were excluded due to school transfer or unexplained absence, 2 children due to refusal to continue taking the drug, and 3 due to self reported side effects. At the end of the supplementation period, 6 children were excluded due to not having reached the minimum total of 12 doses of supplement or placebo, due to absences on the day of the week that supplementation took place. 60 children, who had one or more gaps in anthropometric measurements in December 2000 and/or March 2001, were also excluded. One hypothesis for this large loss is that some children changed neighbourhoods during the semester, but had not changed schools so as not to disrupt school performance. But at the end of the school year, these children went to new schools, because of their proximity to their new dwellings Comment: a large proportion of data is missing, and neither reasons for, nor amounts of, missing data were reported separately for the zinc versus the placebo group
Selective reporting (reporting bias)	High risk	Comment: side effects, such as nausea and epigastric pain, were measured, but are not reported in a way that can be meta-analysed
Other bias	Low risk	Comment: appears to be free of other bias

Dehbozorgi 2007

Methods	CRCT?: IRCT; Cross-over?: non-cross-over
Participants	Country: Iran; Setting: 2 villages east of Shiraz; Urbanicity: rural Inclusion criteria: N/A Exclusion criteria: heart failure; Down syndrome *Baseline characteristics* Avg age (mo): N/A; Min age (mo): 72; Max age (mo): 144; % Female: 0 Avg HAZ: N/A; Stunting: unclear; Avg height (cm): N/A; Avg zinc concentration (μg/dL): N/A Total N: 60; Group 1 N: 30; Group 2 N: 30
Interventions	*Group 1:* zinc Formulation: solution; Compound: sulfate; Frequency: daily; Duration (mo): 6; Dose (mg): 8; Co-intervention(s): N/A *Group 2*: no zinc Placebo given; Co-intervention(s): N/A
Outcomes	Height, weight Time point (wk): 24
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "…randomized clinical trial…children were selected randomly and divided into two groups…One child was assigned to the experimental group and another one was placed in the control group until the total size was reached." Comment: insufficient details available to make a judgement as to whether or not an allocation sequence was generated using a truly random method
Allocation concealment (selection bias)	Unclear risk	Quote: N/A Comment: insufficient details available to make a judgement
Blinding of participants (performance bias) All outcomes	Low risk	Quote: "…double-blind…clinical trial…The syrups containing zinc sulfate and placebo were identical and the taste and smell of the solutions were the same…The placebo was provided in completely similar bottles..." Comment: sufficient blinding seems likely

Dehbozorgi 2007 (*Continued*)

Blinding of personnel (performance bias) All outcomes	Low risk	Quote: "…double-blind…clinical trial…The syrups containing zinc sulfate and placebo were identical and the taste and smell of the solutions were the same…The placebo was provided in completely similar bottles..." Comment: sufficient blinding seems likely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "…double-blind…clinical trial…The syrups containing zinc sulfate and placebo were identical and the taste and smell of the solutions were the same…The placebo was provided in completely similar bottles..." Comment: sufficient blinding seems likely
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	% Missing: N/A Reasons/details: N/A Comment: amount of, and reasons for, missing data were not reported
Selective reporting (reporting bias)	High risk	Comment: side effects were measured, but are not reported
Other bias	Low risk	Comment: appears to be free of other bias

DiGirolamo 2010

Methods	CRCT?: IRCT; Cross-over?: non-cross-over
Participants	Country: Guatemala; Setting: low-income community in Guatemala City; Urbanicity: urban Inclusion criteria: in grades 1 to 4 Exclusion criteria: any known severe illness shown to affect zinc status such as sickle cell disease, cystic fibrosis, renal or liver disease, severe burns, or acrodermatitis enteropathica; any other severe or chronic illness not necessarily linked to zinc status (e.g. cancer, diabetes, or seizures) *Baseline characteristics* Avg age (mo): 108; Min age (mo): 72; Max age (mo): 132; % Female: 50 Avg HAZ: -1.2; Stunting: both - separate data not given; Avg height (cm): N/A; Avg zinc concentration (μg/dL): 75.3 Total N: 750; Group 1 N: 378; Group 2 N: 372
Interventions	*Group 1:* zinc Formulation: pill/tablet; Compound: oxide; Frequency: 5 days/wk; Duration (mo): 5.8; Dose (mg): 10; Co-intervention(s): N/A *Group 2*: no zinc Placebo given; Co-intervention(s): N/A

Outcomes	Height, weight, serum or plasma zinc concentration, prevalence of zinc deficiency Time point (wk): 24
Notes	"At approximately the time our study began, the local government in the study community implemented a school-based fortified milk program. Children in 4 out of the 5 schools received 200 mL whole milk/d fortified with" approximately 1.6 mg zinc per 200 mL along with multiple micronutrients. "Children in the fifth school…received" a daily "food supplement", which contained "2.1 mg zinc" along with multiple micronutrients. However, these government-provided nutrients would have been received by both zinc the zinc group and the placebo group, "and the randomized controlled trial design of the study makes it very unlikely that this biased" its "results, as there is no reason to believe that one group received more of these nutrients than the other group."

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Individual children within each classroom were randomly assigned by using a computer-generated list on the basis of a 1:1:1:1 allocation ratio without blocking constraints." Comment: N/A
Allocation concealment (selection bias)	Low risk	Quote: "The zinc and placebo tablets were divided into color-coded vials (2 colors assigned to zinc; 2 colors assigned to placebo) by a staff member at INCAP who was not involved in the study...All study participants and members of the study team were blinded to the treatment code, which was maintained in sealed envelopes at INCAP and Rollins School of Public Health. The envelopes were opened at the end of the study after preliminary data analyses had been completed." Comment: sufficient allocation concealment seems likely
Blinding of participants (performance bias) All outcomes	Low risk	Quote: "...double-blind, controlled trial…The placebo was similar in taste and appearance to the zinc tablet. ..All study participants…were blinded to the treatment code, which was maintained in sealed envelopes at INCAP and Rollins School of Public Health. The envelopes were opened at the end of the study after preliminary data analyses had been com-

		pleted." Comment: sufficient blinding seems likely
Blinding of personnel (performance bias) All outcomes	Low risk	Quote: ". ..double-blind, controlled trial…The zinc and placebo tablets were divided into color-coded vials (2 colors assigned to zinc; 2 colors assigned to placebo) by a staff member at INCAP who was not involved in the study…Individuals who administered the supplements (n = 7) received a list of all children in their classroom enrolled in the study and their assigned color group...The placebo was similar in taste and appearance to the zinc tablet." Comment: sufficient blinding seems likely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "...double-blind, controlled trial…The placebo was similar in taste and appearance to the zinc tablet...All…members of the study team were blinded to the treatment code, which was maintained in sealed envelopes at INCAP and Rollins School of Public Health. The envelopes were opened at the end of the study after preliminary data analyses had been completed." Comment: sufficient blinding seems likely
Incomplete outcome data (attrition bias) All outcomes	Low risk	% Missing: 4.7 Reasons/details: "Of the 750 children, 30 (4.0%) children never received treatment or completed the baseline assessment. Of the children who received at least one tablet in the zinc group, 3 were lost: 1 participant was lost due to "parent refusal", 1 "did not go to final evaluation", and 1 had a change of address. Of the children who received at least one tablet in the zinc group, 2 were lost: 1 participant was lost due to a change of address, and 1 due to "parent refusal." Comment: missing data seem too minimal to impact results
Selective reporting (reporting bias)	Unclear risk	Comment: weight and height were reported, but were not pre-specified in the protocol for this study. However, these were not reported as primary outcomes Protocol identifier: NCT00283660

Other bias	Low risk	Comment: appears to be free of other bias

Ebrahimi 2006

Methods	CRCT?: IRCT; Cross-over?: non-cross-over
Participants	Country: Iran; Setting: Yasuj city, in the southwest of Iran; Urbanicity: urban Inclusion criteria: N/A Exclusion criteria: N/A *Baseline characteristics* Avg age (mo): N/A; Min age (mo): 96; Max age (mo): 132; % Female: 53 Avg HAZ: N/A; Stunting: unclear; Avg height (cm): N/A; Avg zinc concentration (μg/dL): N/A Total N: 804; Group 1 N: 386; Group 2 N: 418
Interventions	*Group 1:* zinc Formulation: solution; Compound: unclear; Frequency: 6 days/wk; Duration (mo): 7; Dose (mg): 10; Co-intervention(s): N/A *Group 2*: no zinc Placebo given; Co-intervention(s): N/A
Outcomes	Height, weight Time point (wk): 28
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Children were randomly assigned to zinc or placebo group…" Comment: insufficient details available to make a judgement as to whether or not an allocation sequence was generated using a truly random method
Allocation concealment (selection bias)	Unclear risk	Quote: N/A Comment: insufficient details available to make a judgement
Blinding of participants (performance bias) All outcomes	Low risk	Quote: "…double blind placebo controlled trial...Zinc and also placebo were administrated to the children, between meals, in an identical form (syrup) and identical precoded containers." Comment: sufficient blinding seems likely

Ebrahimi 2006 (*Continued*)

Blinding of personnel (performance bias) All outcomes	Low risk	Quote: "…double blind placebo controlled trial...Zinc and also placebo were administrated to the children, between meals, in an identical form (syrup) and identical precoded containers." Comment: sufficient blinding seems likely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "…double blind placebo controlled trial...Zinc and also placebo were administrated to the children, between meals, in an identical form (syrup) and identical precoded containers." Comment: sufficient blinding seems likely
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	% Missing: N/A Reasons/details: N/A Comment: amount of, and reasons for, missing data were not reported
Selective reporting (reporting bias)	Unclear risk	Comment: no trial protocol referenced by the study
Other bias	Low risk	Comment: appears to be free of other bias

Fallahi 2007

Methods	CRCT?: IRCT; Cross-over?: non-cross-over
Participants	Country: Iran; Setting: Khorramabad city, capital of Lorestan province in western Iran; Urbanicity: urban Inclusion criteria: in 5th grade Exclusion criteria: renal failure, thalassaemia, tuberculosis, parasitic diseases, or infections; taking supplementary vitamins and minerals *Baseline characteristics* Avg age (mo): 133.2; Min age (mo): 132; Max age (mo): 143; % Female: 62 Avg HAZ: N/A; Stunting: unclear; Avg height (cm): 139.6; Avg zinc concentration (μg/dL): 71.7 Total N: 53; Group 1 N: 26; Group 2 N: 27
Interventions	*Group 1:* zinc Formulation: capsule; Compound: sulfate; Frequency: 6 days/wk; Duration (mo): 4; Dose (mg): 20; Co-intervention(s): 20 mg iron *Group 2*: no zinc Placebo given; Co-intervention(s): 20 mg iron
Outcomes	Serum or plasma zinc concentration, blood haemoglobin concentration, serum or plasma ferritin concentration Time point (wk): 16

Notes	- In addition to the study groups mentioned in this table, there was a group of participants who received zinc only; but there was no placebo group to which this zinc group could be compared in this review. So, baseline characteristics reported in this table are weighted averages of all groups except this zinc group, since this group is not included in any meta-analyses in this review - The number of participants randomised might be off by 1 person, given discrepant numbers stated in the trial report - Though the unit of baseline height is not explicitly stated, it seems likely that the unit is cm. Assuming that the unit is cm, then the baseline height is 139.6 cm

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "…children...were randomly supplemented..." Comment: insufficient details available to make a judgement as to whether or not an allocation sequence was generated using a truly random method
Allocation concealment (selection bias)	Unclear risk	Quote: N/A Comment: insufficient details available to make a judgement
Blinding of participants (performance bias) All outcomes	Unclear risk	Quote: "…double-blind clinical trial…" Comment: insufficient details available to make a judgement
Blinding of personnel (performance bias) All outcomes	Unclear risk	Quote: "…double-blind clinical trial…" Comment: insufficient details available to make a judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "…double-blind clinical trial…" Comment: insufficient details available to make a judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	% Missing: N/A Reasons/details: "Only one child dropped out of the study before the end of the 4 months." Comment: it is unclear which study group this one participant belonged to. However, even if this participant was in the iron group or the iron + zinc group, only approximately 2% of data would be missing for participants eligible for this review. The

		amount of missing data seems too minimal to impact results
Selective reporting (reporting bias)	Unclear risk	Comment: no trial protocol referenced by the study
Other bias	Low risk	Comment: appears to be free of other bias

Friis 1997

Methods	CRCT?: IRCT; Cross-over?: non-cross-over
Participants	Country: Zimbabwe; Setting: Chiredzi District in southeastern Zimbabwe; Urbanicity: rural Inclusion criteria: attending grades 3 to 6 Exclusion criteria: N/A *Baseline characteristics* Avg age (mo): 132; Min age (mo): 132; Max age (mo): 204; % Female: 54 Avg HAZ: -1.18; Stunting: unclear; Avg height (cm): N/A; Avg zinc concentration (μg/dL): 77.8 Total N: 313; Group 1 N: 156; Group 2 N: 157
Interventions	*Group 1:* zinc Formulation: pill/tablet; Compound: sulfate; Frequency: "On school days"; Duration (mo): 12; Dose (mg): 30 mg to children weighing below 29.5 kg; 50 mg to children weighing 29.5 kg or above; Co-intervention(s): N/A *Group 2*: no zinc Placebo given; Co-intervention(s): N/A
Outcomes	Height, weight, weight-to-height ratio, serum or plasma zinc concentration Time point (wk): 52
Notes	- "Of the 370 d long study period, school leaves, weekends and public holidays comprised 185 d. The maximum number of tablets that could be taken by a child was thus 185, equivalent to a tablet every other day." - Due to "severe drought" a "school-based food supplementation programme" was introduced "in the middle of June 1992, after completion of the three-month follow-up examination, and was still in operation at the time of cessation of the zinc/placebo supplementation. The food supplementation programme provided the children with imported maize, dried fish, sugar beans and oil."

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Children were allocated to either zinc or placebo according to the result of simple randomization."

		Comment: insufficient details available to make a judgement as to whether or not an allocation sequence was generated using a truly random method
Allocation concealment (selection bias)	Unclear risk	Quote: "The code was not broken before the data entry, cleaning and analysis were completed." Comment: despite this statement, the method of allocation concealment is not described in sufficient detail to allow a definite judgement
Blinding of participants (performance bias) All outcomes	Low risk	Quote: "...double-blind, placebo-controlled trial…zinc sulphate tablets or identical-looking placebo tablets...The code was not broken before the data entry, cleaning and analysis were completed." Comment: sufficient blinding seems likely
Blinding of personnel (performance bias) All outcomes	Low risk	Quote: "...double-blind, placebo-controlled trial…zinc sulphate tablets or identical-looking placebo tablets...The code was not broken before the data entry, cleaning and analysis were completed." Comment: sufficient blinding seems likely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "...double-blind, placebo-controlled trial…zinc sulphate tablets or identical-looking placebo tablets...The code was not broken before the data entry, cleaning and analysis were completed." Comment: sufficient blinding seems likely
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	% Missing: 11.8 Reasons/details: "…among the 37 (11.8%) children lost to 12-months follow-up, 22 were in the placebo and 15 in the zinc group…" Comment: no information was reported on reasons for missing data
Selective reporting (reporting bias)	High risk	Comment: change in serum ferritin concentration was measured, but is not reported in a way that can be meta-analysed. Prevalence of zinc deficiency and iron de-

		ficiency may have been measured as outcomes, but are not reported
Other bias	Low risk	Comment: appears to be free of other bias

Garcia 1998

Methods	CRCT?: IRCT; Cross-over?: cross-over
Participants	Country: Chile; Setting: N/A; Urbanicity: unclear Inclusion criteria: idiopathic short stature; diminished growth velocity; no other pathological condition nor GH deficiency; zinc intake < 10 mg/day Exclusion criteria: N/A *Baseline characteristics* Avg age (mo): 93.6; Min age (mo): 66; Max age (mo): 159.6; % Female: 0 Avg HAZ: -2.6; Stunting: both - separate data not given; Avg height (cm): 111.8; Avg zinc concentration (μg/dL): 110 Total N: 33; Group 1 N: 16; Group 2 N: 17
Interventions	*Group 1:* zinc Formulation: unclear; Compound: acetate; Frequency: daily; Duration (mo): 6; Dose (mg): 20; Co-intervention(s): N/A *Group 2*: no zinc Placebo given; Co-intervention(s): N/A
Outcomes	Height, weight, serum or plasma zinc concentration Time point (wk): 24
Notes	- The country in which this study took place was not explicitly stated. However, based on the trial authors' affiliations, the language in which the trial report for this study was written, and the hospital from which ethical approval for this study was obtained, it seems that the study took place in Chile - The trial report for this study is written in Spanish, so quotes from it are English translations

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "…a study was carried out in 33 eutrophic prepubertal boys…They were randomly assigned…" Comment: insufficient details available to make a judgement as to whether or not an allocation sequence was generated using a truly random method

Garcia 1998 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Quote: "They were randomly assigned in a double blind fashion…Pharmaceutical preparations were not identifiable…" Comment: despite this statement, the method of allocation concealment is not described in sufficient detail to allow a definite judgement
Blinding of participants (performance bias) All outcomes	Low risk	Quote: "…in a double blind fashion…The pharmaceutical preparations were not identifiable…" Comment: sufficient blinding seems likely
Blinding of personnel (performance bias) All outcomes	Low risk	Quote: "…in a double blind fashion…The pharmaceutical preparations were not identifiable…" Comment: sufficient blinding seems likely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "…in a double blind fashion…The pharmaceutical preparations were not identifiable…" Comment: sufficient blinding seems likely
Incomplete outcome data (attrition bias) All outcomes	Low risk	% Missing: 3 Reasons/details: 1 patient, who started puberty during the study, was excluded Comment: though it is unclear whether exclusion based on initiation of puberty is likely to bias results, the amount of missing data seems too minimal to impact results
Selective reporting (reporting bias)	Unclear risk	Comment: no trial protocol referenced by the study
Other bias	Low risk	Comment: appears to be free of other bias

Gibson 1989

Methods	CRCT?: IRCT; Cross-over?: non-cross-over
Participants	Country: Canada; Setting: southern Ontario; Urbanicity: unclear Inclusion criteria: male; height-for-age ≤ 15th percentile according to reference data of the National Center for Health Statistics (NCHS); midparent height > 25th percentile; Caucasian; full term with weight-for-height appropriate for gestational age; apparently healthy with no detectable medical reasons for poor growth Exclusion criteria: N/A *Baseline characteristics* Avg age (mo): 75.8; Min age (mo): 59; Max age (mo): 95; % Female: 0 Avg HAZ: -1.39; Stunting: both - separate data not given; Avg height (cm): 110.9; Avg

Gibson 1989 (*Continued*)

	zinc concentration (μg/dL): 105 Total N: 60; Group 1 N: 30; Group 2 N: 30
Interventions	*Group 1:* zinc Formulation: solution; Compound: sulfate; Frequency: daily; Duration (mo): 12; Dose (mg): 10; Co-intervention(s): N/A *Group 2*: no zinc Placebo given; Co-intervention(s): N/A
Outcomes	Height, weight, weight-to-height ratio, serum or plasma zinc concentration Time point (wk): 52
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "The subjects were…pair-matched as closely as possible for initial height percentile…initial hair Zn concentrations…age…midpoint height percentile, and reported presence or absence of a picky appetite. The first member of each pair was randomly assigned..." Comment: insufficient details available to make a judgement as to whether or not an allocation sequence was generated using a truly random method
Allocation concealment (selection bias)	Low risk	Quote: "The first member of each pair was randomly assigned by an investigator not involved in the project…" Comment: indicates central randomisation (i.e. randomisation by someone not involved with enrolling patients) to conceal allocation
Blinding of participants (performance bias) All outcomes	Low risk	Quote: "A double-blind, pair-matched 12-mo study…The control children received 1 mL of a placebo solution indistinguishable from the Zn solution in color and flavor, which was administered in a similar manner." Comment: sufficient blinding seems likely
Blinding of personnel (performance bias) All outcomes	Low risk	Quote: "A double-blind, pair-matched 12-mo study…The control children received 1 mL of a placebo solution indistinguishable

Gibson 1989 (*Continued*)

		from the Zn solution in color and flavor, which was administered in a similar manner." Comment: sufficient blinding seems likely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "A double-blind, pair-matched 12-mo study…The control children received 1 mL of a placebo solution indistinguishable from the Zn solution in color and flavor, which was administered in a similar manner." Comment: sufficient blinding seems likely
Incomplete outcome data (attrition bias) All outcomes	Low risk	% Missing: 0 Reasons/details: N/A Comment: N/A
Selective reporting (reporting bias)	Unclear risk	Comment: no trial protocol referenced by the study
Other bias	Low risk	Comment: appears to be free of other bias

Gracia 2005

Methods	CRCT?: IRCT; Cross-over?: non-cross-over
Participants	Country: Colombia; Setting: Cali; Urbanicity: urban Inclusion criteria: healthy at the moment of the examination for selecting study participants; without chronic illness or clinical manifestations of malnutrition; adequate food consumption that satisfied their energy and protein requirements Exclusion criteria: N/A *Baseline characteristics* Avg age (mo): N/A; Min age (mo): 24; Max age (mo): 59; % Female: N/A Avg HAZ: 0; Stunting: both - separate data not given; Avg height (cm): 95.84; Avg zinc concentration (μg/dL): 72.6 Total N: 350; Group 1 N: 175; Group 2 N: 175
Interventions	*Group 1:* zinc Formulation: unclear; Compound: unclear; Frequency: daily; Duration (mo): 8; Dose (mg): 12; Co-intervention(s): mineral and vitamin supplement *Group 2*: no zinc Placebo given; Co-intervention(s): mineral and vitamin supplement
Outcomes	Height, weight-to-height ratio Time point (wk): 32
Notes	- Though the exact numbers of participants randomised to each study group was not explicitly stated, the trial report does state that they planned to have 2 study groups of

	equal numbers - In this study, all children with parasites at baseline were treated - Though the English abstract for this trial report states that zinc and placebo were provided for 9 months, the Spanish abstract and the full text of this trial report state that zinc and placebo were provided for 8 months - The trial report for this study is written in Spanish, so quotes from it are English translations

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "...they were randomly divided in two groups…" Comment: insufficient details available to make a judgement as to whether or not an allocation sequence was generated using a truly random method
Allocation concealment (selection bias)	Unclear risk	Quote: N/A Comment: insufficient details available to make a judgement
Blinding of participants (performance bias) All outcomes	Low risk	Quote: "...a double blind study…The packaging of the two preparations were identical…and its composition was kept secret until the end of the analysis…Neither…nor the parents knew the composition of the supplement that corresponded to each child." Comment: sufficient blinding seems likely
Blinding of personnel (performance bias) All outcomes	Low risk	Quote: "...a double blind study…The packaging of the two preparations were identical…and its composition was kept secret until the end of the analysis." Comment: sufficient blinding seems likely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "...a double blind study…The packaging of the two preparations were identical…and its composition was kept secret until the end of the analysis…Neither the group of investigators nor...knew the composition of the supplement that corresponded to each child...The codes of the two supplements were only opened once the analysis was concluded." Comment: sufficient blinding seems likely

Gracia 2005 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	% Missing: 34 Reasons/details: of the 350 children with which the study began, 22% were missing due to migration from the study area, and a few withdrew because the physician suggested it or due to the family's decision Comment: migration was the most common reason for missing data, and this reason is unlikely to bias results. However, 12% of data were missing for reasons other than migration, and reasons for, and amount of, missing data is not reported separately for either study group
Selective reporting (reporting bias)	High risk	Comment: serum zinc concentration was measured, but is not reported in a way that can be meta-analysed. Prevalence of stunting was measured as an outcome, but is not reported as an outcome
Other bias	Low risk	Comment: appears to be free of other bias

Gupta 2003

Methods	CRCT?: IRCT; Cross-over?: non-cross-over
Participants	Country: India; Setting: 3 adjoining villages about 10 km away from Kolkata, West Bengal; Urbanicity: rural Inclusion criteria: residing permanently in these villages with their parents Exclusion criteria: N/A *Baseline characteristics* Avg age (mo): N/A; Min age (mo): 6; Max age (mo): 41; % Female: 53.93 Avg HAZ: N/A; Stunting: unclear; Avg height (cm): N/A; Avg zinc concentration (μg/dL): N/A Total N: 280; Group 1 N: 186; Group 2 N: 94
Interventions	*Group 1:* zinc Formulation: solution; Compound: sulfate; Frequency: 5 days/wk or weekly; Duration (mo): 4; Dose (mg): 10 mg or 50 mg; Co-intervention(s): N/A *Group 2*: no zinc Placebo given; Co-intervention(s): N/A
Outcomes	Incidence of all-cause diarrhoea Time point (wk): 16
Notes	95 children received "10 mg zinc for 5 d wk-1", 91 children received "50 mg zinc once weekly", and 94 children received placebo

Gupta 2003 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "The randomization was done by a statistician using random number tables." Comment: N/A
Allocation concealment (selection bias)	Low risk	Quote: "The two zinc syrups and placebo were...prepared in identical bottles...bottles were numbered according to the random number by the pharmaceutical company, which kept the code number to maintain confidentiality." Comment: indicates central randomisation (i.e. randomisation by someone not involved with enrolling patients) and sequentially numbered drug containers of identical appearance to conceal allocation
Blinding of participants (performance bias) All outcomes	Low risk	Quote: "...double-blind…The two zinc syrups and placebo were similar in colour and taste and were prepared in identical bottles." Comment: sufficient blinding seems likely
Blinding of personnel (performance bias) All outcomes	Low risk	Quote: "...double-blind…The two zinc syrups and placebo were similar in colour and taste and were prepared in identical bottles." Comment: sufficient blinding seems likely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "...double-blind…The two zinc syrups and placebo were similar in colour and taste and were prepared in identical bottles." Comment: sufficient blinding seems likely
Incomplete outcome data (attrition bias) All outcomes	Low risk	% Missing: 0 Reasons/details: N/A Comment: though the authors did not explicitly report that there was no missing data, it seems from the text and tables that there were no missing data
Selective reporting (reporting bias)	High risk	Comment: side effects (e.g. vomiting) were measured, but are not reported in a way that can be meta-analysed

Gupta 2003 (*Continued*)

Other bias	Low risk	Comment: appears to be free of other bias

Gupta 2007

Methods	CRCT?: CRCT; Cross-over?: non-cross-over
Participants	Country: India; Setting: 11 villages located 35 km from Kolkata; Urbanicity: rural Inclusion criteria: N/A Exclusion criteria: N/A *Baseline characteristics* Avg age (mo): N/A; Min age (mo): 6; Max age (mo): 48; % Female: 51 Avg HAZ: N/A; Stunting: unclear; Avg height (cm): N/A; Avg zinc concentration (μg/dL): N/A Total N: 1878; Group 1 N: 943; Group 2 N: 935 Total clusters: 30; Group 1 clusters: N/A; Group 2 clusters: N/A
Interventions	*Group 1:* zinc Formulation: solution; Compound: unclear; Frequency: weekly; Duration (mo): 6; Dose (mg): 50; Co-intervention(s): vitamin B complex *Group 2*: no zinc Placebo given; Co-intervention(s): vitamin B complex
Outcomes	Incidence of all-cause diarrhoea, participants with $\geq$ 1 vomiting episode Time point (wk): 52 (incidence of all-cause diarrhoea), 24 (participants with $\geq$ 1 vomiting episode)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "For distribution of the children into 2 groups, areas of 30 surveillance workers were randomly divided into 2 groups." Comment: insufficient details available to make a judgement as to whether or not an allocation sequence was generated using a truly random method
Allocation concealment (selection bias)	Unclear risk	Quote: N/A Comment: insufficient details available to make a judgement
Blinding of participants (performance bias) All outcomes	Low risk	Quote: "...double blind study…The zinc and placebo syrups in vitamin B-complex base were prepared with identical color,

		taste, and odor. The syrups were supplied in similar sized amber colored bottles...Each bottle was labeled with a code number...For maintenance of confidentiality, the code numbers of each group were kept with a third person who was not directly associated with the study." Comment: sufficient blinding seems likely
Blinding of personnel (performance bias) All outcomes	Low risk	Quote: "...double blind study…The zinc and placebo syrups in vitamin B-complex base were prepared with identical color, taste, and odor. The syrups were supplied in similar sized amber colored bottles...Each bottle was labeled with a code number...For maintenance of confidentiality, the code numbers of each group were kept with a third person who was not directly associated with the study." Comment: sufficient blinding seems likely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "...double blind study…The zinc and placebo syrups in vitamin B-complex base were prepared with identical color, taste, and odor. The syrups were supplied in similar sized amber colored bottles...Each bottle was labeled with a code number...For maintenance of confidentiality, the code numbers of each group were kept with a third person who was not directly associated with the study." Comment: sufficient blinding seems likely
Incomplete outcome data (attrition bias) All outcomes	High risk	% Missing: 9 Reasons/details: "One hundred and sixty-six children were excluded from the study because the guardians of 45 children refused to accept the syrup, 67 children left the area, 50 discontinued syrup, 2 children died, 1 due to drowning and another due to snake bite and 2 children had cardiac disorders." (However, 45 + 67 + 50 + 2 + 1 + 2 = 167, not 166). Among the 50 children for whom syrup was discontinued, "In 17...it was because of vomiting and in 33...because of advice from the local doctor/guardians of the family." In addition, "Ninety-five...guardians of the study children could not be motivated", and it is un-

		clear whether or not some, or all, of the children of these guardians were excluded and/or were among the 45 children who "refused to accept the syrup." Comment: a somewhat sizeable proportion of data is missing, and neither reasons for, nor amounts of, missing data were reported separately for the zinc versus the placebo group. It is also unclear what implications for missing data might result from the fact that "Ninety-five...guardians of the study children could not be motivated."
Selective reporting (reporting bias)	High risk	Comment: all-cause mortality was measured, but is not reported in a way that can be meta-analysed
Other bias	Low risk	Comment: appears to be free of other bias

Hambidge 1978

Methods	CRCT?: IRCT; Cross-over?: non-cross-over
Participants	Country: United States of America; Setting: Denver, Colorado; Urbanicity: urban Inclusion criteria: height-for-age percentiles below the 10th for McCammon's standards; hair zinc concentration less than 105 μg/g Exclusion criteria: N/A *Baseline characteristics* Avg age (mo): 52.6; Min age (mo): 38; Max age (mo): 61; % Female: 44 Avg HAZ: N/A; Stunting: unclear; Avg height (cm): N/A; Avg zinc concentration (μg/dL): N/A Total N: 75; Group 1 N: 38; Group 2 N: 37
Interventions	*Group 1:* zinc Formulation: solution; Compound: sulfate; Frequency: 5 days/wk; Duration (mo): 6; Dose (mg): 14; Co-intervention(s): N/A *Group 2*: no zinc Placebo given; Co-intervention(s): N/A
Outcomes	Height, weight Time point (wk): 24
Notes	"At the completion of this study, parents were requested to administer the zinc sulfate (or placebo) for a further 6 month period at home. Twenty-two test children and 25 controls (including 10 of the male pairs) remained in this study, but many of them did not take the syrup regularly."
Risk of bias	

Hambidge 1978 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The zinc-supplemented and control children were pair-matched as closely as possible according to sex, ethnic origin, age, initial height percentile and initial hair zinc level." "The first member of each pair was assigned randomly to receive either the zinc supplement or the placebo." Comment: insufficient details available to make a judgement as to whether or not an allocation sequence was generated using a truly random method
Allocation concealment (selection bias)	Unclear risk	Quote: N/A Comment: insufficient details available to make a judgement
Blinding of participants (performance bias) All outcomes	Unclear risk	Quote: "The study was designed as a double-blind controlled investigation." Comment: insufficient details available to make a judgement
Blinding of personnel (performance bias) All outcomes	Unclear risk	Quote: "The study was designed as a double-blind controlled investigation." Comment: insufficient details available to make a judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "The study was designed as a double-blind controlled investigation." Comment: insufficient details available to make a judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	% Missing: 11 Reasons/details: in the zinc group, 2 participants were missing. In the control group, 6 participants were missing Comment: the control group had a larger amount of missing data than the zinc group, and reasons for missing data were not reported
Selective reporting (reporting bias)	Unclear risk	Comment: no trial protocol referenced by the study
Other bias	Low risk	Comment: appears to be free of other bias

Han 2002

Methods	CRCT?: IRCT; Cross-over?: non-cross-over
Participants	Country: China; Setting: Luoyang City, Henan Province; Urbanicity: urban Inclusion criteria: height below -1 SD height-for-age of the standard; living in their local communities for at least 2 years; without any chronic or acute diseases Exclusion criteria: absent from the kindergarten for a continuous period of more than 30 days *Baseline characteristics* Avg age (mo): 48.17; Min age (mo): 36; Max age (mo): 60; % Female: 50 Avg HAZ: N/A; Stunting: unclear; Avg height (cm): 95.9; Avg zinc concentration (μg/dL): N/A Total N: 119; Group 1 N: 34; Group 2 N: 28; Group 3 N: 28; Group 4 N: 29
Interventions	*Group 1:* zinc Formulation: tablets or added to milk powder; Compound: unclear; Frequency: 5 days/wk; Duration (mo): 12; Dose (mg): 3.5; Co-intervention(s): N/A *Group 2*: no zinc Placebo given; Co-intervention(s): N/A *Group 3:* zinc Co-intervention(s): 250 mg calcium; 200 μg vitamin A *Group 4*: no zinc Placebo given; Co-intervention(s): 250 mg calcium; 200 μg vitamin A
Outcomes	Incidence of all-cause diarrhoea, height, weight Time point (wk): 52
Notes	- In addition to the study groups mentioned in this table, there were 2 other groups. One was a group of 37 participants who, received zinc and calcium. The other was a group of 34 participants of normal height, who received placebo. Baseline characteristics reported in this table are weighted averages of all groups except these 2 groups, since these 2 groups are not included in any meta-analyses in this review - The trial reports for this study state that, "Micronutrients were added to milk powder or in the form of tablets and provided alternately."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "...children...were randomly assigned to five groups...children were divided into five groups and randomly assigned to different supplementations…" Comment: insufficient details available to make a judgement as to whether or not an allocation sequence was generated using a truly random method

Allocation concealment (selection bias)	Unclear risk	Quote: N/A Comment: insufficient details available to make a judgement
Blinding of participants (performance bias) All outcomes	Low risk	Quote: "A double-blind placebo-controlled trial was conducted…The placebos were indistinguishable from the supplements in both appearance and taste." Comment: sufficient blinding seems likely
Blinding of personnel (performance bias) All outcomes	Low risk	Quote: "A double-blind placebo-controlled trial was conducted…The placebos were indistinguishable from the supplements in both appearance and taste." Comment: sufficient blinding seems likely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "A double-blind placebo-controlled trial was conducted…The placebos were indistinguishable from the supplements in both appearance and taste." Comment: sufficient blinding seems likely
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	% Missing: 12 Reasons/details: N/A Comment: 12% of the randomised participants eligible for our review had data missing for diarrhoea outcomes; this 12% missing figure includes all groups except the zinc + calcium group and the normal height placebo group, since these 2 groups are not included in any meta-analyses in this review. For diarrhoea outcomes: 1, 6, 4, and 3 participants were missing in the zinc, placebo, zinc + calcium + vitamin A, and calcium + vitamin A groups, respectively. No information was reported on reasons for missing data
Selective reporting (reporting bias)	Unclear risk	Comment: incidence and prevalence of respiratory illness, which meets the criteria of this review, may have been measured and reported; but it is unclear how respiratory illness was defined in this study. No trial protocol referenced by the study
Other bias	Low risk	Comment: appears to be free of other bias

Han 2002 (2)

Methods	
Participants	
Interventions	
Outcomes	Incidence of all-cause diarrhoea, height, weight
Notes	As Han 2002 above

Hettiarachchi 2008

Methods	CRCT?: CRCT; Cross-over?: non-cross-over
Participants	Country: Sri Lanka; Setting: Galle District; Urbanicity: multiple Inclusion criteria: haemoglobin level ≥ 80 g/L Exclusion criteria: suffering from acute or chronic diseases; inflammatory conditions; a history of any drug consumption other than paracetamol or antihistamines for minor ailments; currently consuming nutrient supplements; donated blood or received a blood transfusion within the last 4 months *Baseline characteristics* Avg age (mo): 145.35; Min age (mo): 144; Max age (mo): 155; % Female: 65 Avg HAZ: -1.16; Stunting: both - separate data not given; Avg height (cm): 143.25; Avg zinc concentration (μg/dL): 56.17 Total N: 341; Group 1 N: 107; Group 2 N: 59; Group 3 N: 127; Group 4 N: 48 Total clusters: 14; Group 1 clusters: N/A; Group 2 clusters: N/A; Group 3 clusters: N/A; Group 4 clusters: N/A
Interventions	*Group 1:* zinc Formulation: capsule; Compound: sulfate; Frequency: 5 days/wk; Duration (mo): 6; Dose (mg): 14; Co-intervention(s): N/A *Group 2*: no zinc Placebo given; Co-intervention(s): N/A *Group 3:* zinc Co-intervention(s): 50 mg iron *Group 4*: no zinc Placebo given; Co-intervention(s): 50 mg iron
Outcomes	Height, weight, prevalence of stunting, serum or plasma zinc concentration, prevalence of zinc deficiency, blood haemoglobin concentration, prevalence of anaemia, serum or plasma ferritin concentration, prevalence of iron deficiency Time point (wk): 25
Notes	- All baseline and outcome data from this study included in this review apply only to the subset of this study's participants who were less than 13 years of age at baseline - "All the study subjects were treated for parasites by giving mebendazole (500 mg) as a single oral dose (mass-treatment) approximately 2 weeks before the start of the study."

Risk of bias

Hettiarachchi 2008 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "...randomized into one of four groups…" Comment: insufficient details available to make a judgement as to whether or not an allocation sequence was generated using a truly random method
Allocation concealment (selection bias)	Unclear risk	Quote: "...randomized into one of four groups...using a double-blind approach." Comment: insufficient details available to make a judgement
Blinding of participants (performance bias) All outcomes	Low risk	Quote: "...double-blind approach." "...All capsules (iron, zinc, combined & Placebo) were of same colour capsule in same mean weight" Comment: sufficient blinding seems likely
Blinding of personnel (performance bias) All outcomes	Low risk	Quote: "...double-blind approach." "...the class teacher who gave the supplement during breakfast break were not aware about the content of the supplement...All capsules (iron, zinc, combined & Placebo) were of same colour capsule in same mean weight" Comment: sufficient blinding seems likely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "...double-blind approach." "Research assistant who distribute supplements to the class...were not aware about the content of the supplement...All capsules (iron, zinc, combined & Placebo) were of same colour capsule in same mean weight" Comment: sufficient blinding seems likely
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	% Missing: 16 Reasons/details: 7, 18, 13, and 18 participants from the zinc, placebo, iron + zinc, and iron groups, respectively, were "dropped for various reasons: withdrawal from the study…refusal to give blood after supplementation…and absence on the day of the post-supplementation blood collection..." Comment: a fairly large proportion of data is missing, and reasons for missing data

Hettiarachchi 2008 (*Continued*)

		were not reported separately for each study group
Selective reporting (reporting bias)	Unclear risk	Comment: no trial protocol referenced by the study
Other bias	Low risk	Comment: appears to be free of other bias

Hettiarachchi 2008 (2)

Methods	
Participants	
Interventions	
Outcomes	Height, weight, prevalence of stunting, serum or plasma zinc concentration, prevalence of zinc deficiency, blood haemoglobin concentration, prevalence of anaemia, serum or plasma ferritin concentration, prevalence of iron deficiency
Notes	As Hettiarachchi 2008 above

Hong 1982

Methods	CRCT?: IRCT; Cross-over?: cross-over
Participants	Country: China; Setting: villages, Anhui Province, and Shanghai City; Urbanicity: multiple Inclusion criteria: weight lower than the 10th percentile for children at equivalent height and age Exclusion criteria: hereditary, endocrine, and metabolic disorders *Baseline characteristics* Avg age (mo): N/A; Min age (mo): 4; Max age (mo): 72; % Female: 49.4 Avg HAZ: N/A; Stunting: both - separate data not given; Avg height (cm): N/A; Avg zinc concentration (μg/dL): 70.3 Total N: 158; Group 1 N: N/A; Group 2 N: N/A
Interventions	*Group 1:* zinc Formulation: solution; Compound: sulfate; Frequency: daily; Duration (mo): 2.4; Dose (mg): unclear; Co-intervention(s): vitamin B complex *Group 2*: no zinc Placebo given; Co-intervention(s): vitamin B complex
Outcomes	Height, weight, serum or plasma zinc concentration Time point (wk): 10

Hong 1982 (*Continued*)

Notes	- Of the 158 participants randomised, 119 were 12 months of age or older - 64 participants in the zinc group and 67 participants in the control group completed the study; but the number of participants randomised to each group was not reported - 92 children in the trial, who were found to be anaemic, were provided iron; the trial report did not state the dose or the duration of iron provided, nor did it state how many of these children were in the zinc group or the placebo group - The trial report for this study is written in Chinese, so quotes from it are English translations

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "…randomly assigned…" Comment: insufficient details available to make a judgement as to whether or not an allocation sequence was generated using a truly random method
Allocation concealment (selection bias)	Unclear risk	Quote: N/A Comment: insufficient details available to make a judgement
Blinding of participants (performance bias) All outcomes	Unclear risk	Quote: "…double blind…" Comment: insufficient details available
Blinding of personnel (performance bias) All outcomes	Unclear risk	Quote: "…double blind…" Comment: insufficient details available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "…double blind…" Comment: insufficient details available
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	% Missing: 19 Reasons/details: N/A Comment: the following were not reported: number of participants randomised to each group, amount of missing data for each group, reasons for missing data in each group
Selective reporting (reporting bias)	Unclear risk	Comment: no trial protocol referenced by the study
Other bias	Low risk	Comment: appears to be free of other bias

Ince 1995

Methods	CRCT?: IRCT; Cross-over?: non-cross-over
Participants	Country: Turkey; Setting: Ankara; Urbanicity: urban Inclusion criteria: height between the 3rd and 10th percentiles for age; product of a term pregnancy; birth measurements appropriate for gestational age; no detectable medical reasons for poor growth Exclusion criteria: N/A *Baseline characteristics* Avg age (mo): 50; Min age (mo): 25; Max age (mo): 76; % Female: 12 Avg HAZ: -1.55; Stunting: non-stunted; Avg height (cm): 94.2; Avg zinc concentration (μg/dL): N/A Total N: 25; Group 1 N: 16; Group 2 N: 9
Interventions	*Group 1:* zinc Formulation: solution; Compound: sulfate; Frequency: daily; Duration (mo): 12; Dose (mg): 10; Co-intervention(s): N/A *Group 2*: no zinc Placebo given; Co-intervention(s): N/A
Outcomes	Height, weight Time point (wk): 52
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The participants for the study were randomized to study or control groups" by "a lottery"." Comment: it seems likely that the allocation sequence was generated using a truly random method
Allocation concealment (selection bias)	Unclear risk	Quote: N/A Comment: insufficient details available to make a judgement
Blinding of participants (performance bias) All outcomes	Low risk	Quote: "…double-blind study design." Comment: sufficient blinding seems likely
Blinding of personnel (performance bias) All outcomes	Low risk	Quote: "…double-blind study design…Zinc and placebo were given to children by their kindergarten teachers…Test and control groups were not known by the kindergarten teachers…" Comment: sufficient blinding seems likely

Ince 1995 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "…double-blind study design…Test and control groups were not known by…the investigator who performed anthropometry..." Comment: sufficient blinding seems likely
Incomplete outcome data (attrition bias) All outcomes	Low risk	% Missing: 0 Reasons/details: N/A Comment: N/A
Selective reporting (reporting bias)	Unclear risk	Comment: no trial protocol referenced by the study
Other bias	Low risk	Comment: appears to be free of other bias

Kartasurya 2012

Methods	CRCT?: IRCT; Cross-over?: non-cross-over	
Participants	Country: Indonesia; Setting: Semarang; Urbanicity: unclear Inclusion criteria: apparently healthy children Exclusion criteria: moderately and severely malnourished children *Baseline characteristics* Avg age (mo): 42.24; Min age (mo): 24; Max age (mo): 60; % Female: 48% Avg HAZ: -1.73; Stunting: non-stunted; Avg height (cm): Not reported; Avg zinc concentration (μg/dL): Not reported Total N: 826; Group 1 N: 415; Group 2 N: 411	
Interventions	*Group 1:* zinc Formulation: solution; Compound: sulfate; Frequency: daily; Duration (mo): 4; Dose (mg): 10; Co-intervention(s): vitamin A *Group 2*: no zinc Placebo given; Co-intervention(s): vitamin A	
Outcomes	All-cause mortality	
Notes		

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "one of the physicians (not investigators) used random numbers to allocate each child"

Kartasurya 2012 (*Continued*)

Allocation concealment (selection bias)	Low risk	Quote: "one of the physicians (not investigators) used random numbers to allocate each child"
Blinding of participants (performance bias) All outcomes	Low risk	Quote: "Supplements were prepared and labelled with alphabetic codes by the Pharmacy Department of Diponegoro University. There was no difference between the syrups in taste or appearance."
Blinding of personnel (performance bias) All outcomes	Low risk	Quote: "Supplements were prepared and labelled with alphabetic codes by the Pharmacy Department of Diponegoro University. There was no difference between the syrups in taste or appearance."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Supplements were prepared and labelled with alphabetic codes by the Pharmacy Department of Diponegoro University. There was no difference between the syrups in taste or appearance."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Stopped taking zinc or placebo" Comment: 3% missing
Selective reporting (reporting bias)	High risk	Registered retrospectively: ACTRN 12611000659909 Comment: only mortality reported - morbidity not reported
Other bias	Low risk	Comment: appears to be free of other bias

Kikafunda 1998

Methods	CRCT?: IRCT; Cross-over?: non-cross-over
Participants	Country: Uganda; Setting: a suburb of Kampala; Urbanicity: peri-urban Inclusion criteria: N/A Exclusion criteria: major medical or physical problems *Baseline characteristics* Avg age (mo): 55.8; Min age (mo): 33; Max age (mo): 89; % Female: 46 Avg HAZ: -0.7; Stunting: unclear; Avg height (cm): 103.4; Avg zinc concentration (μg/dL): N/A Total N: 155; Group 1 N: 79; Group 2 N: 76
Interventions	*Group 1:* zinc Formulation: pill/tablet; Compound: sulfate; Frequency: 5 days/wk; Duration (mo): 6; Dose (mg): 10; Co-intervention(s): N/A

	Group 2: no zinc Placebo given; Co-intervention(s): N/A
Outcomes	Height, weight Time point (wk): 32
Notes	"Because of the nature of school terms in Uganda, the treatment period was 2-phased, each phase lasting 3 mo with a 2-mo period in between with no supplements when the children were on vacation."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The randomization procedure was stratified according to sex…" Comment: insufficient details available to make a judgement as to whether or not an allocation sequence was generated using a truly random method
Allocation concealment (selection bias)	Unclear risk	Quote: N/A Comment: insufficient details available to make a judgement
Blinding of participants (performance bias) All outcomes	Low risk	Quote: "The study was randomized, double-blind…The zinc and placebo tablets, which were indistinguishable in both color and taste..." Comment: sufficient blinding seems likely
Blinding of personnel (performance bias) All outcomes	Low risk	Quote: "The study was randomized, double-blind…The zinc and placebo tablets, which were indistinguishable in both color and taste..." Comment: sufficient blinding seems likely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The study was randomized, double-blind…The zinc and placebo tablets, which were indistinguishable in both color and taste..." Comment: sufficient blinding seems likely
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	% Missing: 27 Reasons/details: "Two children from school 3, one from the zinc and the other from the control group, dropped out of the trial before the end of phase 1 because of insufficient funds for tuition...Forty chil-

		dren...did not return for phase 2 of the trial, mainly because of a change of schools or insufficient funds." "Phase 1" refers to months 0 to 3 and "phase 2" refers to months 6 to 8 Comment: a large proportion of data is missing, and no information was reported for "phase 2" on differences between study groups in numbers of participants who dropped out
Selective reporting (reporting bias)	High risk	Comment: diarrhoea incidence and malaria incidence were measured, but are not reported
Other bias	Low risk	Comment: appears to be free of other bias

Kurugöl 2006

Methods	CRCT?: IRCT; Cross-over?: non-cross-over
Participants	Country: Turkey; Setting: the city of Izmir; Urbanicity: urban Inclusion criteria: overall good health Exclusion criteria: known chronic disease; immunodeficiency disorder; asthma; history of sensitivity to or an idiosyncratic experience with zinc; parents who were unwilling or unable to comply with clinical study procedures *Baseline characteristics* Avg age (mo): 67.2; Min age (mo): 24; Max age (mo): 120; % Female: 50.5 Avg HAZ: N/A; Stunting: unclear; Avg height (cm): N/A; Avg zinc concentration (μg/dL): N/A Total N: 200; Group 1 N: 100; Group 2 N: 100
Interventions	*Group 1:* zinc Formulation: solution; Compound: sulfate; Frequency: daily; Duration (mo): 7; Dose (mg): 15; Co-intervention(s): N/A *Group 2*: no zinc Placebo given; Co-intervention(s): N/A
Outcomes	Study withdrawal, participants with $\geq$ 1 side effect, participants with $\geq$ 1 vomiting episode Time point (wk): 28
Notes	The dose was increased to 2 times per day (30 mg of zinc) at the onset of cold, until symptoms resolved

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Random sequence generation (selection bias)	Low risk	Quote: "A statistical consultant programmed a computer-generated randomization code…" Comment: N/A
Allocation concealment (selection bias)	Low risk	Quote: "A statistical consultant programmed a computer-generated randomization code and prepared the packages of medication. The packages were randomly distributed to the study personnel, all of whom were blind to the group assignments. " Comment: indicates central randomisation to conceal allocation
Blinding of participants (performance bias) All outcomes	Low risk	Quote: "This randomized, double-blind, placebo-controlled, prospective study... Placebo and active syrups were identical in appearance, texture and flavouring content, except that the placebo lacked the zinc component...All parents were also blind to the group assignments." Comment: sufficient blinding seems likely
Blinding of personnel (performance bias) All outcomes	Low risk	Quote: "This randomized, double-blind, placebo-controlled, prospective study... Placebo and active syrups were identical in appearance, texture and flavouring content, except that the placebo lacked the zinc component...The packages were randomly distributed to the study personnel, all of whom were blind to the group assignments. " Comment: sufficient blinding seems likely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "This randomized, double-blind, placebo-controlled, prospective study... Placebo and active syrups were identical in appearance, texture and flavouring content, except that the placebo lacked the zinc component...The packages were randomly distributed to the study personnel, all of whom were blind to the group assignments. " Comment: sufficient blinding seems likely
Incomplete outcome data (attrition bias) All outcomes	Low risk	% Missing: 3 Reasons/details: overall, 97% (n = 194) of the children (97 in the zinc group and 97

		in the placebo group) completed the 7-mo study period; 6 (3%) discontinued, 4 for non-compliance and 2 for adverse effects due to medication Comment: amount of missing data was similar between study groups. Missing data seem too minimal to impact results
Selective reporting (reporting bias)	Unclear risk	Comment: no trial protocol referenced by the study
Other bias	Low risk	Comment: appears to be free of other bias

Larson 2010

Methods	CRCT?: IRCT; Cross-over?: non-cross-over
Participants	Country: Bangladesh; Setting: Mirpur district, Dhaka; Urbanicity: urban Inclusion criteria: an acute episode of diarrhoea of 24 to 72 h duration Exclusion criteria: severe dehydration; suspected cholera or pneumonia; bipedal oedema; currently receiving zinc; a weight-for-height z-score below -3; already participating in another study involving nutritional or therapeutic interventions *Baseline characteristics* Avg age (mo): 15.4; Min age (mo): 6; Max age (mo): 24; % Female: 50 Avg HAZ: -1.72; Stunting: unclear; Avg height (cm): 73.6; Avg zinc concentration (μg/dL): N/A Total N: 353; Group 1 N: 176; Group 2 N: 177
Interventions	*Group 1:* zinc Formulation: solution; Compound: sulfate; Frequency: daily; Duration (mo): 3; Dose (mg): 10; Co-intervention(s): N/A *Group 2*: no zinc Placebo given; Co-intervention(s): N/A
Outcomes	All-cause mortality, incidence of all-cause diarrhoea, blood haemoglobin concentration Time point (wk): 6 (blood haemoglobin concentration), 36 (all-cause mortality, incidence of all-cause diarrhoea)
Notes	- All children received 10 days of zinc treatment (20 mg/day) for an episode of acute childhood diarrhoea before they were divided into zinc versus placebo groups for the preventive supplementation randomised controlled trial phase of this study - It is unclear whether the maximum age of eligible trial participants at baseline was 23 or 24 months

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Random sequence generation (selection bias)	Low risk	Quote: "…lots were numbered and randomly assigned in permuted blocks of six (three placebo, three zinc)." Comment: N/A
Allocation concealment (selection bias)	Low risk	Quote: "All placebo and zinc-containing bottles of syrup…were serially numbered in lots of 100. These lots were listed and then sequentially selected based upon random assignment…each child received a 3-month supply of syrup (five bottles) and the lot number was recorded. The randomization code was not broken until after all children had completed the trial and the data had been entered and verified." Comment: seems to indicate sequentially numbered drug containers of identical appearance to conceal allocation
Blinding of participants (performance bias) All outcomes	Low risk	Quote: "...double-blind field trial…The randomization code was not broken until after all children had completed the trial and the data had been entered and verified." "…children received 10 mg/d zinc (zinc sulfate, syrup formulation) or placebo (placebo syrup, similar in appearance and taste)…" Comment: sufficient blinding seems likely
Blinding of personnel (performance bias) All outcomes	Low risk	Quote: "...double-blind field trial…The randomization code was not broken until after all children had completed the trial and the data had been entered and verified." "…children received 10 mg/d zinc (zinc sulfate, syrup formulation) or placebo (placebo syrup, similar in appearance and taste)…" Comment: sufficient blinding seems likely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "...double-blind field trial…The randomization code was not broken until after all children had completed the trial and the data had been entered and verified." "…children received 10 mg/d zinc (zinc sulfate, syrup formulation) or placebo (placebo syrup, similar in appearance and taste)…" Comment: sufficient blinding seems likely

Larson 2010 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	% Missing: 6 Reasons/details: In the zinc group: 12 children were lost and 1 died. In the placebo group: 7 children were lost Comment: reasons for, and amount of, missing data were similar between study groups. Missing data seem too minimal to impact results
Selective reporting (reporting bias)	High risk	Comment: height-for age z-score, weight-for age z-score, weight-for-height z-score, serum zinc concentration, and serum copper concentration were measured, but are not reported in a way that can be meta-analysed. Of these outcomes, only serum zinc concentration was pre-specified in the protocol for this study. Haemoglobin concentration was reported, but was not pre-specified in the protocol for this study Protocol identifier: NCT00408356
Other bias	Low risk	Comment: appears to be free of other bias

Lind 2003

Methods	CRCT?: IRCT; Cross-over?: non-cross-over
Participants	Country: Indonesia; Setting: Purworejo district, central Java; Urbanicity: rural Inclusion criteria: healthy; singleton; mother who had been monitored during pregnancy and birth Exclusion criteria: metabolic or neurologic disorders; physical handicaps affecting development, feeding, or activity; severe or protracted illness; haemoglobin concentrations < 90 g/L on assessment of eligibility *Baseline characteristics* Avg age (mo): 6; Min age (mo): 6; Max age (mo): 6; % Female: 48 Avg HAZ: -0.34; Stunting: both - separate data not given; Avg height (cm): 65.4; Avg zinc concentration (μg/dL): 60.8 Total N: 680; Group 1 N: 170; Group 2 N: 170; Group 3 N: 170; Group 4 N: 170
Interventions	*Group 1:* zinc Formulation: solution; Compound: sulfate; Frequency: daily; Duration (mo): 6; Dose (mg): 10; Co-intervention(s): 30 mg ascorbic acid *Group 2*: no zinc Placebo given; Co-intervention(s): 30 mg ascorbic acid *Group 3:* zinc Co-intervention(s): 10 mg iron; 30 mg ascorbic acid *Group 4*: no zinc Placebo given; Co-intervention(s): 10 mg iron; 30 mg ascorbic acid

Outcomes	All-cause mortality, incidence of all-cause diarrhoea, incidence of LRTI, height, weight, weight-to-height ratio, prevalence of stunting, serum or plasma zinc concentration, prevalence of zinc deficiency, participants with ≥ 1 side effect, participants with ≥ 1 vomiting episode, blood haemoglobin concentration, prevalence of anaemia, serum or plasma ferritin concentration, prevalence of iron deficiency, serum or plasma copper concentration Time point (wk): 24
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomization was planned and generated by an independent statistician, and was performed in blocks of 20." Comment: insufficient details available to make a judgement as to whether or not an allocation sequence was generated using a truly random method
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was planned and generated by an independent statistician…" Comment: indicates central randomisation (i.e. randomisation by someone not involved with enrolling patients) to conceal allocation
Blinding of participants (performance bias) All outcomes	Low risk	Quote: "…double blind, placebo-controlled trial…The pharmaceutical company marked the 4 different supplements with letter codes, blinded to...participants. Information on group assignment was kept in a safe at the administrative offices of Gadjah Mada and Umeå Universities until after the intent-to-treat analysis." Comment: sufficient blinding seems likely
Blinding of personnel (performance bias) All outcomes	Low risk	Quote: "…double blind, placebo-controlled trial…The pharmaceutical company marked the 4 different supplements with letter codes, blinded to researchers... Information on group assignment was kept in a safe at the administrative offices of Gadjah Mada and Umeå Universities until after the intent-to-treat analysis."

		Comment: sufficient blinding seems likely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "…double blind, placebo-controlled trial…The pharmaceutical company marked the 4 different supplements with letter codes, blinded to researchers... Information on group assignment was kept in a safe at the administrative offices of Gadjah Mada and Umeå Universities until after the intent-to-treat analysis. The laboratory assessing the biochemical outcomes was not aware of the randomization groups. " Comment: sufficient blinding seems likely
Incomplete outcome data (attrition bias) All outcomes	Low risk	% Missing: 2 Reasons/details: for all outcomes: 1, 1, 3, and 4 participants in the zinc, placebo, zinc + iron, and iron groups, respectively, "refused supplement...discontinued intervention"; 2 from the zinc group died; and 3 from the zinc + iron group moved. For height, weight, and weight-to-height ratio outcomes: 5, 5, 3, and 3 participants in the zinc, placebo, zinc + iron, and iron groups, respectively, were "excluded from analysis" due to "incomplete anthropometric data." For serum zinc, haemoglobin, serum ferritin, and serum copper outcomes: 13, 14, 9, and 10 participants in the zinc, placebo, zinc + iron, and iron groups, respectively, were "excluded from analysis" because they "refused 2nd blood sample"; and 20, 12, 19, and 20 participants in the zinc, placebo, zinc + iron, and iron groups, respectively, were "excluded from analysis" because there was "insufficient serum volume" from them Comment: reasons for, and amount of, missing data were similar between study groups. Missing data seems too minimal to impact results
Selective reporting (reporting bias)	Low risk	Comment: all pre-specified outcomes reported using pre-specified methods Protocol identifier: N/A - obtained through an email from a study author
Other bias	Low risk	Comment: appears to be free of other bias

Lind 2003 (2)

Methods	
Participants	
Interventions	
Outcomes	All-cause mortality, incidence of all-cause diarrhoea, incidence of LRTI, height, weight, weight-to-height ratio, prevalence of stunting, serum or plasma zinc concentration, prevalence of zinc deficiency, participants with ≥ 1 side effect, participants with ≥ 1 vomiting episode, blood haemoglobin concentration, prevalence of anaemia, serum or plasma ferritin concentration, prevalence of iron deficiency, serum or plasma copper concentration
Notes	As Lind 2003 above

Long 2006

Methods	CRCT?: IRCT; Cross-over?: non-cross-over
Participants	Country: Mexico; Setting: La Magdalena Atlicpac, a peri-urban community located on the eastern periphery of Mexico City; Urbanicity: peri-urban Inclusion criteria: N/A Exclusion criteria: diseases causing immunosuppression; any congenital or acquired alteration of the digestive tract that could alter the absorption of micronutrients; taking vitamin supplements *Baseline characteristics* Avg age (mo): 9.8; Min age (mo): 6; Max age (mo): 15; % Female: 51 Avg HAZ: 0.1; Stunting: both - separate data not given; Avg height (cm): 73.79; Avg zinc concentration (μg/dL): N/A Total N: 786; Group 1 N: 196; Group 2 N: 198; Group 3 N: N/A; Group 4 N: N/A
Interventions	*Group 1:* zinc Formulation: solution; Compound: methionine; Frequency: daily; Duration (mo): 12; Dose (mg): 20; Co-intervention(s): N/A *Group 2*: no zinc Placebo given; Co-intervention(s): N/A *Group 3:* zinc Co-intervention(s): 20,000 IU retinol every 2 months if age ≤ 12 months, 45,000 IU retinol every 2 months if age > 12 months *Group 4*: no zinc Placebo given; Co-intervention(s): 20,000 IU retinol every 2 months if age ≤ 12 months, 45,000 IU retinol every 2 months if age > 12 months
Outcomes	Incidence of all-cause diarrhoea, incidence of persistent diarrhoea, incidence of LRTI, height, weight, prevalence of stunting Time point (wk): 52
Notes	- In the Long et al 2006 trial report, it is reported that 193 participants were randomised to the vitamin A + zinc group and 199 participants were randomised to the vitamin A group. In contrast, in the Long et al 2007 and Rosado et al 2009 trial reports, it is reported that 199 participants were randomised to the vitamin A + zinc group and 193

	participants were randomised to the vitamin A group - There is some discrepancy between the average, minimum, and maximum ages reported in the different trial reports for this study. However, the mean age of participants in all trial reports falls within the age range of this review

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomization sequence was generated by using a random-number table…" Comment: N/A
Allocation concealment (selection bias)	Low risk	Quote: "The randomization sequence was generated...by project personnel from CENSIA, a division of the Mexican Ministry of Health." "On acceptance, the child was randomly assigned to 1 of the 4 groups by the project field coordinator, who was blinded to these groups." Comment: sufficient allocation concealment seems likely
Blinding of participants (performance bias) All outcomes	Low risk	Quote: "...double-blind randomized trial…The vitamin A, zinc, and vitamin A zinc supplements were prepared by personnel at the National Institute of Nutrition in 5-mL solutions that were similar in taste and appearance." Comment: sufficient blinding seems likely
Blinding of personnel (performance bias) All outcomes	Low risk	Quote: "...double-blind randomized trial…The vitamin A, zinc, and vitamin A zinc supplements were prepared by personnel at the National Institute of Nutrition in 5-mL solutions that were similar in taste and appearance...These solutions were packaged in consecutively numbered, color-coded, opaque plastic droplet bottles to ensure that field personnel and the principal investigator were blinded." Comment: sufficient blinding seems likely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "...double-blind randomized trial…The vitamin A, zinc, and vitamin A zinc supplements were prepared by personnel at the National Institute of Nutrition in 5-mL solutions that were similar

Long 2006 (*Continued*)

		in taste and appearance...These solutions were packaged in consecutively numbered, color-coded, opaque plastic droplet bottles to ensure that field personnel and the principal investigator were blinded." Comment: sufficient blinding seems likely
Incomplete outcome data (attrition bias) All outcomes	Low risk	% Missing: 6 Reasons/details: "Seven children migrated from the area with their families immediately after being randomly assigned…" In addition to these seven, some participants were "lost to follow-up", others "discontinued interventions", and others were "excluded from analysis." The exact numbers of participants who were lost, who discontinued interventions, or who were excluded varies slightly between trial reports. However, in the Long 2006 trial report, which reports most of the outcomes of interest to this review: in the zinc group, 5 were lost, 3 discontinued, and 5 were excluded; in the placebo group, 3 were lost, 5 discontinued, and 6 were excluded; in the vitamin A + zinc group, 5 were lost, 1 discontinued, and 4 were excluded; in the vitamin A group, 2 were lost, 2 discontinued, and 2 were excluded Comment: reasons for, and amount of, missing data were similar between study groups. Missing data seems too minimal to impact results
Selective reporting (reporting bias)	Unclear risk	Comment: side effects may have been measured, but are not reported for the placebo group. No trial protocol referenced by the study
Other bias	Low risk	Comment: appears to be free of other bias

Long 2006 (2)

Methods	
Participants	
Interventions	

Long 2006 (2) (*Continued*)

Outcomes	Incidence of all-cause diarrhoea, incidence of persistent diarrhoea, incidence of LRTI, height, weight, prevalence of stunting
Notes	As Long 2006 above.

Mahloudji 1975

Methods	CRCT?: IRCT; Cross-over?: non-cross-over
Participants	Country: Iran; Setting: the village of Kherak, near Shiraz in southern Iran; Urbanicity: rural Inclusion criteria: N/A Exclusion criteria: N/A *Baseline characteristics* Avg age (mo): N/A; Min age (mo): 72; Max age (mo): 144; % Female: 8 Avg HAZ: N/A; Stunting: unclear; Avg height (cm): N/A; Avg zinc concentration (μg/dL): 64.8 Total N: 50; Group 1 N: 25; Group 2 N: 25
Interventions	*Group 1:* zinc Formulation: capsule; Compound: carbonate; Frequency: 6 days/wk; Duration (mo): 16; Dose (mg): 20; Co-intervention(s): 20 mg iron; vitamin and mineral supplements, which contained multiple micronutrients; egg white and corn oil supplements *Group 2*: no zinc Placebo given; Co-intervention(s): 20 mg iron; vitamin and mineral supplements, which contained multiple micronutrients; egg white and corn oil supplements
Outcomes	Serum or plasma zinc concentration, blood haemoglobin concentration Time point (wk): 80
Notes	- The supplement and placebo were given "during the school year...Treatment was discontinued in May 1969 and resumed in October of the same year." It seems that treatment was started in October 1968, discontinued in May 1969, started again in October 1969, and ended in May 1970 - In addition to the study groups mentioned in this table, there was a group of 25 participants who received "placebo capsules containing lactose and simulated supplement"; but there was no zinc group to which this placebo group could be compared. So, this group is not included in any meta-analyses in this review

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Care was taken to ensure that the grouping was by chance." Comment: insufficient details available to make a judgement as to whether or not an

Mahloudji 1975 (*Continued*)

		allocation sequence was generated using a truly random method
Allocation concealment (selection bias)	Unclear risk	Quote: N/A Comment: insufficient details available to make a judgement
Blinding of participants (performance bias) All outcomes	Low risk	Quote: "The supplement and simulated supplement looked and tasted alike…" Comment: sufficient blinding seems likely
Blinding of personnel (performance bias) All outcomes	Low risk	Quote: "The supplement and simulated supplement looked and tasted alike…" Comment: sufficient blinding seems likely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The supplement and simulated supplement looked and tasted alike…" Comment: sufficient blinding seems likely
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	% Missing: N/A Reasons/details: N/A Comment: the study reported that, "Seventy-five children…were divided into three groups." However, results were reported as being out "of 59 children." Nothing (such as reasons for missing data, and number of participants with missing data, for each study group) was reported to explain this 75 versus 59 children inconsistency
Selective reporting (reporting bias)	High risk	Comment: height, weight, prevalence of zinc deficiency, and prevalence of anaemia were measured, but are not reported in a way that can be meta-analysed
Other bias	Low risk	Comment: appears to be free of other bias

Malik 2013

Methods	CRCT?: IRCT; Cross-over?: non-cross-over
Participants	Country: India; Setting: Delhi; Urbanicity: urban Inclusion criteria: all children 6 to 11 months of age residing in Gokulpuri, an urban re-settlement colony in North East District of Delhi, India and who were likely to stay until the completion of the study. To achieve the final sample size additional children were recruited from the similar adjacent area of Gangavihar Exclusion criteria: any child receiving zinc supplement at the time of study or in the past 3 months, or severely malnourished, immune-deficient or on steroid therapy, severely

	ill children requiring hospitalisation, or children of families likely to migrate from the study area *Baseline characteristics* Avg age (mo): not mentioned; Min age (mo): 6 months; Max age (mo): 11; % Female: not given Avg HAZ: not given; Stunting: unclear; Avg height (cm): not given; Avg zinc concentration (μg/dL): not given Total N: 158; Group 1 N: 134; Group 2 N: 124
Interventions	*Group 1:* zinc Formulation: solution; Compound: unclear; Frequency: daily; Duration (mo): 0.46; Dose (mg): 20; Co-intervention(s): none *Group 2*: no zinc Placebo given; Co-intervention(s): none
Outcomes	Mortality due to all-cause diarrhoea, incidence of all-cause diarrhoea, incidence of persistent diarrhoea, prevalence of all-cause diarrhoea, vomiting Time point (wk): 22
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "We randomized the treatment allocation; by simple randomization using computer generated random numbers."
Allocation concealment (selection bias)	Low risk	Quote: "We randomized the treatment allocation; by simple randomization using computer generated random numbers."
Blinding of participants (performance bias) All outcomes	Low risk	Quote: "The field investigator and parents were blinded to the treatment allocation and were unblinded at the end of the follow-up period."
Blinding of personnel (performance bias) All outcomes	Low risk	Quote: "The field investigator and parents were blinded to the treatment allocation and were unblinded at the end of the follow-up period."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The field investigator and parents were blinded to the treatment allocation and were unblinded at the end of the follow-up period."

Malik 2013 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Generalized Estimating Equations (GEE) were used to obtain an incident rate ratio (IRR) with 95% confidence intervals, in order to compare month-wise number of episodes and duration of diarrhea using Poisson log linear distribution, by intention to treat analysis...We included all children who had taken at least two doses of the intervention for the analyses. The follow-up visits for which the infant outcomes were not available were imputed using the worst case (2 episodes of diarrhea) and best case scenarios (no episodes). However this did not change the study results thus missing data was excluded from the final analysis." Comment: 7/141 and 7/131 not included in the analysis
Selective reporting (reporting bias)	High risk	Quote: "part of a larger study taking in to account four primary outcomes, viz. decrease in incidence of diarrhea and acute respiratory tract infections (ARI) and increase in length and weight" "We decided to adjust the IRRs for covariates which appeared to be different at baseline in the two groups. " Trial registration: CTRI/2010/091/001417
Other bias	Low risk	Comment: appears to be free of other bias

Marinho 1991

Methods	CRCT?: IRCT; Cross-over?: non-cross-over
Participants	Country: Brazil; Setting: a poor district of Manaus (Amazonas); Urbanicity: urban Inclusion criteria: parasitised with *A. lumbricoides* and/or *G. lamblia* Exclusion criteria: N/A *Baseline characteristics* Avg age (mo): N/A; Min age (mo): 36; Max age (mo): 84; % Female: 50 Avg HAZ: N/A; Stunting: both - separate data not given; Avg height (cm): N/A; Avg zinc concentration (μg/dL): N/A Total N: 240; Group 1 N: 60; Group 2 N: 60; Group 3 N: 60; Group 4 N: 60
Interventions	*Group 1:* zinc Formulation: unclear; Compound: acetate; Frequency: daily; Duration (mo): 1; Dose (mg): 5; Co-intervention(s): N/A *Group 2*: no zinc

	Placebo given; Co-intervention(s): N/A *Group 3:* zinc Co-intervention(s): 500 mg vitamin A *Group 4*: no zinc Placebo given; Co-intervention(s): 500 mg vitamin A
Outcomes	No outcomes of interest reported in a way that can be meta-analysed
Notes	"One-hundred-and-twenty of the parasitized children…were treated with mebendazol…for *A. lumbricoides* and with metronidazol…for G. lamblia…The efficiency of the parasitosis treatment was checked by carrying out another stool analysis." 30 of these treated children were randomised to each study group; thus, each study group was comprised of 30 treated participants, and 30 untreated participants

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "The parasitized and non-parasitized groups were randomly assigned to four sub-groups…" Comment: insufficient details available to make a judgement as to whether or not an allocation sequence was generated using a truly random method
Allocation concealment (selection bias)	Unclear risk	Quote: N/A Comment: insufficient details available to make a judgement
Blinding of participants (performance bias) All outcomes	Unclear risk	Quote: N/A Comment: insufficient details available to make a judgement
Blinding of personnel (performance bias) All outcomes	Unclear risk	Quote: N/A Comment: insufficient details available to make a judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: N/A Comment: insufficient details available to make a judgement.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	% Missing: N/A Reasons/details: N/A Comment: reasons for, and amount of, missing data were not reported for either study group

Marinho 1991 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	Comment: no trial protocol referenced by the study
Other bias	Low risk	Comment: appears to be free of other bias

Mazariegos 2010

Methods	CRCT?: IRCT; Cross-over?: non-cross-over
Participants	Country: Guatemala; Setting: the town of San Juan Comalapa, in the province of Chimaltenango, in the Western Highlands of Guatemala; Urbanicity: rural Inclusion criteria: living within 12 km of the township of Comalapa; apparently healthy (based on maternal history without any prenatal or natal concerns and no history of serious illness postnatally); home-cooked maize as the major family food staple Exclusion criteria: refused verbal screening; did not eat tortillas in the home; family who did not plan to stay in the geographical area for the next year *Baseline characteristics* Avg age (mo): 6; Min age (mo): 6; Max age (mo): 6; % Female: 49.5 Avg HAZ: -2.09; Stunting: both - separate data not given; Avg height (cm): 62.1; Avg zinc concentration (μg/dL): 110.5 Total N: 412; Group 1 N: 104; Group 2 N: 105; Group 3 N: 100; Group 4 N: 103
Interventions	*Group 1:* zinc Formulation: pill/tablet; Compound: unclear; Frequency: daily; Duration (mo): 6; Dose (mg): 5; Co-intervention(s): isohybrid control maize *Group 2*: no zinc Placebo given; Co-intervention(s): isohybrid control maize *Group 3:* zinc Co-intervention(s): low-phytate maize *Group 4*: no zinc Placebo given; Co-intervention(s): low-phytate maize
Outcomes	Height, weight, weight-to-height ratio, serum or plasma zinc concentration, study withdrawal, participants with $\geq$ 1 side effect, vomiting episodes, participants with $\geq$ 1 vomiting episode Time point (wk): 24
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "At the time of enrolment, families were assigned to receive maize labeled with 1 of 6 randomization colors. Permuted blocks were used in the generation of the

		randomization list. At age 6 mo, infants were further randomized to the zinc supplementation trial. The infants were randomized to the treatment or control group within the family's maize group assignment, also using permuted blocks." Comment: N/A
Allocation concealment (selection bias)	Low risk	Quote: in response to the question, "Could you describe how you ensured that participants, and investigators enrolling participants, could not tell which group a new participant would be assigned to?" an author of this study replied as follows: "The randomization was undertaken by RTI-totally detached from all investigators." RTI stands for "Research Triangle Institute", which was involved with data management for the study Comment: sufficient allocation concealment seems likely
Blinding of participants (performance bias) All outcomes	Low risk	Quote: "...doubly masked trial…" Comment: sufficient blinding seems likely
Blinding of personnel (performance bias) All outcomes	Low risk	Quote: "...doubly masked trial…Quality control checks of maize…undertaken by one of the investigating team (V. R.) at the USDA facility in Aberdeen, Idaho, to verify correct delivery of the assigned maize. Apart from the members of the Data Management Center at RTI, V.R. was the only unmasked member of the investigating team." Comment: sufficient blinding seems likely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "...doubly masked trial…Quality control checks of maize…undertaken by one of the investigating team (V. R.) at the USDA facility in Aberdeen, Idaho, to verify correct delivery of the assigned maize. Apart from the members of the Data Management Center at RTI, V.R. was the only unmasked member of the investigating team." Comment: sufficient blinding seems likely

Mazariegos 2010 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	% Missing: 7 Reasons/details: in the zinc group: 4 were "missing" for the "12 mo visit", 4 "moved", and 8 "withdrew consent." In the placebo group, 4 were "missing" for the "12 mo visit", 4 "moved", and 4 "withdrew consent." "The small attrition rate in participant retention was primarily due to relocation from the area or withdrawal of consent because of perceived study burden." Comment: reasons for, and amount of, missing data were similar between study groups. Missing data seem too minimal to impact results
Selective reporting (reporting bias)	High risk	Comment: diarrhoea prevalence, LRTI incidence, and stunting rates were measured, but are not reported in a way that can be meta-analysed
Other bias	Low risk	Comment: appears to be free of other bias

Meeks Gardner 1998

Methods	CRCT?: IRCT; Cross-over?: non-cross-over
Participants	Country: Jamaica; Setting: Kingston; Urbanicity: urban Inclusion criteria: singleton; stunted (below -2.0 SD length-for-age and less than the median weight-for-length, NCHS references) Exclusion criteria: obvious physical or mental handicap; provided vitamin-mineral supplements which contained iron and/or zinc by their caretakers *Baseline characteristics* Avg age (mo): 14.1; Min age (mo): 6; Max age (mo): 24; % Female: 57 Avg HAZ: -2.9; Stunting: stunted; Avg height (cm): 68.7; Avg zinc concentration (μg/dL): N/A Total N: 61; Group 1 N: 31; Group 2 N: 30
Interventions	*Group 1:* zinc Formulation: solution; Compound: sulfate; Frequency: daily; Duration (mo): 3; Dose (mg): 5; Co-intervention(s): multivitamin supplement (Tropivite vitamin drops) *Group 2*: no zinc Placebo given; Co-intervention(s): multivitamin supplement (Tropivite vitamin drops)
Outcomes	All-cause hospitalisation, incidence of all-cause diarrhoea, incidence of LRTI, height, weight Time point (wk): 12 (morbidity outcomes), 52 (growth outcomes)

Notes	"Food supplements were expected to be provided by the nutrition clinics as part of their routine care, but delivery was extremely irregular and caretakers had food supplements on average only 1 week during the 12 week supplementation period."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "…children were...randomly assigned..." Comment: insufficient details available to make a judgement as to whether or not an allocation sequence was generated using a truly random method
Allocation concealment (selection bias)	Unclear risk	Quote: N/A Comment: insufficient details available to make a judgement
Blinding of participants (performance bias) All outcomes	Low risk	Quote: "…double-blind, placebo-controlled trial...Caretakers were blind to the children's group assignment." Comment: sufficient blinding seems likely
Blinding of personnel (performance bias) All outcomes	Low risk	Quote: "…double-blind, placebo-controlled trial…" Comment: sufficient blinding seems likely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "...double-blind, placebo-controlled trial…All interviews and measurements were carried out by members of the study team who were unaware of the children's group assignments." Comment: sufficient blinding seems likely
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	% Missing: 7 Reasons/details: 4 children, "all from the control group, were hospitalized during the study", and "stayed in hospital for more than one night...It was necessary to exclude them since in some cases hospitalization may have included zinc supplements and the feeding regimes would have been markedly different from the situation at home." Comment: children who were hospitalised probably represented the most severe cases of illness and excluding 4 of them may have

		reduced the likelihood of finding significant differences between the groups in the other morbidity variables examined
Selective reporting (reporting bias)	Unclear risk	Comment: no trial protocol referenced by the study
Other bias	Low risk	Comment: appears to be free of other bias

Meeks Gardner 2005

Methods	CRCT?: IRCT; Cross-over?: non-cross-over
Participants	Country: Jamaica; Setting: the parishes of Kingston, St. Andrew, and St. Catherine; Urbanicity: unclear Inclusion criteria: current weight-for-age z scores below -1.5 SDs of the National Center for Health Statistics references; weight-for-age below -2 SDs in the previous 3 mo Exclusion criteria: twins; physical or mental impairments that could affect development *Baseline characteristics* Avg age (mo): 18.8; Min age (mo): 9; Max age (mo): 30; % Female: 61 Avg HAZ: -1.42; Stunting: unclear; Avg height (cm): 77.1; Avg zinc concentration (μg/dL): N/A Total N: 126; Group 1 N: 35; Group 2 N: 42; Group 3 N: 26; Group 4 N: 23
Interventions	*Group 1:* zinc Formulation: solution; Compound: sulfate; Frequency: daily; Duration (mo): 6; Dose (mg): 10; Co-intervention(s): 0.5 ml vitamin-iron drop, which contained multiple micronutrients *Group 2*: no zinc Placebo given; Co-intervention(s): 0.5 ml vitamin-iron drop, which contained multiple micronutrients *Group 3:* zinc Co-intervention(s): psychosocial stimulation; 0.5 ml vitamin-iron drop, which contained multiple micronutrients *Group 4*: no zinc Placebo given; Co-intervention(s): psychosocial stimulation; 0.5 ml vitamin-iron drop, which contained multiple micronutrients
Outcomes	Incidence of all-cause diarrhoea, incidence of LRTI, height, weight, weight-to-height ratio, study withdrawal Time point (wk): 24
Notes	"For logistic reasons, we could not extend the stimulation program. To achieve sufficient power to detect an effect of zinc, we continued enrolling children for a further 2 mo to the zinc trial only."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "...children were...randomly assigned…" Comment: insufficient details available to make a judgement as to whether or not an allocation sequence was generated using a truly random method
Allocation concealment (selection bias)	Unclear risk	Quote: N/A Comment: insufficient details available to make a judgement
Blinding of participants (performance bias) All outcomes	Low risk	Quote: "...double-blind trial…parents or guardians, who were unaware of the children's assignment to zinc or placebo..." Comment: sufficient blinding seems likely
Blinding of personnel (performance bias) All outcomes	Low risk	Quote: "...double-blind trial…" Comment: sufficient blinding seems likely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "...double-blind trial…testers were unaware of the assignment to interventions" Comment: sufficient blinding seems likely
Incomplete outcome data (attrition bias) All outcomes	Low risk	% Missing: 10 Reasons/details: "Reasons for withdrawal given by the parents from the zinc-supplemented group were as follows: children became anorexic (n = 2), child would vomit after the supplement (n = 1), the fathers refused to allow participation after the mother had given consent (n = 2) , and family moved away (n = 1). From the placebo group, parents reported illness (jaundice and liver problems; n = 2), families moved away (n = 2), the mother was unhappy with the doctors from the research unit (n = 1), or the mother felt that giving the supplement daily was too onerous (n = 1)." Comment: amount of missing data was similar between study groups. Reasons for missing data were varied. However, there was no reason that a large proportion of children in one study group did have but that children in the other study group did

Meeks Gardner 2005 (*Continued*)

		not have
Selective reporting (reporting bias)	Unclear risk	Comment: no trial protocol referenced by the study
Other bias	Unclear risk	Comment: "Children who received placebo were significantly taller than those who received zinc." This baseline difference could have influenced height outcomes, which were reported only as post-treatment scores, rather than as changes from baseline

Mozaffari-Khosravi 2009

Methods	CRCT?: IRCT; Cross-over?: non-cross-over
Participants	Country: Iran; Setting: Azad-shahr suburb of Yazd city in central Iran; Urbanicity: peri-urban Inclusion criteria: below the 25th percentile of height-for-age according to National Center for Health Statistics (NCHS) data Exclusion criteria: N/A *Baseline characteristics* Avg age (mo): 38.8; Min age (mo): 25; Max age (mo): 69; % Female: 55.3 Avg HAZ: -1.59; Stunting: both - separate data not given; Avg height (cm): 91.2; Avg zinc concentration (μg/dL): N/A Total N: 90; Group 1 N: 45; Group 2 N: 45
Interventions	*Group 1:* zinc Formulation: solution; Compound: sulfate; Frequency: daily; Duration (mo): 6; Dose (mg): 5; Co-intervention(s): N/A *Group 2*: no zinc Placebo given; Co-intervention(s): N/A
Outcomes	Height, weight, weight-to-height ratio, prevalence of stunting Time point (wk): 52
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Participates were randomly allocated into one of two groups (zinc supplemented and Placebo group) using randomized numbers table." Comment: N/A

Allocation concealment (selection bias)	Low risk	Quote: "Vahidi pharmacy assigned codes to the different syrups and sent them to corresponding researcher, where they were kept secured until the end of the study." Comment: sufficient allocation concealment seems likely
Blinding of participants (performance bias) All outcomes	Low risk	Quote: "...double-blind, placebo-controlled supplementation trial…" The placebo group "received the same syrup in color, odor, and taste without zinc" as the zinc group. "Vahidi pharmacy assigned codes to the different syrups and sent them to corresponding researcher, where they were kept secured until the end of the study." Comment: sufficient blinding seems likely
Blinding of personnel (performance bias) All outcomes	Low risk	Quote: "...double-blind, placebo-controlled supplementation trial…" The placebo group "received the same syrup in color, odor, and taste without zinc" as the zinc group. "Vahidi pharmacy assigned codes to the different syrups and sent them to corresponding researcher, where they were kept secured until the end of the study." Comment: sufficient blinding seems likely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "...double-blind, placebo-controlled supplementation trial…" The placebo group "received the same syrup in color, odor, and taste without zinc" as the zinc group. "Vahidi pharmacy assigned codes to the different syrups and sent them to corresponding researcher, where they were kept secured until the end of the study." Comment: sufficient blinding seems likely
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	% Missing: 6 Reasons/details: "Five children from ZG group stepped out on grounds of going on trips, illness or other reasons…" Comment: all missing data are from the zinc group and data missing due to "illness or other reasons" might impact results

Selective reporting (reporting bias)	Unclear risk	Comment: no English language trial protocol referenced by the study. Only a Persian language trial protocol was available and this Persian language protocol could not be translated
Other bias	Low risk	Comment: appears to be free of other bias

Muller 2001

Methods	CRCT?: IRCT; Cross-over?: non-cross-over
Participants	Country: Burkina Faso; Setting: 18 villages in the Nouna district of northwestern Burkina Faso; Urbanicity: rural Inclusion criteria: permanent resident of the study area Exclusion criteria: serious underlying illness *Baseline characteristics* Avg age (mo): 18.1; Min age (mo): 6; Max age (mo): 30; % Female: 49 Avg HAZ: -1.6; Stunting: both - separate data given; Avg height (cm): 75.8; Avg zinc concentration (μg/dL): 76.5 Total N: 709; Group 1 N: 356; Group 2 N: 353
Interventions	*Group 1:* zinc Formulation: pill/tablet; Compound: sulfate; Frequency: 6 days/wk; Duration (mo): 6; Dose (mg): 12.5; Co-intervention(s): N/A *Group 2*: no zinc Placebo given; Co-intervention(s): N/A
Outcomes	All-cause mortality, incidence of all-cause diarrhoea, prevalence of all-cause diarrhoea, incidence of LRTI, prevalence of LRTI, incidence of malaria, prevalence of malaria, height, weight, weight-to-height ratio, serum or plasma zinc concentration, prevalence of zinc deficiency Time point (wk): 12 (biochemical outcomes), 24 (morbidity, mortality, and growth outcomes)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Children were allocated zinc or placebo in blocks of 30 (15 zinc, 15 placebo) by computer generated randomly permutated codes (prepared by the World Health Organization)." Comment: N/A

Muller 2001 (*Continued*)

Allocation concealment (selection bias)	Low risk	Quote: "The randomisation code was broken after the database was closed." "Randomization was done independently before the trial started. Investigators were not involved. Fieldworkers had to follow the randomization scheme." Comment: sufficient allocation concealment seems likely
Blinding of participants (performance bias) All outcomes	Low risk	Quote: "Our study was designed as a. ..double blind efficacy trial...The tablets were identical in appearance and taste... The randomisation code was broken after the database was closed" Comment: sufficient blinding seems likely
Blinding of personnel (performance bias) All outcomes	Low risk	Quote: "Our study was designed as a. ..double blind efficacy trial...The tablets were identical in appearance and taste... The randomisation code was broken after the database was closed" Comment: sufficient blinding seems likely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Our study was designed as a. ..double blind efficacy trial...The tablets were identical in appearance and taste... The randomisation code was broken after the database was closed" Comment: sufficient blinding seems likely
Incomplete outcome data (attrition bias) All outcomes	Low risk	% Missing: 6 Reasons/details: "...we excluded from the final analysis those who were absent from the study area for more than 14 consecutive days." Also, 5 children in the intervention group and 12 children in the placebo group died during the study Comment: missing data seem too minimal to impact results
Selective reporting (reporting bias)	Unclear risk	Comment: no trial protocol referenced by the study
Other bias	Low risk	Comment: appears to be free of other bias

Nakamura 1993

Methods	CRCT?: IRCT; Cross-over?: non-cross-over
Participants	Country: Japan; Setting: N/A; Urbanicity: unclear Inclusion criteria: height-for-age < -2.0 SD; apparent good health with no evidence of endocrinologic disorder, peak serum GH level >10 ng/ml in insulin and clonidine stimulation tests, and > 20 ng/ml in the growth hormone releasing factor loading test; mild-to-moderate zinc deficiency identified by zinc kinetic studies (zinc body clearance ≥ 20 ml/kg per hour); prepubertal status (Tanner breast and genitalia growth stage) throughout the study period Exclusion criteria: N/A *Baseline characteristics* Avg age (mo): 70.3; Min age (mo): N/A; Max age (mo): N/A; % Female: 47.6 Avg HAZ: -2.44; Stunting: stunted; Avg height (cm): N/A; Avg zinc concentration (μg/dL): 82 Total N: 21; Group 1 N: 10; Group 2 N: 11
Interventions	*Group 1:* zinc Formulation: unclear; Compound: sulfate; Frequency: daily; Duration (mo): 6; Dose (mg): 5 mg/kg; Co-intervention(s): N/A *Group 2*: no zinc Placebo not given; Co-intervention(s): N/A
Outcomes	Height, serum or plasma zinc concentration Time point (wk): 24
Notes	The authors report that, "A total of 21 Japanese children (11 boys) with short stature were studied. They were selected by the following tests: a Tanner evaluation, growth hormone provocation test, and body zinc clearance test. The tests were performed on 220 patients with short stature hospitalized in our clinic." However, it seems that the trial participants were only in the clinic for tests, and were living in the community at the start of the trial

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "...children were divided randomly into two groups…" Comment: insufficient details available to make a judgement as to whether or not an allocation sequence was generated using a truly random method
Allocation concealment (selection bias)	Unclear risk	Quote: N/A Comment: insufficient details available to make a judgement

Nakamura 1993 (*Continued*)

Blinding of participants (performance bias) All outcomes	Unclear risk	Quote: "None of the control subjects was given placebo." Comment: given that no placebo was provided, it seems likely that people involved with the study were aware of which study group participants were in. It is unclear how measured outcomes might be influenced by this lack of blinding
Blinding of personnel (performance bias) All outcomes	Unclear risk	Quote: "None of the control subjects was given placebo." Comment: given that no placebo was provided, it seems likely that people involved with the study were aware of which study group participants were in. It is unclear how measured outcomes might be influenced by this lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "None of the control subjects was given placebo." Comment: given that no placebo was provided, it seems likely that people involved with the study were aware of which study group participants were in. It is unclear how measured outcomes might be influenced by this lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	% Missing: N/A Reasons/details: N/A Comment: insufficient details available to make a judgement
Selective reporting (reporting bias)	Unclear risk	Comment: no trial protocol referenced by the study
Other bias	Low risk	Comment: appears to be free of other bias

Ninh 1996

Methods	CRCT?: IRCT; Cross-over?: non-cross-over
Participants	Country: Vietnam; Setting: an area near Hano, Vietnam; Urbanicity: rural Inclusion criteria: growth retardation evidenced by a WAZ score below -2 and an HAZ score below -2 as calculated from US National Center for Health Statistics reference data; otherwise healthy Exclusion criteria: obvious medical reasons for poor growth *Baseline characteristics* Avg age (mo): 17.6; Min age (mo): 4; Max age (mo): 36; % Female: 54

	Avg HAZ: -2.61; Stunting: stunted; Avg height (cm): 71.3; Avg zinc concentration (μg/dL): N/A Total N: 210; Group 1 N: 105; Group 2 N: 105
Interventions	*Group 1:* zinc Formulation: solution; Compound: sulfate; Frequency: daily; Duration (mo): 5; Dose (mg): 10; Co-intervention(s): N/A *Group 2*: no zinc Placebo given; Co-intervention(s): N/A
Outcomes	Height, weight, weight-to-height ratio Time point (wk): 20
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "The subjects were pair-matched...Each member of a pair was randomly assigned to take either a zinc supplement or a placebo." Comment: insufficient details available to make a judgement as to whether or not an allocation sequence was generated using a truly random method
Allocation concealment (selection bias)	Unclear risk	Quote: "The group to which the patient was assigned was unknown to the child's family and to the members of the investigation team." Comment: despite this statement, the method of allocation concealment is not described in sufficient detail to allow a definite judgement
Blinding of participants (performance bias) All outcomes	Low risk	Quote: "...double-blind study…The group to which the patient was assigned was unknown to the child's family...The two syrups were indistinguishable in taste and color." Comment: sufficient blinding seems likely
Blinding of personnel (performance bias) All outcomes	Low risk	Quote: "...double-blind study…The group to which the patient was assigned was unknown to the...members of the investigation team...The two syrups were indistinguishable in taste and color."

Ninh 1996 (*Continued*)

		Comment: sufficient blinding seems likely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "...double-blind study…The group to which the patient was assigned was unknown to the...members of the investigation team...The two syrups were indistinguishable in taste and color." Comment: sufficient blinding seems likely
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	% Missing: 30 Reasons/details: "Thirty-two pairs were excluded from analysis for various reasons: relocation (n = 3), accident (n = 2), voluntary withdrawal by parent (n = 12), poor compliance with syrup administration (n = 5), poor compliance with anthropometric measurements (n = 4), concurrent use of multivitamin-trace element preparations including zinc (n = 4), and hospitalization (n = 2)." Comment: amount of missing data was not reported separately for each study group. Thus, for instance, the placebo group could have more missing data for reasons such as withdrawal, non-compliance, and hospitalisation, while the zinc group could have more missing data due to the fact that "pairs were excluded" and that zinc group members thus had to be excluded when their corresponding placebo group members were
Selective reporting (reporting bias)	High risk	Comment: all-cause hospitalisation was measured, but is not reported in a way that can be meta-analysed
Other bias	Low risk	Comment: appears to be free of other bias

Penny 2004

Methods	CRCT?: IRCT; Cross-over?: non-cross-over
Participants	Country: Peru; Setting: Canto Grande, a shanty town on the outskirts of Lima; Urbanicity: peri-urban Inclusion criteria: diarrhoea for $\geq$ 14 days; intention to remain in the study area Exclusion criteria: been taking vitamins or minerals within the last 6 weeks; major congenital malformation affecting growth (e.g. trisomy 21) *Baseline characteristics* Avg age (mo): 18.9; Min age (mo): 6; Max age (mo): 35; % Female: 50

	Avg HAZ: -1.56; Stunting: both - separate data not given; Avg height (cm): 76.4; Avg zinc concentration (μg/dL): 70.3 Total N: 164; Group 1 N: 81; Group 2 N: 83
Interventions	*Group 1:* zinc Formulation: solution; Compound: gluconate; Frequency: daily; Duration (mo): 6; Dose (mg): 10; Co-intervention(s): N/A *Group 2*: no zinc Placebo given; Co-intervention(s): N/A
Outcomes	All-cause mortality, incidence of all-cause diarrhoea, prevalence of all-cause diarrhoea, incidence of severe diarrhoea, incidence of LRTI, height, weight, serum or plasma zinc concentration, vomiting episodes, blood haemoglobin concentration, serum or plasma ferritin concentration Time point (wk): 24
Notes	- In addition to the study groups mentioned in this table, there was a group of 82 participants who received "zinc plus vitamins and other minerals at 1-2 times recommended daily intakes." Baseline characteristics reported in this table are weighted averages of all groups except this zinc + multiple micronutrient group, since this group is not included in any meta-analyses in this review - "The study was carried out in 2 phases. During the first phase we evaluated the effect of zinc or multiple micronutrient supplementation on the recovery from persistent diarrhea. During the second phase we assessed the effect of continued supplementation on morbidity from new infections during the following 6 mo." - 29 children in the placebo group and 28 children in the Zn group "consumed additional iron, either as prescribed by the study team because of anemia at baseline (hemoglobin < 9.0 g/dL) or for family-determined reasons;" of these children, 22 in the placebo group and 18 in the zinc group received additional iron for $\geq$ 7 d. Additionally, "Children were offered a wafer biscuit and sugar candy after administration of the supplement because this had been shown in pretesting to reduce the nauseating aftertaste that was sometimes experienced with the supplement."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Children were stratified by current breast-feeding status and assigned a consecutive study number within each stratum. With the use of a computer-generated, block randomization scheme, each study number had been linked previously to 1 of 9 letter codes, each of which indicated 1 of the 3 treatment groups." Comment: N/A

Allocation concealment (selection bias)	Unclear risk	Quote: "The identities of the codes were not available to the field staff or investigators until after the data had been cleaned and analyzed." Comment: despite this statement, the method of allocation concealment is not described in sufficient detail to allow a definite judgement
Blinding of participants (performance bias) All outcomes	Low risk	Quote: "...double-masked, placebo-controlled, community-based trial…Further flavoring and coloring agents and ascorbic acid were added in Lima to ensure that the supplements were indistinguishable in appearance and taste and to improve their acceptability. These additions were made by staff of the Instituto de Investigación Nutricional who had no other involvement in the study." Comment: sufficient blinding seems likely
Blinding of personnel (performance bias) All outcomes	Low risk	Quote: "...double-masked, placebo-controlled, community-based trial…Further flavoring and coloring agents and ascorbic acid were added in Lima to ensure that the supplements were indistinguishable in appearance and taste and to improve their acceptability. These additions were made by staff of the Instituto de Investigación Nutricional who had no other involvement in the study." "The identities of the codes were not available to the field staff or investigators until after the data had been cleaned and analyzed." Comment: sufficient blinding seems likely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "...double-masked, placebo-controlled, community-based trial…Further flavoring and coloring agents and ascorbic acid were added in Lima to ensure that the supplements were indistinguishable in appearance and taste and to improve their acceptability. These additions were made by staff of the Instituto de Investigación Nutricional who had no other involvement in the study." "The identities of the codes were not available to the field staff or investigators until after the data had been cleaned

		and analyzed." Comment: sufficient blinding seems likely
Incomplete outcome data (attrition bias) All outcomes	Low risk	% Missing: 16 Reasons/details: in the zinc group: 10 participants were lost due to "permanent departure from the area", and 4 were lost due to "parental decision to withdraw." In the placebo group: 2 participants "died", 5 were lost due to "permanent departure from the area", and 6 were lost due to "parental decision to withdraw" Comment: 16% of the randomised participants eligible for our review had data missing; this 16% missing figure includes all groups except the zinc + multiple micronutrient group, since this group is not included in any meta-analyses in this review. Numbers of participants lost due to death or parental decision to withdraw were similar between study groups. Though more participants in the zinc group moved, missing data due to migration are unlikely to bias results
Selective reporting (reporting bias)	Unclear risk	Comment: no trial protocol referenced by the study
Other bias	Low risk	Comment: appears to be free of other bias

Rahman 2001

Methods	CRCT?: IRCT; Cross-over?: non-cross-over
Participants	Country: Bangladesh; Setting: slums of Dhaka; Urbanicity: urban Inclusion criteria: N/A Exclusion criteria: received any vitamin A supplementation within the past 4 mo; severe malnutrition (weight-for-age < 60% of the National Center for Health Statistics median) ; signs or symptoms of vitamin A or zinc deficiency; any systemic illness such as diarrhoea, respiratory infection, fever, or any other illness that warranted medical intervention at the time of enrolment *Baseline characteristics* Avg age (mo): 23.7; Min age (mo): 12; Max age (mo): 35; % Female: 47 Avg HAZ: -2.41; Stunting: both - separate data not given; Avg height (cm): N/A; Avg zinc concentration (μg/dL): 72.3 Total N: 800; Group 1 N: 200; Group 2 N: 200; Group 3 N: 200; Group 4 N: 200

Interventions	*Group 1:* zinc Formulation: solution; Compound: sulfate; Frequency: daily; Duration (mo): 0.5; Dose (mg): 20; Co-intervention(s): N/A *Group 2*: no zinc Placebo given; Co-intervention(s): N/A *Group 3:* zinc Co-intervention(s): 200,000 IU vitamin A capsule on day 14 *Group 4*: no zinc Placebo given; Co-intervention(s): 200,000 IU vitamin A capsule on day 14
Outcomes	Incidence of all-cause diarrhoea, prevalence of all-cause diarrhoea, incidence of persistent diarrhoea, prevalence of persistent diarrhoea, incidence of LRTI, prevalence of LRTI, height, weight, weight-to-height ratio, serum or plasma zinc concentration Time point (wk): 12 (serum or plasma zinc concentration), 24 (morbidity and growth outcomes)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The children were randomly assigned by a person not involved in the study who used permuted blocks of random numbers." Comment: N/A
Allocation concealment (selection bias)	Low risk	Quote: "The children were randomly assigned by a person not involved in the study..." "Sets of two bottles of syrup and a capsule were serially numbered according to the randomisation list and corresponding to the study serial numbers. The enrolled children were assigned the numbered bottles in the order in which they were enrolled...The zinc and placebo syrups were supplied in bottles that looked identical... The randomisation code was kept sealed until the completion of the study." Comment: indicates central randomisation (i.e. randomisation by someone not involved with enrolling patients) and sequentially numbered drug containers of identical appearance to conceal allocation
Blinding of participants (performance bias) All outcomes	Low risk	Quote: "This was a randomized, double-blind, placebo-controlled trial." "The zinc and placebo syrups were supplied in bottles

		that looked identical, and the appearance and consistency of the syrups were similar. ..The randomisation code was kept sealed until the completion of the study." Comment: sufficient blinding seems likely
Blinding of personnel (performance bias) All outcomes	Low risk	Quote: "This was a randomized, double-blind, placebo-controlled trial." "The zinc and placebo syrups were supplied in bottles that looked identical, and the appearance and consistency of the syrups were similar. ..The randomisation code was kept sealed until the completion of the study." Comment: sufficient blinding seems likely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "This was a randomized, double-blind, placebo-controlled trial." "The zinc and placebo syrups were supplied in bottles that looked identical, and the appearance and consistency of the syrups were similar. ..The randomisation code was kept sealed until the completion of the study." Comment: sufficient blinding seems likely
Incomplete outcome data (attrition bias) All outcomes	Low risk	% Missing: 17 Reasons/details: 17% of the 800 randomised participants had data missing for diarrhoea, LRTI, weight, and length outcomes: "Eighty-five children (16 in the zinc group, 31 in the A group, 14 in the ZA group, and 24 in the placebo group) were excluded from the study because they received an extra dose of vitamin A (a 60 000-RE capsule) through the Bangladesh 'National Vitamin A Week' campaign. Forty-nine children were subsequently lost to follow-up." In addition, "weight and length measurements at 6 mo were missing for 13 children." Comment: reasons for, and amount of, missing data were similar between study groups. Receiving an additional dose of vitamin A from campaigns unrelated to the study was the most common reason for missing data, and this reason is unlikely to bias results. Also, "the baseline characteristics of the excluded children were not significantly different from those of the children who continued the study."

Rahman 2001 (*Continued*)

Selective reporting (reporting bias)	High risk	Comment: vomiting was measured, but is not reported in a way that can be meta-analysed
Other bias	Low risk	Comment: appears to be free of other bias

Rahman 2001 (2)

Methods	
Participants	
Interventions	
Outcomes	Incidence of all-cause diarrhoea, prevalence of all-cause diarrhoea, incidence of persistent diarrhoea, prevalence of persistent diarrhoea, incidence of LRTI, prevalence of LRTI, height, weight, weight-to-height ratio, serum or plasma zinc concentration
Notes	As Rahman 2001 above

Richard 2006

Methods	CRCT?: IRCT; Cross-over?: non-cross-over
Participants	Country: Peru; Setting: the village of Santa Clara; Urbanicity: rural Inclusion criteria: N/A Exclusion criteria: chronic illness (absence of congenital diseases or major illness requiring medical care and/or medication determined by the physician at baseline evaluation); severe malnutrition (weight-for-height z-score less than 2 SDs below the National Center for Health Statistics (Hyattsville, MD) reference population or clinical signs of marasmus or kwashiorkor) *Baseline characteristics* Avg age (mo): N/A; Min age (mo): 6; Max age (mo): 180; % Female: 51.7 Avg HAZ: -2.08; Stunting: both - separate data not given; Avg height (cm): N/A; Avg zinc concentration (μg/dL): 69 Total N: 855; Group 1 N: 214; Group 2 N: 215; Group 3 N: 214; Group 4 N: 212
Interventions	*Group 1:* zinc Formulation: solution; Compound: sulfate; Frequency: daily; Duration (mo): 7; Dose (mg): 20; Co-intervention(s): N/A *Group 2*: no zinc Placebo given; Co-intervention(s): N/A *Group 3:* zinc Co-intervention(s): 15 mg iron *Group 4*: no zinc Placebo given; Co-intervention(s): 15 mg iron

Outcomes	All-cause mortality, incidence of all-cause diarrhoea, incidence of LRTI, incidence of malaria, height, weight-to-height ratio, serum or plasma zinc concentration, blood haemoglobin concentration Time point (wk): 28
Notes	Based on the distribution of participants in the 0 to 4, 5 to 9, and 10 to 15 year age groups in this study, it seems extremely likely that the majority of participants in this study were between 6 months and 12 years of age

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Using an algorithm in SAS version 6...we randomized children meeting the entry criteria in blocks of four into four supplement groups…" Comment: N/A
Allocation concealment (selection bias)	Unclear risk	Quote: N/A Comment: insufficient details available to make a judgement
Blinding of participants (performance bias) All outcomes	Low risk	Quote: "…double-blind, placebo-controlled trial…The supplements were similar in appearance and taste, bottled in similar containers, and labeled with a supplement code...The participants...were...masked throughout the study to the supplement contents." Comment: sufficient blinding seems likely
Blinding of personnel (performance bias) All outcomes	Low risk	Quote: "…double-blind, placebo-controlled trial…The supplements were similar in appearance and taste, bottled in similar containers, and labeled with a supplement code...study personnel were...masked throughout the study to the supplement contents." Comment: sufficient blinding seems likely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "…double-blind, placebo-controlled trial…The supplements were similar in appearance and taste, bottled in similar containers, and labeled with a supplement code...study personnel were...masked throughout the study to the supplement contents. The data an-

		alyst was masked for the seminal analyses and was unmasked for additional analyses and sub-analyses. No data were excluded or altered after unmasking." Comment: sufficient blinding seems likely
Incomplete outcome data (attrition bias) All outcomes	Low risk	% Missing: 12.5 Reasons/details: in the zinc group: 6, 1, and 16 participants "migrated", "refused", and were lost for "other" reasons, respectively. In the placebo group: 12, 1, and 13 participants "migrated", "refused", and were lost for "other" reasons, respectively. In the iron group: 9, 2, and 18 participants "migrated", "refused", and were lost for "other" reasons, respectively. In the iron + zinc group: 7, 5, and 17 participants "migrated", "refused", and were lost for "other" reasons, respectively Comment: reasons for, and amount of, missing data were similar between study groups
Selective reporting (reporting bias)	Unclear risk	Comment: prevalence of stunting, zinc deficiency, anaemia, and iron deficiency may have been measured as outcomes, but are not reported. No trial protocol referenced by the study
Other bias	Low risk	Comment: appears to be free of other bias

Richard 2006 (2)

Methods	
Participants	
Interventions	
Outcomes	All-cause mortality, incidence of all-cause diarrhoea, incidence of LRTI, incidence of malaria, height, weight-to-height ratio, serum or plasma zinc concentration, blood haemoglobin concentration
Notes	As Richard 2006 above

Rosado 1997

Methods	CRCT?: IRCT; Cross-over?: non-cross-over
Participants	Country: Mexico; Setting: 5 communities in the Valley of Solís region of central Mexico; Urbanicity: rural Inclusion criteria: N/A Exclusion criteria: N/A *Baseline characteristics* Avg age (mo): 28.4; Min age (mo): 18; Max age (mo): 36; % Female: N/A Avg HAZ: -1.6; Stunting: both - separate data given; Avg height (cm): 83.3; Avg zinc concentration (μg/dL): 96.7 Total N: 219; Group 1 N: N/A; Group 2 N: N/A; Group 3 N: N/A; Group 4 N: N/A
Interventions	*Group 1:* zinc Formulation: solution; Compound: methionine; Frequency: 6 days/wk; Duration (mo) : 12; Dose (mg): 20; Co-intervention(s): N/A *Group 2*: no zinc Placebo given; Co-intervention(s): N/A *Group 3:* zinc Co-intervention(s): 20 mg iron *Group 4*: no zinc Placebo given; Co-intervention(s): 20 mg iron
Outcomes	Incidence of all-cause diarrhoea, height, weight, weight-to-height ratio, serum or plasma zinc concentration, prevalence of zinc deficiency, blood haemoglobin concentration, prevalence of anaemia, serum or plasma ferritin concentration, prevalence of iron deficiency Time point (wk): 52
Notes	Table 1 in the Rosado et al 1997 trial report, which reports baseline characteristics, states that the numbers of children at the beginning of the study are 54, 55, 55, and 53, for the zinc, placebo, zinc + iron, and iron groups respectively. However, these numbers do not add up to the 219 children which were reported to have enrolled in the study

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Children were…randomly assigned…" Comment: insufficient details available to make a judgement as to whether or not an allocation sequence was generated using a truly random method
Allocation concealment (selection bias)	Unclear risk	Quote: N/A Comment: insufficient details available to make a judgement

Blinding of participants (performance bias) All outcomes	Low risk	Quote: "...double-blind, randomized community trial…Both the zinc and the iron salts were dissolved in a solution to disguise their bad taste and to ensure similar appearance...The solutions were coded...and the code was not broken until the end of data analysis." Comment: sufficient blinding seems likely
Blinding of personnel (performance bias) All outcomes	Low risk	Quote: "...double-blind, randomized community trial…Both the zinc and the iron salts were dissolved in a solution to disguise their bad taste and to ensure similar appearance...The solutions were coded in such a way that their content was unknown to any of the project personnel, and the code was not broken until the end of data analysis." Comment: sufficient blinding seems likely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "...double-blind, randomized community trial…Both the zinc and the iron salts were dissolved in a solution to disguise their bad taste and to ensure similar appearance...The solutions were coded in such a way that their content was unknown to any of the project personnel, and the code was not broken until the end of data analysis." Comment: sufficient blinding seems likely
Incomplete outcome data (attrition bias) All outcomes	Low risk	% Missing: 11 Reasons/details: "Only 25 children were dropped from the study before the end of the 12 mo, primarily because of a changing family situation." Comment: "Changing family situation" was the primary reason for missing data, and this reason is unlikely to bias results
Selective reporting (reporting bias)	Unclear risk	Comment: LRTI (i.e. "lower respiratory disease") that meets the criteria of this review may have been measured, but is not reported in a way that can be meta-analysed. No trial protocol referenced by the study
Other bias	Low risk	Comment: appears to be free of other bias

Rosado 1997 (2)

Methods	
Participants	
Interventions	
Outcomes	Incidence of all-cause diarrhoea, height, weight, weight-to-height ratio, serum or plasma zinc concentration, prevalence of zinc deficiency, blood haemoglobin concentration, prevalence of anaemia, serum or plasma ferritin concentration, prevalence of iron deficiency
Notes	As Rosado 1997 above

Rosales 2004

Methods	CRCT?: IRCT; Cross-over?: non-cross-over
Participants	Country: Guatemala; Setting: Guatemala City; Urbanicity: urban Inclusion criteria: good health; absence of chronic diseases Exclusion criteria: N/A *Baseline characteristics* Avg age (mo): N/A; Min age (mo): 96; Max age (mo): 132; % Female: 52 Avg HAZ: N/A; Stunting: unclear; Avg height (cm): N/A; Avg zinc concentration (μg/dL): 65.4 Total N: 76; Group 1 N: 18; Group 2 N: 20; Group 3 N: 20; Group 4 N: 18
Interventions	*Group 1:* zinc Formulation: solution; Compound: sulfate; Frequency: 5 days/wk; Duration (mo): 2; Dose (mg): 42.5; Co-intervention(s): N/A *Group 2*: no zinc Placebo given; Co-intervention(s): N/A *Group 3:* zinc Co-intervention(s): 20 mg iron *Group 4*: no zinc Placebo given; Co-intervention(s): 20 mg iron
Outcomes	Serum or plasma zinc concentration, prevalence of zinc deficiency, blood haemoglobin concentration, serum or plasma ferritin concentration, prevalence of iron deficiency Time point (wk): 8
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "They were systematically blocked randomized…" In response to a question about sequence generation, an author of this study replied as follows: "I believe that

		at the CeSSIAM center they used a table of random numbers to generate the random allocation sequence." Comment: N/A
Allocation concealment (selection bias)	Unclear risk	Quote: N/A Comment: insufficient details available to make a judgement
Blinding of participants (performance bias) All outcomes	Low risk	Quote: "Children were masked to the content of the mixture, which was prepared every day at the school kitchen by one of the investigators…To maintain masking,...the children had no contact with the preparation area, and the drafts were assigned by code number." Comment: sufficient blinding seems likely
Blinding of personnel (performance bias) All outcomes	Low risk	Quote: "To maintain masking...the drafts were assigned by code number." Comment: sufficient blinding seems likely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "To maintain masking, the investigator never had direct contact with the subjects,...and the drafts were assigned by code number." Comment: sufficient blinding seems likely
Incomplete outcome data (attrition bias) All outcomes	Low risk	% Missing: 14 Reasons/details: 2, 5, 1, and 3 children were excluded from the zinc, placebo, iron and zinc, and iron alone groups, respectively. All 11 of these children were excluded because they "missed 5 or more days of classes and did not receive at least 90% of the supplementation dosage." Comment: reasons for, and amount of, missing data were similar between study groups
Selective reporting (reporting bias)	Unclear risk	Comment: no trial protocol referenced by the study
Other bias	Low risk	Comment: appears to be free of other bias

Rosales 2004 (2)

Methods	
Participants	
Interventions	
Outcomes	Serum or plasma zinc concentration, prevalence of zinc deficiency, blood haemoglobin concentration, serum or plasma ferritin concentration, prevalence of iron deficiency
Notes	As Rosales 2004 above

Ruel 1997

Methods	CRCT?: IRCT; Cross-over?: non-cross-over
Participants	Country: Guatemala; Setting: the village of Santa Maria de Jesus; Urbanicity: rural Inclusion criteria: N/A Exclusion criteria: N/A *Baseline characteristics* Avg age (mo): 7.62; Min age (mo): 6; Max age (mo): 9; % Female: 43 Avg HAZ: -2.16; Stunting: both - separate data not given; Avg height (cm): 144.6; Avg zinc concentration (μg/dL): N/A Total N: 108; Group 1 N: 55; Group 2 N: 53
Interventions	*Group 1:* zinc Formulation: solution; Compound: sulfate; Frequency: daily; Duration (mo): 7; Dose (mg): 10; Co-intervention(s): N/A *Group 2*: no zinc Placebo given; Co-intervention(s): N/A
Outcomes	Incidence of all-cause diarrhoea, prevalence of all-cause diarrhoea, height, weight, weight-to-height ratio Time point (wk): 28
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "…randomized community trial…" Comment: insufficient details available to make a judgement as to whether or not an allocation sequence was generated using a truly random method

Allocation concealment (selection bias)	Unclear risk	Quote: N/A Comment: insufficient details available to make a judgement
Blinding of participants (performance bias) All outcomes	Low risk	Quote: "...double-blind placebo-controlled study. ..The supplements were indistinguishable, and neither the families nor...were aware of the treatment group to which the infants belonged." Comment: sufficient blinding seems likely
Blinding of personnel (performance bias) All outcomes	Low risk	Quote: "...double-blind placebo-controlled study. ..The supplements were indistinguishable, and neither...nor the study staff were aware of the treatment group to which the infants belonged." Comment: sufficient blinding seems likely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "...double-blind placebo-controlled study. ..The supplements were indistinguishable, and neither...nor the study staff were aware of the treatment group to which the infants belonged." Comment: sufficient blinding seems likely
Incomplete outcome data (attrition bias) All outcomes	Low risk	% Missing: 18 Reasons/details: 19 children (10 from the zinc group and 9 from the placebo group) "dropped out of the study attributable to migration, or inability to comply with the project requirements because of maternal work, or late parental refusal." Comment: amount of missing data was similar between study groups. Reasons for missing data are unlikely to bias results
Selective reporting (reporting bias)	Unclear risk	Comment: no trial protocol referenced by the study
Other bias	Low risk	Comment: appears to be free of other bias

Ruz 1997

Methods	CRCT?: IRCT; Cross-over?: non-cross-over
Participants	Country: Chile; Setting: Santiago; Urbanicity: peri-urban Inclusion criteria: apparently healthy, a preschool child, of middle-to-low or low socioeconomic status Exclusion criteria: a clinical condition predisposing to growth failure *Baseline characteristics* Avg age (mo): 39.8; Min age (mo): 27; Max age (mo): 50; % Female: 53 Avg HAZ: -0.52; Stunting: both - separate data not given; Avg height (cm): 95.6; Avg zinc concentration (μg/dL): 114.1 Total N: 98; Group 1 N: 49; Group 2 N: 49
Interventions	*Group 1:* zinc Formulation: solution; Compound: sulfate; Frequency: daily; Duration (mo): 14; Dose (mg): 10; Co-intervention(s): N/A *Group 2*: no zinc Placebo given; Co-intervention(s): N/A
Outcomes	Height, serum or plasma zinc concentration, blood haemoglobin concentration, serum or plasma copper concentration Time point (wk): 24 (biochemical outcomes), 56 (height)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Subjects were pair matched according to sex and age and randomly assigned to two experimental groups…The randomization procedure was followed strictly. It yielded comparable groups for most of the variables of interest." Comment: insufficient details available to make a judgement as to whether or not an allocation sequence was generated using a truly random method
Allocation concealment (selection bias)	Low risk	Quote: "The study was conducted in a doubly-blinded fashion, and the code was broken only after the project had been finished. The random allocation of each member of the pair to the experimental groups (identified as group A or B, to avoid bias) was done by a member of our staff not involved with the study...The code was only known to the pharmacist in charge." Comment: indicates central randomisation

		(i.e. randomisation by someone not involved with enrolling patients) to conceal allocation
Blinding of participants (performance bias) All outcomes	Low risk	Quote: "…double-blind zinc supplementation trial…The study was conducted in a doubly-blinded fashion, and the code was broken only after the project had been finished...The zinc and placebo solutions were indistinguishable in appearance and taste." Comment: sufficient blinding seems likely
Blinding of personnel (performance bias) All outcomes	Low risk	Quote: "…double-blind zinc supplementation trial…The study was conducted in a doubly-blinded fashion, and the code was broken only after the project had been finished...The zinc and placebo solutions were indistinguishable in appearance and taste." Comment: sufficient blinding seems likely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "…double-blind zinc supplementation trial…The study was conducted in a doubly-blinded fashion, and the code was broken only after the project had been finished...The zinc and placebo solutions were indistinguishable in appearance and taste." Comment: sufficient blinding seems likely
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	% Missing: 43 Reasons/details: "After 6 mo of intervention, 19 individuals had dropped out of the study, leaving 79; after 14 mo, the total number of children still participating was 56." Thus, 19% of data was missing for zinc, haemoglobin, ferritin, and copper concentrations (which were only measured at baseline and 6 months), and 43% of data were missing for all other outcomes. No reasons for dropout were reported Comment: a large proportion of data is missing, and no information was reported on differential dropout between study groups or reasons for dropout
Selective reporting (reporting bias)	High risk	Comment: diarrhoea, weight, weight-to-height ratio, and serum ferritin were measured, but are not reported in a way that can be meta-analysed. LRTI, which meets the criteria for this review, may have been

		measured; but it is not reported in a way that can be meta-analysed, and it is unclear how LRTI was defined in this study
Other bias	Low risk	Comment: appears to be free of other bias

Sandstead 1998

Methods	CRCT?: CRCT; Cross-over?: non-cross-over
Participants	Country: China; Setting: the 3 cities of Chonqing, Qingdao, and Shanghai; Urbanicity: urban Inclusion criteria: 1st grader Exclusion criteria: N/A *Baseline characteristics* Avg age (mo): N/A; Min age (mo): 72; Max age (mo): 108; % Female: N/A Avg HAZ: N/A; Stunting: unclear; Avg height (cm): N/A; Avg zinc concentration (μg/dL): N/A Please see 'Notes' for details about number of participants.
Interventions	*Group 1:* zinc Formulation: pill/tablet; Compound: unclear; Frequency: 6 days/wk; Duration (mo): 2.5; Dose (mg): 20; Co-intervention(s): micronutrient mixture *Group 2*: no zinc Placebo given; Co-intervention(s): micronutrient mixture
Outcomes	No outcomes of interest reported in a way that can be meta-analysed
Notes	- It was reported that "Subjects were divided equally between treatments"; but due to inconsistent numbers reported across the 2 trial reports (Penland et al 1997 reports 372 participants and Sandstead et al 1998 reports 740 participants), it is unclear how many participants were in the trial - In addition to the study groups mentioned in this table, there was a group of participants who received zinc only; but there was no placebo group to which this zinc group could be compared. So, this zinc group is not included in any meta-analyses in this review - Baseline plasma zinc was reported as 87.25 μg/dL in Penland 1997 and 86.37 μg/dL in Sandstead 1998

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "...randomized, controlled trial…" Comment: insufficient details available to make a judgement as to whether or not an allocation sequence was generated using a truly random method

Allocation concealment (selection bias)	Unclear risk	Quote: N/A Comment: insufficient details available to make a judgement
Blinding of participants (performance bias) All outcomes	Low risk	Quote: "Double-blind randomized controlled treatment trial…Treatments were…administered double-blind for 10 weeks...identical appearing white tablets." Comment: sufficient blinding seems likely
Blinding of personnel (performance bias) All outcomes	Low risk	Quote: "Double-blind randomized controlled treatment trial…Treatments were…administered double-blind for 10 weeks...identical appearing white tablets." Comment: sufficient blinding seems likely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Double-blind randomized controlled treatment trial…Treatments were…administered double-blind for 10 weeks...identical appearing white tablets." Comment: sufficient blinding seems likely
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	% Missing: N/A Reasons/details: N/A Comment: numbers of participants randomised into each intervention group are not clearly reported, and different numbers of participants are reported in Penland 1997 versus Sandstead 1998
Selective reporting (reporting bias)	High risk	Comment: plasma zinc concentration, haemoglobin, anaemia, serum ferritin concentration, and iron deficiency were measured, but are not reported in a way that can be meta-analysed. The reported means and number of participants analysed for plasma zinc concentration are different between the Penland 1997 and Sandstead 1998 trial reports
Other bias	Low risk	Comment: appears to be free of other bias

Sandstead 2008

Methods	CRCT?: IRCT; Cross-over?: non-cross-over
Participants	Country: United States of America; Setting: Brownsville, Texas; Urbanicity: urban Inclusion criteria: N/A Exclusion criteria: N/A *Baseline characteristics* Avg age (mo): N/A; Min age (mo): 72; Max age (mo): 84; % Female: 33 Avg HAZ: N/A; Stunting: unclear; Avg height (cm): N/A; Avg zinc concentration (μg/dL): 97.4 Total N: 54; Group 1 N: 27; Group 2 N: 27
Interventions	*Group 1:* zinc Formulation: unclear; Compound: sulfate; Frequency: 5 days/wk; Duration (mo): 2.5; Dose (mg): 20; Co-intervention(s): multiple micronutrients *Group 2*: no zinc Placebo given; Co-intervention(s): multiple micronutrients
Outcomes	Serum or plasma zinc concentration, serum or plasma ferritin concentration Time point (wk): 10
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "They were divided into 2 groups of similar composition and assigned randomly…to one of the treatments…" Comment: insufficient details available to make a judgement as to whether or not an allocation sequence was generated using a truly random method
Allocation concealment (selection bias)	Low risk	Quote: "The statistician assigned the treatments without specific knowledge of the subjects and held the code until completion of the trial." Comment: indicates central randomisation to conceal allocation
Blinding of participants (performance bias) All outcomes	Low risk	Quote: "…treated in double-blind fashion in equal numbers…They were divided into 2 groups of similar composition and assigned…in a double-blind fashion to one of the treatments…The statistician assigned the treatments without specific knowledge of the subjects and held the code until completion of the trial."

		Comment: sufficient blinding seems likely
Blinding of personnel (performance bias) All outcomes	Low risk	Quote: "…treated in double-blind fashion in equal numbers…They were divided into 2 groups of similar composition and assigned…in a double-blind fashion to one of the treatments…The statistician assigned the treatments without specific knowledge of the subjects and held the code until completion of the trial." Comment: sufficient blinding seems likely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "…treated in double-blind fashion in equal numbers…They were divided into 2 groups of similar composition and assigned…in a double-blind fashion to one of the treatments…The statistician assigned the treatments without specific knowledge of the subjects and held the code until completion of the trial." Comment: sufficient blinding seems likely
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	% Missing: 15 Reasons/details: N/A Comment: the amount of missing data was similar between study groups. In the zinc + micronutrients group, 2 were missing for the plasma zinc outcome, and 3 were missing for the serum ferritin outcome. In the micronutrients group, 2 were missing for the plasma zinc outcome, and 4 were missing for the serum ferritin outcome. However, a somewhat sizeable proportion of data is missing, and reasons for missing data were not stated. Also, Table 2 lists an inconsistent number of subjects for the serum ferritin outcome (stating that 46 subjects were analysed for this outcome, 24 in the zinc + micronutrients group, and 23 in the micronutrients group)
Selective reporting (reporting bias)	Unclear risk	Comment: no trial protocol referenced by the study
Other bias	Low risk	Comment: appears to be free of other bias

Sanjur 1990

Methods	CRCT?: IRCT; Cross-over?: non-cross-over
Participants	Country: United States of America; Setting: Denver, Colorado; Urbanicity: urban Inclusion criteria: healthy; spoke English as a main language at home Exclusion criteria: N/A *Baseline characteristics* Avg age (mo): 21; Min age (mo): 12; Max age (mo): 24; % Female: 51 Avg HAZ: N/A; Stunting: unclear; Avg height (cm): N/A; Avg zinc concentration (μg/dL): N/A Total N: N/A; Group 1 N: N/A; Group 2 N: N/A; Group 3 N: N/A; Group 4 N: N/A
Interventions	*Group 1:* zinc Formulation: pill/tablet; Compound: unclear; Frequency: daily; Duration (mo): 6; Dose (mg): unclear; Co-intervention(s): multivitamin *Group 2*: no zinc Placebo given; Co-intervention(s): multivitamin *Group 3:* zinc Co-intervention(s): multivitamin; iron *Group 4*: no zinc Placebo given; Co-intervention(s): multivitamin; iron
Outcomes	No outcomes of interest reported in a way that can be meta-analysed
Notes	- "The study sample consisted of 90 healthy children...Approximately 15 to 22 children were assigned" to each study group. In addition to the study groups mentioned in this table, there was a group of participants who received placebo only; but there was no zinc group to which this placebo group could be compared in this review. The 90 participants who were randomised in this study includes this group of participants who only received placebo - In addition, the authors report that "The present examination of the diet and nutrient intake of children 1 to 2 years old is part of a larger investigation undertaken by the University of Colorado Health Sciences Center. The primary objective of the larger study was to evaluate the efficacy of vitamin and mineral supplements in very young children. " However, no information was available about this larger investigation

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "The toddlers were randomly assigned…" Comment: insufficient details available to make a judgement as to whether or not an allocation sequence was generated using a truly random method
Allocation concealment (selection bias)	Unclear risk	Quote: N/A Comment: insufficient details available to make a judgement

Sanjur 1990 (*Continued*)

Blinding of participants (performance bias) All outcomes	Low risk	Quote: "…double-blind study…Group assignment was unknown to the toddlers and their families..." Comment: sufficient blinding seems likely
Blinding of personnel (performance bias) All outcomes	Low risk	Quote: "…double-blind study…Group assignment was unknown to...the members of the investigating team." Comment: sufficient blinding seems likely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "…double-blind study…Group assignment was unknown to...the members of the investigating team." Comment: sufficient blinding seems likely
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	% Missing: N/A Reasons/details: N/A Comment: the following were not reported: number of participants randomised to each group, amount of missing data for each group, reasons for missing data in each group
Selective reporting (reporting bias)	Unclear risk	Comment: no trial protocol referenced by the study
Other bias	Low risk	Comment: appears to be free of other bias

Sayeg Porto 2000

Methods	CRCT?: IRCT; Cross-over?: non-cross-over
Participants	Country: Brazil; Setting: Rio de Janeiro; Urbanicity: urban Inclusion criteria: height-for-age -2 SD according to NCHS data; attendance at the Pediatric Endocrinology Service for at least 1 year without previous treatment; normal hematological values and biochemical analysis - calcium, phosphorus, alkaline phosphatase, iron, urea, creatinine, albumin, and globulins; normal endocrine function with normal thyroid hormones (T3, T4, and TSH); insulin growth factor-1 (IGF-1) level and growth hormone (GH) post-exercise above 10 ng/dl; bone age equivalent to height age Exclusion criteria: pubertal signs; in a family with a history of psychological problems; malabsorption; chronic infections; other known causes of growth failure *Baseline characteristics* Avg age (mo): 118.44; Min age (mo): 84; Max age (mo): 120; % Female: 24 Avg HAZ: -2.67; Stunting: stunted; Avg height (cm): 121.6; Avg zinc concentration (μg/dL): 100.7 Total N: 21; Group 1 N: N/A; Group 2 N: N/A

Sayeg Porto 2000 (*Continued*)

Interventions	*Group 1:* zinc Formulation: solution; Compound: sulfate; Frequency: daily; Duration (mo): 6; Dose (mg): 5 mg/kg; Co-intervention(s): N/A *Group 2*: no zinc Placebo given; Co-intervention(s): N/A
Outcomes	Height, weight, serum or plasma zinc concentration, prevalence of zinc deficiency Time point (wk): 24 (biochemical outcomes), 52 (growth outcomes)
Notes	The number of participants randomised to each study group is not reported, nor is the number of participants in either study group who completed the study, nor is any number of participants analysed for any outcome reported. However, it is assumed that participants were split approximately evenly between study groups

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "The study was designed as a…randomized, controlled trial…Children were randomized to two groups..." Comment: insufficient details available to make a judgement as to whether or not an allocation sequence was generated using a truly random method
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was performed by a person not involved in the clinical management of the children." Comment: indicates central randomisation (i.e. randomisation by someone not involved with enrolling patients) to conceal allocation
Blinding of participants (performance bias) All outcomes	Low risk	Quote: "The study was designed as a double-blind…controlled trial…In the Pharmacy Department, two syrups were made with the same color and flavor, one of which contained zinc sulfate…Assignment to the zinc or placebo group was not known by the families..." Comment: sufficient blinding seems likely
Blinding of personnel (performance bias) All outcomes	Low risk	Quote: "The study was designed as a double-blind…controlled trial…In the Pharmacy Department, two syrups were made with the same color and flavor, one of which

Sayeg Porto 2000 (*Continued*)

		contained zinc sulfate…Assignment to the zinc or placebo group was not known by the…investigators." Comment: sufficient blinding seems likely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The study was designed as a double-blind…controlled trial…In the Pharmacy Department, two syrups were made with the same color and flavor, one of which contained zinc sulfate…Assignment to the zinc or placebo group was not known by the…investigators." Comment: sufficient blinding seems likely
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	% Missing: 14 Reasons/details: "During the supplementation period, three boys presented initial signs of puberty and were excluded from the study." Comment: amount of missing data is not reported separately for each study group
Selective reporting (reporting bias)	High risk	Comment: side effects were measured but are not reported in a way that can be meta-analysed
Other bias	Low risk	Comment: appears to be free of other bias

Sazawal 1996

Methods	CRCT?: IRCT; Cross-over?: non-cross-over
Participants	Country: India; Setting: Kalkaji, New Delhi; Urbanicity: urban Inclusion criteria: reported passage of at least 4 unformed stools in the previous 24 h; a diarrhoeal duration of < 7 d; permanent residence in the Kalkaji area Exclusion criteria: malnutrition judged clinically to be sufficiently severe to require hospitalisation *Baseline characteristics* Avg age (mo): 16; Min age (mo): 6; Max age (mo): 35; % Female: 47.7 Avg HAZ: N/A; Stunting: both - separate data not given; Avg height (cm): N/A; Avg zinc concentration (μg/dL): 64.8 Total N: 609; Group 1 N: 298; Group 2 N: 311
Interventions	*Group 1:* zinc Formulation: solution; Compound: gluconate; Frequency: daily; Duration (mo): 6; Dose (mg): 10; Co-intervention(s): multiple micronutrients *Group 2*: no zinc Placebo given; Co-intervention(s): multiple micronutrients

Sazawal 1996 (*Continued*)

Outcomes	Incidence of all-cause diarrhoea, prevalence of all-cause diarrhoea, incidence of persistent diarrhoea, incidence of LRTI, prevalence of LRTI, serum or plasma zinc concentration, blood haemoglobin concentration, serum or plasma copper concentration, prevalence of copper deficiency Time point (wk): 17 (biochemical outcomes), 24 (morbidity outcomes)
Notes	"…a subgroup of children enrolled in a trial of the therapeutic effect of zinc supplementation…were randomly selected at the time of initial enrollment to enter a 6-mo follow-up trial after recovery from the enrollment diarrheal episode." The data in this review apply to the 6-mo follow-up trial. In this follow-up trial, during episodes of diarrhoeal illness, the dose of zinc was doubled to provide for excess stool losses

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization schedules with permuted blocks of fixed length of 10, appropriate for double-blind studies, were used." "At WHO two separate randomization schedules were first made for long and short follow up children, then the two were combined into a single schedule such that allocation to long and short follow up was also random." Comment: N/A
Allocation concealment (selection bias)	Low risk	Quote: "The company prepared bottles with labels of A, B, C, D, R, F, three of these with zinc (intervention group solution) and the other three without zinc (control group solution). The identity of codes A-F was communicated to WHO by the company and was not revealed to the investigators in Delhi until the end of the study. Both sets of bottles...were identical in all respects... The randomization schedule prepared by WHO gave serial numbers in each of the 4 strata, with letter A through F denoting which code bottle should be assigned to the child. This randomization schedule was mailed by WHO directly to clinical pharmacology at AIIMS where only the pharmacy assistant was aware of the allocation. He relabelled the bottles with stratum serial numbers and provided the bottles as required. At the clinic, on enrollment, each child was assigned a stratum serial number

		corresponding to a bottle of supplement, which was also labeled with the child's identification number and name. The investigators and the field staff were unaware of A-F allocation." Comment: indicates central randomisation (i.e. randomisation by someone not involved with enrolling patients) and sequentially numbered drug containers of identical appearance to conceal allocation
Blinding of participants (performance bias) All outcomes	Low risk	Quote: "…double-blind randomized trial. ..Both sets of bottles and solutions were identical in all respects including color and taste." Comment: sufficient blinding seems likely
Blinding of personnel (performance bias) All outcomes	Low risk	Quote: "…double-blind randomized trial. ..The identity of codes A-F was…not revealed to the investigators in Delhi until the end of the study. Both sets of bottles and solutions were identical in all respects including color and taste." Comment: sufficient blinding seems likely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "…double-blind randomized trial. ..The identity of codes A-F was…not revealed to the investigators in Delhi until the end of the study. Both sets of bottles and solutions were identical in all respects including color and taste." ""…duplicate blind measurements were taken by the two study physicians throughout the course of the study…" Comment: sufficient blinding seems likely
Incomplete outcome data (attrition bias) All outcomes	Low risk	% Missing: 7 Reasons/details: for diarrhoea outcomes: "Of the 609 children, 40 (Z 12, C 28) with actual follow-up of less than 30 d were excluded from the analysis." For LRTI outcomes: "Out of 609 children...6 children (zinc, n = 1; control, n = 5)" were excluded from the analysis, because "their total surveillance was less than 15 days" due to being "absent continuously." Comment: missing data seem too minimal to impact results

Sazawal 1996 (*Continued*)

Selective reporting (reporting bias)	High risk	Comment: height and weight were measured as outcomes, but are not reported. Prevalence of zinc deficiency was measured, but is not reported in a way that can be meta-analysed due to different numbers reported in different trial reports
Other bias	Low risk	Comment: appears to be free of other bias

Sazawal 2006

Methods	CRCT?: CRCT; Cross-over?: non-cross-over
Participants	Country: Zanzibar; Setting: Pemba, an island of Zanzibar; Urbanicity: multiple Inclusion criteria: likely to remain resident in the study area Exclusion criteria: severe malnutrition needing rehabilitation *Baseline characteristics* Avg age (mo): 18.2; Min age (mo): 1; Max age (mo): 35; % Female: 50 Avg HAZ: -1.5; Stunting: both - separate data not given; Avg height (cm): N/A; Avg zinc concentration (μg/dL): 78.5 Total N: 60,225; Group 1 N: 21,274; Group 2 N: 21,272; Group 3 N: 8914; Group 4 N: 8765 Total clusters: 33,899; Group 1 clusters: N/A; Group 2 clusters: N/A; Group 3 clusters: N/A; Group 4 clusters: N/A
Interventions	*Group 1:* zinc Formulation: pill/tablet; Compound: sulfate; Frequency: daily; Duration (mo): 16; Dose (mg): 5 mg to children aged younger than 12 months; 10 to children aged 12 months or older; Co-intervention(s): 200,000 IU of vitamin A every 6 months to children aged 12 months or older, 100,000 IU of vitamin A every 6 months to children aged younger than 12 months *Group 2*: no zinc Placebo given; Co-intervention(s): 200,000 IU of vitamin A every 6 months to children aged 12 months or older, 100,000 IU of vitamin A every 6 months to children aged younger than 12 months *Group 3:* zinc Co-intervention(s): 6.25 mg iron and 25 µg folic acid to children aged younger than 12 months; 12.5 mg iron and 50 µg folic acid to children aged 12 months or older; 100,000 IU of vitamin A every 6 months to children aged younger than 12 months; 200,000 IU of vitamin A every 6 months to children aged 12 months or older *Group 4*: no zinc Placebo given; Co-intervention(s): 6.25 mg iron and 25 µg folic acid to children aged younger than 12 months; 12.5 mg iron and 50 µg folic acid to children aged 12 months or older; 100,000 IU of vitamin A every 6 months to children aged younger than 12 months; 200,000 IU of vitamin A every 6 months to children aged 12 months or older

Outcomes	All-cause mortality, mortality due to all-cause diarrhoea, mortality due to LRTI, mortality due to malaria, height, weight, blood haemoglobin concentration, prevalence of anaemia, prevalence of iron deficiency Time point (wk): 24 to 52 (biochemical and growth outcomes), 55 to 69 (morbidity and mortality outcomes)
Notes	- "On recommendation of the Data and Safety Monitoring Board (DSMB)" of the study, the iron + folic acid + zinc (IFAZ) and iron + folic acid (IFA) groups "were stopped on Aug 19, 2003 because of overwhelming evidence of increased hospital admissions and a trend for increased mortality associated with iron supplementation...Children from the IFAZ and non-zinc IFA groups were switched to the zinc and placebo groups, respectively. " The numbers of participants listed in this table as being randomised to the zinc and placebo groups do not include those from the IFA and IFAZ groups who were switched to zinc or placebo - "Children received zinc or placebo supplements until they were 48 months of age", or, in the case of the IFAZ and IFA groups, "until the iron and folic acid-containing groups were stopped." "At the time of stopping the trial, mean duration of follow-up in the study was 383 days" in the IFAZ and IFA groups reported in the Sazawal et al 2006 trial report. "The mean duration of supplementation was 484.7 days" in the zinc and placebo groups reported in the Sazawal et al 2007 trial report - Iron deficiency was defined as zinc protoporphyrin $\geq$ 90 μmol/mol heme

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was by household, by an allocation sequence (permuted block randomisation with block length of 16) computer-generated by WHO." Comment: N/A
Allocation concealment (selection bias)	Low risk	Quote: "The supplement code, which was not known to the investigators, was maintained at WHO. To ensure masking, we labeled the strips of supplements with 16 letter codes - four for each of the groups. This letter code was hidden in the batch number on each strip of tablets. On enrolment, we assigned every child a code. Labels with the child's name on were then printed from a computer database and attached by the pharmacy to the appropriate strip of supplements." Comment: indicates central randomisation (i.e. randomisation by someone not involved with enrolling patients) to conceal allocation

Blinding of participants (performance bias) All outcomes	Low risk	Quote: "...double-masked, placebo-controlled trial…To ensure masking, we labelled the strips of supplements with 16 letter codes - four for each of the groups. This letter code was hidden in the batch number on each strip of tablets." "The halting of the IFAZ and IFA arms and switching of children to the other groups were done with the help of WHO and the DSMB statistician. The trial initially used 16-letter codes (four-letter codes assigned to the individual supplementation groups) and two-stage blinding. The four-letter codes for every group were known only to WHO and the manufacturer; the pharmacy dispensing the supplements knew only which letter code was assigned to each child, and the…family knew neither. At the time of switch, WHO and the DSMB statistician provided an alternative letter code for all of the redundant eight-letter codes...Tablets...were similar in packaging, appearance, taste, and inactive ingredients." Comment: sufficient blinding seems likely
Blinding of personnel (performance bias) All outcomes	Low risk	Quote: "...double-masked, placebo-controlled trial…To ensure masking, we labelled the strips of supplements with 16 letter codes - four for each of the groups. This letter code was hidden in the batch number on each strip of tablets." "The halting of the IFAZ and IFA arms and switching of children to the other groups were done with the help of WHO and the DSMB statistician. The trial initially used 16-letter codes (four-letter codes assigned to the individual supplementation groups) and two-stage blinding. The four-letter codes for every group were known only to WHO and the manufacturer; the pharmacy dispensing the supplements knew only which letter code was assigned to each child, and the study worker…knew neither. At the time of switch, WHO and the DSMB statistician provided an alternative letter code for all of the redundant eight-letter codes... Tablets...were similar in packaging, appearance, taste, and inactive ingredients." Comment: sufficient blinding seems likely

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "...double-masked, placebo-controlled trial…To ensure masking, we labelled the strips of supplements with 16 letter codes - four for each of the groups. This letter code was hidden in the batch number on each strip of tablets." "The halting of the IFAZ and IFA arms and switching of children to the other groups were done with the help of WHO and the DSMB statistician. The trial initially used 16-letter codes (four-letter codes assigned to the individual supplementation groups) and two-stage blinding. The four-letter codes for every group were known only to WHO and the manufacturer; the pharmacy dispensing the supplements knew only which letter code was assigned to each child, and the study worker…knew neither. At the time of switch, WHO and the DSMB statistician provided an alternative letter code for all of the redundant eight-letter codes. ..Tablets...were similar in packaging, appearance, taste, and inactive ingredients." Teams that assessed causes of death "were masked to supplement allocation." Comment: sufficient blinding seems likely
Incomplete outcome data (attrition bias) All outcomes	Low risk	% Missing: 17 Reasons/details: in the zinc + iron + folic acid group reported in Sazawal 2006: 1075 participants "withdrew", 480 "outmigrated", and 146 "died". In the iron + folic acid group reported in Sazawal 2006: 1059 participants "withdrew", 445 "outmigrated", and 149 "died". In the placebo group reported in Sazawal 2007a: 865 participants "withdrew", 2018 "outmigrated", and 483 "died". In the zinc group reported in Sazawal 2007a: 1090 participants "withdrew", 2141 "outmigrated", and 401 "died" Comment: reasons for, and amount of, missing data were similar between the placebo and zinc groups. Reasons for, and amount of, missing data were similar between the iron + folic acid and zinc + iron + folic acid groups

Sazawal 2006 (*Continued*)

Selective reporting (reporting bias)	High risk	Comment: all-cause hospital admissions was pre-specified as a secondary outcome in the protocol for this study and was measured, but is not reported for the study group that received zinc. Hospitalisation due to diarrhoea, hospitalisation due to pneumonia, and hospitalisation due to malaria seem to be measured, but were not pre-specified in the protocol for this study, and are not reported; however, the related outcome of all-cause hospitalisation was pre-specified as a secondary outcome in the protocol for this study. Weight-for-height z-score was measured, but was not pre-specified in the protocol for this study, and is not reported. Malaria prevalence was measured, but was not pre-specified in the protocol for this study, and is not reported in a way that can be meta-analysed. Blood haemoglobin concentration, anaemia prevalence, prevalence of iron deficiency, height, and weight were reported, but were not pre-specified in the protocol for this study. Mortality due to diarrhoea, mortality due to pneumonia, and mortality due to malaria were reported, but were not pre-specified in the protocol for this study; however, the related outcome of all-cause mortality was pre-specified as a secondary outcome in the protocol for this study Protocol identifier: ISRCTN59549825
Other bias	Low risk	Comment: appears to be free of other bias

Sazawal 2006 (2)

Methods	
Participants	
Interventions	
Outcomes	All-cause mortality, all-cause hospitalisation, height, weight, blood haemoglobin concentration, prevalence of anaemia, prevalence of iron deficiency
Notes	As Sazawal 2006 above

Schultink 1997

Methods	CRCT?: IRCT; Cross-over?: non-cross-over
Participants	Country: Indonesia; Setting: Tambora district of Jakarta; Urbanicity: urban Inclusion criteria: pre-school children; stunted, as indicated by a height-for-age Z score below -1.5; anaemic, as indicated by a haemoglobin concentration below 110 g/L Exclusion criteria: N/A *Baseline characteristics* Avg age (mo): 38; Min age (mo): 24; Max age (mo): 60; % Female: 52 Avg HAZ: -2.5; Stunting: both - separate data not given; Avg height (cm): 85.9; Avg zinc concentration (μg/dL): 87.3 Total N: 85; Group 1 N: 43; Group 2 N: 42
Interventions	*Group 1:* zinc Formulation: solution; Compound: phosphate; Frequency: daily; Duration (mo): 2; Dose (mg): 15; Co-intervention(s): 30 mg iron *Group 2*: no zinc Placebo given; Co-intervention(s): 30 mg iron
Outcomes	Serum or plasma zinc concentration, blood haemoglobin concentration, serum or plasma ferritin concentration Time point (wk): 8
Notes	"…all children received a deworming treatment (100 mg of pyrantel pamoate and 150 mg of mebendazole) before the start of the supplementation."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The children were randomly assigned to two groups." Comment: insufficient details available to make a judgement as to whether or not an allocation sequence was generated using a truly random method
Allocation concealment (selection bias)	Unclear risk	Quote: N/A Comment: insufficient details available to make a judgement
Blinding of participants (performance bias) All outcomes	Low risk	Quote: "Both syrups were similar in appearance and taste, and supplementation was double-blinded." Comment: sufficient blinding seems likely
Blinding of personnel (performance bias) All outcomes	Low risk	Quote: "Both syrups were similar in appearance and taste, and supplementation was double-blinded." Comment: sufficient blinding seems likely

Schultink 1997 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Both syrups were similar in appearance and taste, and supplementation was double-blinded." Comment: sufficient blinding seems likely
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	% Missing: 21 Reasons/details: N/A Comment: 10 participants were missing in the zinc group, and 8 participants were missing in the control group. So, the amount of missing data was similar between study groups. However, reasons for missing data were not reported
Selective reporting (reporting bias)	Unclear risk	Comment: no trial protocol referenced by the study
Other bias	Low risk	Comment: appears to be free of other bias

Sempertegui 1996

Methods	CRCT?: IRCT; Cross-over?: non-cross-over
Participants	Country: Ecuador; Setting: slum in the northeast region of the city of Quito; Urbanicity: urban Inclusion criteria: attended a day-care centre (centro infantil No. 1 CAI, National Institute for the Children and the Family) for at least 6 months; malnourished according to height and weight parameters from the National Center for Health Statistics from the USA (NCHS) Exclusion criteria: N/A *Baseline characteristics* Avg age (mo): 42.3; Min age (mo): 12; Max age (mo): 59; % Female: 43.8 Avg HAZ: -2; Stunting: both - separate data not given; Avg height (cm): N/A; Avg zinc concentration (μg/dL): 86.5 Total N: 50; Group 1 N: 25; Group 2 N: 25
Interventions	*Group 1:* zinc Formulation: solution; Compound: sulfate; Frequency: daily; Duration (mo): 2; Dose (mg): 10; Co-intervention(s): N/A *Group 2*: no zinc Placebo given; Co-intervention(s): N/A
Outcomes	Incidence of LRTI, height, weight, serum or plasma zinc concentration Time point (wk): 9 (serum or plasma zinc concentration), 17 (morbidity and growth outcomes)
Notes	Full text could not be obtained for the Correa León et al 1992 trial report for this study

Sempertegui 1996 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "…children were randomly assigned, by the Moses-Oakford algorithm... " Comment: N/A
Allocation concealment (selection bias)	Unclear risk	Quote: "The code was kept by the Ethical Committee until the end of the study." Comment: insufficient details available to make a judgement
Blinding of participants (performance bias) All outcomes	Low risk	Quote: "…double-blind placebo-controlled trial…Zinc and placebo syrups had an identical appearance and flavor...The NS group received syrup 'A' that contained placebo. The S group was given syrup 'B' that contained zinc...The code was kept by the Ethical Committee until the end of the study." Comment: sufficient blinding seems likely
Blinding of personnel (performance bias) All outcomes	Low risk	Quote: "…double-blind placebo-controlled trial…Zinc and placebo syrups had an identical appearance and flavor…The NS group received syrup 'A' that contained placebo. The S group was given syrup 'B' that contained zinc…the syrups were administered…by two pediatricians...who did not know which group was the actively supplemented group until after the study was completed, and who were not involved in the daily clinical examination of the children. The code was kept by the Ethical Committee until the end of the study." Comment: sufficient blinding seems likely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "…double-blind placebo-controlled trial…Zinc and placebo syrups had an identical appearance and flavor...The NS group received syrup 'A' that contained placebo. The S group was given syrup 'B' that contained zinc...The code was kept by the Ethical Committee until the end of the study."

Sempertegui 1996 (*Continued*)

		Comment: sufficient blinding seems likely
Incomplete outcome data (attrition bias) All outcomes	Low risk	% Missing: 4 Reasons/details: "…two malnourished children from the S group were lost to follow-up when their families moved to another province." Comment: missing data seem too minimal to impact results
Selective reporting (reporting bias)	Unclear risk	Comment: prevalence of zinc deficiency may have been measured, but was not reported in a way that could be meta-analysed. No trial protocol referenced by the study
Other bias	Low risk	Comment: appears to be free of other bias

Shah 2011

Methods	CRCT?: IRCT; Cross-over?: non-cross-over	
Participants	Country: India; Setting: near the Jawaharlal Nehru Medical College Hospital in Aligarh, Uttar Pradesh, India; Urbanicity: urban Inclusion criteria: recurrent acute lower respiratory infections; referred to department of Pediatrics Exclusion criteria: N/A *Baseline characteristics* Avg age (mo): N/A; Min age (mo): 6; Max age (mo): 59; % Female: N/A Avg HAZ: N/A; Stunting: unclear; Avg height (cm): N/A; Avg zinc concentration (μg/dL): N/A Total N: N/A; Group 1 N: N/A; Group 2 N: N/A	
Interventions	*Group 1:* zinc Formulation: unclear; Compound: gluconate; Frequency: unclear; Duration (mo): 2; Dose (mg): 10; Co-intervention(s): N/A *Group 2*: no zinc Placebo given; Co-intervention(s): N/A	
Outcomes	No outcomes of interest reported in a way that can be meta-analysed	
Notes	Though, "The final analysis included 96 children allocated equally to the two groups", the number of participants randomised is not reported, nor is the number of participants randomised to each study group	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Random sequence generation (selection bias)	Unclear risk	Quote: "Children were randomly assigned…" Comment: insufficient details available to make a judgement as to whether or not an allocation sequence was generated using a truly random method
Allocation concealment (selection bias)	Unclear risk	Quote: N/A Comment: insufficient details available to make a judgement
Blinding of participants (performance bias) All outcomes	Unclear risk	Quote: "...double blind controlled trial…" Comment: insufficient details available to make a judgement
Blinding of personnel (performance bias) All outcomes	Unclear risk	Quote: "...double blind controlled trial…" Comment: insufficient details available to make a judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "...double blind controlled trial…" Comment: insufficient details available to make a judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	% Missing: N/A Reasons/details: N/A Comment: the following were not reported: number of participants randomised, number of participants randomised to each group, amount of missing data for each group, reasons for missing data in each group
Selective reporting (reporting bias)	High risk	Comment: LRTI, which meets the criteria of this review, may have been measured and reported; but it is unclear how respiratory illness was defined in this study. Serum zinc concentration was measured, but is not reported in a way that can be meta-analysed
Other bias	Low risk	Comment: appears to be free of other bias

Shankar 2000

Methods	CRCT?: IRCT; Cross-over?: non-cross-over
Participants	Country: Papua New Guinea; Setting: north Wosera District of East Sepik Province, in northwestern Papua New Guinea; Urbanicity: rural Inclusion criteria: planning to reside in the Wosera for at least 1 year; no apparent chronic or debilitating condition Exclusion criteria: signs of severe zinc deficiency or malnutrition *Baseline characteristics* Avg age (mo): N/A; Min age (mo): 6; Max age (mo): 60; % Female: 53 Avg HAZ: -1.9; Stunting: both - separate data not given; Avg height (cm): N/A; Avg zinc concentration (μg/dL): 71 Total N: 274; Group 1 N: 136; Group 2 N: 138
Interventions	*Group 1:* zinc Formulation: pill/tablet; Compound: gluconate; Frequency: 6 days/wk; Duration (mo) : 11.5; Dose (mg): 10; Co-intervention(s): N/A *Group 2*: no zinc Placebo given; Co-intervention(s): N/A
Outcomes	All-cause mortality, mortality due to malaria, prevalence of all-cause diarrhoea, incidence of malaria, height, weight-to-height ratio, serum or plasma zinc concentration, prevalence of zinc deficiency, blood haemoglobin concentration, prevalence of anaemia Time point (wk): 46
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Children within these strata were individually allocated to computer-generated randomly permuted 4-person blocks of two codes, Zn or placebo (PL)." Comment: N/A
Allocation concealment (selection bias)	Low risk	Quote: "The tablets were encoded and the assignment held off-site by personnel not involved in the study...The study code was broken after closing the databases following double entry of all data." Comment: sufficient allocation concealment seems likely
Blinding of participants (performance bias) All outcomes	Low risk	Quote: "...double-blind placebo-controlled trial…The study code was broken after closing the databases following double entry of all data...Placebos were indistinguishable from the sup-

Shankar 2000 (*Continued*)

		plements in color, size, or taste..." Comment: sufficient blinding seems likely
Blinding of personnel (performance bias) All outcomes	Low risk	Quote: "...double-blind placebo-controlled trial…The study code was broken after closing the databases following double entry of all data...Placebos were indistinguishable from the supplements in color, size, or taste..." Comment: sufficient blinding seems likely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "...double-blind placebo-controlled trial…The study code was broken after closing the databases following double entry of all data...Placebos were indistinguishable from the supplements in color, size, or taste..." Comment: sufficient blinding seems likely
Incomplete outcome data (attrition bias) All outcomes	Low risk	% Missing: 23 Reasons/details: in the zinc group: 19 "migrated", 11 "refused", and 3 "died". In the placebo group: 19 "migrated", 9 "refused", and 1 "died" Comment: reasons for, and amount of, missing data were similar between study groups
Selective reporting (reporting bias)	High risk	Comment: side effects were measured, but are not reported in a way that can be meta-analysed
Other bias	Low risk	Comment: appears to be free of other bias

Silva 2006

Methods	CRCT?: IRCT; Cross-over?: non-cross-over
Participants	Country: Brazil; Setting: São Sebastião, Distrito Federal (DF); Urbanicity: unclear Inclusion criteria: N/A Exclusion criteria: diseased, anaemic with haemoglobin levels lower than 9.0 g/dl, on medication or receiving supplementation, parasitic disease *Baseline characteristics* Avg age (mo): 23.5; Min age (mo): 12; Max age (mo): 59; % Female: 56.9 Avg HAZ: -1.9; Stunting: both - separate data not given; Avg height (cm): N/A; Avg zinc concentration (μg/dL): 56.1 Total N: 60; Group 1 N: 30; Group 2 N: 30

Interventions	*Group 1:* zinc Formulation: solution; Compound: sulfate; Frequency: daily; Duration (mo): 4; Dose (mg): 10; Co-intervention(s): 2 kg iron-fortified milk *Group 2*: no zinc Placebo given; Co-intervention(s): 2 kg iron-fortified milk
Outcomes	Height, serum or plasma zinc concentration, blood haemoglobin concentration Time point (wk): 16
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "...the sample consisted of 60 individuals, who were randomly placed in two groups...The children were placed in either of two groups according to the supplementation they received. Of every two mothers or surrogates who allowed their children to participate in the study, one child was assigned to the supplementation group and another one was placed in the control group..." Comment: insufficient details available to make a judgement as to whether or not an allocation sequence was generated using a truly random method
Allocation concealment (selection bias)	Unclear risk	Quote: N/A Comment: insufficient details available to make a judgement
Blinding of participants (performance bias) All outcomes	Unclear risk	Quote: "A blinded randomized clinical trial was carried out…The flask containing zinc sulfate was labeled S...The flask containing the syrup was labeled C. The flasks containing placebo and zinc sulfate were identical and the taste and smell of the solutions were the same." Comment: people involved with the study might have been able to tell which solution was zinc and which was placebo based on the different letter labels on the flasks
Blinding of personnel (performance bias) All outcomes	Unclear risk	Quote: "A blinded randomized clinical trial was carried out…The flask containing zinc

		sulfate was labeled S...The flask containing the syrup was labeled C. The flasks containing placebo and zinc sulfate were identical and the taste and smell of the solutions were the same." Comment: People involved with the study might have been able to tell which solution was zinc and which was placebo based on the different letter labels on the flasks
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "A blinded randomized clinical trial was carried out…The flask containing zinc sulfate was labeled S...The flask containing the syrup was labeled C. The flasks containing placebo and zinc sulfate were identical and the taste and smell of the solutions were the same." Comment: People involved with the study might have been able to tell which solution was zinc and which was placebo based on the different letter labels on the flasks
Incomplete outcome data (attrition bias) All outcomes	Low risk	% Missing: 3 Reasons/details: "In the course of the study, two children from the supplementation group withdrew." Comment: missing data seem too minimal to impact results
Selective reporting (reporting bias)	High risk	Comment: side effects (i.e. "possible gastrointestinal symptoms (nausea, vomiting, diarrhea), and loss of appetite caused by zinc supplementation") were measured, but are not reported. The percentage decrease in the prevalence of anaemia for the placebo group amounts to less than a single person decrease, which seems to be an implausible result. "W/H" is reported, but it is unclear whether or not this refers to weight-for-height or weight-for-age
Other bias	Low risk	Comment: appears to be free of other bias

Smith 1999

Methods	CRCT?: IRCT; Cross-over?: non-cross-over
Participants	Country: Belize; Setting: refugee camps Los Flores and Salvapan in Cayo District; Urbanicity: unclear Inclusion criteria: low/marginal concentrations of both serum vitamin A and zinc Exclusion criteria: fever; serious respiratory infection *Baseline characteristics* Avg age (mo): N/A; Min age (mo): N/A; Max age (mo): N/A; % Female: N/A Avg HAZ: N/A; Stunting: both - separate data not given; Avg height (cm): N/A; Avg zinc concentration (μg/dL): 75.2 Total N: 51; Group 1 N: N/A; Group 2 N: N/A; Group 3 N: N/A; Group 4 N: N/A
Interventions	*Group 1:* zinc Formulation: solution; Compound: gluconate; Frequency: Weekly; Duration (mo): 6; Dose (mg): 70; Co-intervention(s): N/A *Group 2*: no zinc Placebo given; Co-intervention(s): N/A *Group 3:* zinc Co-intervention(s): 3030 RE vitamin A *Group 4*: no zinc Placebo given; Co-intervention(s): 3030 RE vitamin A
Outcomes	Height, weight, serum or plasma zinc concentration, blood haemoglobin concentration Time point (wk): 24
Notes	- The trial reports contradictory information about the maximum age of eligible study participants. So, the minimum age was between 22 and 28 months, and the maximum age was between 66 and 72 months - The number of participants randomised to each study group is not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "The children selected were randomly assigned…" Comment: insufficient details available to make a judgement as to whether or not an allocation sequence was generated using a truly random method
Allocation concealment (selection bias)	Unclear risk	Quote: N/A Comment: insufficient details available to make a judgement
Blinding of participants (performance bias) All outcomes	Unclear risk	Quote: N/A Comment: insufficient details available to make a judgement

Smith 1999 (*Continued*)

Blinding of personnel (performance bias) All outcomes	Unclear risk	Quote: N/A Comment: insufficient details available to make a judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: N/A Comment: insufficient details available to make a judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	% Missing: 16 Reasons/details: "Because of relocation of residence and other causes, eight failed to complete the study…" Comment: migration was the most common reason for missing data, and this reason is unlikely to bias results
Selective reporting (reporting bias)	Unclear risk	Comment: blood haemoglobin concentration and height-for-age z score were measured for the zinc versus vitamin A + zinc comparison, but are not reported in a way that can be meta-analysed. No trial protocol referenced by the study
Other bias	Unclear risk	Comment: "Analysis of pretreatment data indicated that children who subsequently received Zn supplementation were heavier (1.1 kg) than were non-Zn-treated subjects. The effects of these weight differences were significant variations in...weight-for-age Z score (WAZ)." This baseline difference could have influenced weight outcomes, which were reported only as post-treatment scores, rather than as changes from baseline

Soofi 2013

Methods	CRCT?: CRCT; Cross-over?: non-cross-over
Participants	Country: Pakistan; Setting: Bilal Colony and Matiari, Sindh; Urbanicity: mixed Inclusion criteria: randomised at 6 months of age of age Exclusion criteria: not mentioned *Baseline characteristics* Avg age (mo): 6; Min age (mo): 6; Max age (mo): 6; % Female: 50% Avg HAZ: not given; Stunting: both - separate data not given; Avg height (cm): 64.4; Avg zinc concentration (μg/dL): 84.3 Total N: 1305; Group 1 N: 659; Group 2 N: 646

Interventions	*Group 1:* zinc Formulation: powder/paste; Compound: gluconate; Frequency: daily; Duration (mo): 12; Dose (mg): 10; Co-intervention(s): micronutrient powder *Group 2*: no zinc Placebo not given; Co-intervention(s): micronutrient powder
Outcomes	All-cause mortality,incidence of all-cause diarrhoea, incidence of severe diarrhoea, prevalence of all-cause diarrhoea, incidence of persistent diarrhoea, incidence of LRTI, prevalence of LRTI, hospitalisation due to LRTI, prevalence of anaemia, serum ferritin, serum zinc, blood haemoglobin, prevalence of stunting Time point (wk): 52
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "randomly allocated within urban and rural strata using computer-generated random numbers"
Allocation concealment (selection bias)	Low risk	Quote: "MNPs were packaged in individual daily dose sachets which were identical apart from their colour (Group B=Brown, Group C=Green). The colour coding used was known only to the Manager, Genera Pharmaceuticals, Islamabad and the Chair of the trial's Data Monitoring Committee (DMC)"
Blinding of participants (performance bias) All outcomes	Low risk	Quote: "The investigators, field and supervisory staff were blinded to the composition of the MNP preparations until after the results of the trial had been presented to the independent DMC."
Blinding of personnel (performance bias) All outcomes	Low risk	Quote: "The investigators, field and supervisory staff were blinded to the composition of the MNP preparations until after the results of the trial had been presented to the independent DMC."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: ""All data collectors were provided with refresher training at 6 monthly intervals and rotated between clusters to avoid differential interviewer bias across clusters. "

Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Between 18 and 23.9 months of age there did not appear to be any link between treatment allocation and missingness. There was evidence to suggest that children with a high proportion of observed days with diarrhoea tended to have fewer days of completed follow-up." Comment: 18.6% missing, but no difference between groups
Selective reporting (reporting bias)	Low risk	Quote: protocol also includes "serum zinc, serum retinol, hair zinc, CRP and some immune response parameters" Comment: key clinical outcomes reported
Other bias	Low risk	Comment: appears to be free of other bias

Tielsch 2006

Methods	CRCT?: CRCT; Cross-over?: non-cross-over
Participants	Country: Nepal; Setting: Sarlahi District in southern Nepal; Urbanicity: rural Inclusion criteria: N/A Exclusion criteria: N/A *Baseline characteristics* Avg age (mo): N/A; Min age (mo): 1; Max age (mo): 35; % Female: 49 Avg HAZ: N/A; Stunting: both - separate data not given; Avg height (cm): N/A; Avg zinc concentration (μg/dL): N/A Total N: 49,205; Group 1 N: 16,426; Group 2 N: 15,700; Group 3 N: 8951; Group 4 N: 8128 Total clusters: 425; Group 1 clusters: 107; Group 2 clusters: 106; Group 3 clusters: 107; Group 4 clusters: 105
Interventions	*Group 1:* zinc Formulation: pill/tablet; Compound: sulfate; Frequency: daily; Duration (mo): N/A; Dose (mg): 5 mg to children < 1 year old; 10 mg to children 1 year of age or older; Co-intervention(s): N/A *Group 2*: no zinc Placebo given; Co-intervention(s): N/A *Group 3:* zinc Co-intervention(s): 6.25 mg iron and 25 µg folic acid to children < 1 year old; 12.5 mg iron and 50 µg folic acid to children 1 year of age or older *Group 4*: no zinc Placebo given; Co-intervention(s): 6.25 mg iron and 25 µg folic acid to children < 1 year old; 12.5 mg iron and 50 µg folic acid to children 1 year of age or older

Outcomes	All-cause mortality, serum or plasma zinc concentration, prevalence of zinc deficiency, serum or plasma copper concentration, prevalence of copper deficiency Time point (wk): 52 (biochemical outcomes)
Notes	- Greater than 50% of participants analysed in the Tielsch et al Lancet 2006; 367: 144-52 article are within the eligible age range for this review. So, baseline demographic data and most outcome data from this trial report are included in this review. However, this Tielsch et al 2006 trial report provides some outcome data for subsets of participants that potentially are not eligible for this review based on age; these data for potentially ineligible participant subsets are not included in this review. Less than 51% of participants analysed in the Tielsch et al Lancet 2007; 370: 1230-39 article are within the eligible age range for this review. However, this Tielsch et al 2007 trial report provides data on some outcomes for subsets of participants that are eligible for this review based on age; these data for eligible participant subsets are included in this review - "On the basis of recommendations from the data and safety monitoring board, the arms of the trial in which children were given iron and folic acid were stopped in November, 2003, and children in those sectors were randomly reassigned to either placebo or zinc." The Tielsch et al 2007 trial report analyses a "merged set" of data, including: (a) children originally assigned to zinc or placebo, and (b) those who originally received iron/folic acid/zinc or iron/folic acid, and were then reassigned to zinc or placebo. To avoid a unit of analysis error, data from (a) the iron/folic acid/zinc and iron/folic acid groups reported in Tielsch et al 2006, and (b) the zinc and placebo groups reported in Tielsch et al 2007, are not included in the same meta-analysis - The numbers of participants listed in this table as being randomised to the zinc and placebo groups: (a) Do not include those from the iron/folic acid/zinc and iron/folic acid groups who were switched to zinc or placebo, but (b) Do include "7432 children from sectors originally assigned to iron and folic acid or to iron and folic acid with zinc who were not eligible for the original allocation, but were subsequently randomly assigned to either placebo or zinc." - Though some trial reports of this study report that 426 sectors were randomised, the Tielsch et al 2007 trial report, which is the only trial report that provides data on the number of sectors randomised to each study group, states that 425 sectors were randomised - "All children older than 6 months also received vitamin A as part of a national programme or, if missed, by study staff: those aged 12 months or older were given 200 000 IU of vitamin A every 6 months and those aged 6-12 months were given 100 000 IU." - "Children were discharged from the study when they reached 36 months of age", and most children were less than 24 months of age at baseline; the duration of supplementation seemed to be at least 12 months for most participants

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Sectors were randomly assigned to treatment groups in blocks of four…All possible orders of the four treatment groups were written on...paper slips, with roughly

		equal numbers of slips for each order. One slip was randomly drawn to assign treatment codes to four sectors within a VDC. This continued until all sectors were assigned." Comment: seems likely to have used a truly random method to generate an allocation sequence
Allocation concealment (selection bias)	Low risk	Quote: "One slip was randomly drawn to assign treatment codes to...sectors...This continued until all sectors were assigned. " "The Department of Child and Adolescent Health and Development at WHO, Geneva, Switzerland, kept the treatment assignment codes." Comment: sufficient allocation concealment seems likely
Blinding of participants (performance bias) All outcomes	Low risk	Quote: "We did a...double-masked... trial…participants were unaware of assigned treatments." Comment: sufficient blinding seems likely
Blinding of personnel (performance bias) All outcomes	Low risk	Quote: "We did a...double-masked... trial…Investigators, study staff...were unaware of assigned treatments." Comment: sufficient blinding seems likely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "We did a...double-masked... trial…Investigators, study staff...were unaware of assigned treatments." Comment: sufficient blinding seems likely
Incomplete outcome data (attrition bias) All outcomes	Low risk	% Missing: 16 Reasons/details: besides the "7432 children from sectors originally assigned to iron and folic acid or to iron and folic acid with zinc who were not eligible for the original allocation, but were subsequently randomly assigned to either placebo or zinc", there were 12,133 participants originally assigned to the placebo group, and 12,885 participants originally assigned to the zinc group. Among these 12,133 placebo group participants: 595 refused, 917 were lost or moved, and 224 died. Among these 12,885 zinc group participants: 947 refused, 916 were lost or moved, and 225 died. Among

Tielsch 2006 (*Continued*)

		the 8128 participants assigned to the iron + folic acid group: 952 refused, 347 moved, and 112 died before this group was stopped in November 2003. Among the 8951 participants assigned to the iron + folic acid + zinc group: 1186 refused, 354 moved, and 119 died before this group was stopped in November 2003 Comment: reasons for, and amount of, missing data were similar between the placebo and zinc groups. Reasons for, and amount of, missing data were similar between the iron + folic acid and zinc + iron + folic acid groups
Selective reporting (reporting bias)	Unclear risk	Comment: serum zinc, blood haemoglobin, serum ferritin, and serum copper concentrations; prevalence of zinc, iron, and copper deficiency; and prevalence of anaemia were reported, but were not prespecified in the trial protocol. However all of these were stated to be secondary, not primary, outcomes in the trial reports Protocol identifier: NCT00109551
Other bias	Low risk	Comment: appears to be free of other bias

Tielsch 2006 (2)

Methods	
Participants	
Interventions	
Outcomes	Mortality due to all-cause diarrhoea, mortality due to LRTI, blood haemoglobin concentration, prevalence of anaemia, serum or plasma ferritin concentration, prevalence of iron deficiency
Notes	As Tielsch 2006 above

Tupe 2009

Methods	CRCT?: CRCT; Cross-over?: non-cross-over
Participants	Country: India; Setting: Pune City, Maharashtra State, Western India; Urbanicity: urban Inclusion criteria: N/A Exclusion criteria: current illness such as fever or respiratory or gastrointestinal infection; taking medical treatment; suffered from any illness in the recent past; taking multivitamin

	mineral supplements *Baseline characteristics* Avg age (mo): 144; Min age (mo): 120; Max age (mo): 155; % Female: 100 Avg HAZ: -1.3; Stunting: both - separate data not given; Avg height (cm): 142; Avg zinc concentration (μg/dL): 59 Total N: 88; Group 1 N: 44; Group 2 N: 44 Total clusters: 2; Group 1 clusters: 1; Group 2 clusters: 1
Interventions	*Group 1:* zinc Formulation: pill/tablet; Compound: unclear; Frequency: 6 days/wk; Duration (mo): 2.5; Dose (mg): 16.6; Co-intervention(s): N/A *Group 2*: no zinc Placebo not given; Co-intervention(s): N/A
Outcomes	Height, weight, serum or plasma zinc concentration, prevalence of zinc deficiency, blood haemoglobin concentration, prevalence of anaemia, serum or plasma ferritin concentration Time point (wk): 10
Notes	- In addition to the study groups mentioned in this table, there was a group of participants who received "zinc- and micronutrient-rich food supplements." Baseline characteristics reported in this table are weighted averages of all groups except the "zinc- and micronutrient-rich food supplements" group, since this group is not included in any meta-analyses in this review - This trial included some participants who were 13 years of age and older at baseline. However, baseline characteristics reported in this table were calculated based on data from participants less than 13 years of age. Data on all outcomes (except for prevalence of zinc deficiency and prevalence of anaemia) were also calculated based on data from participants less than 13 years of age. Even though zinc deficiency and anaemia prevalence are partially based on data from participants older than 13 years, the average age of participants analysed for these outcomes is less than 13 years - "Ayurvedic zinc tablet (jasad bhasma) was chosen as a natural elemental zinc supplement…Tablets containing 20 mg of jasad bhasma of a standard ayurvedic company were procured. Analysis of the jasad tablet in our laboratory indicated that each tablet contained 16.6 mg elemental zinc, 0.74 mg iron, and the remaining part as starch." We deemed the 0.74 mg iron to be too insignificant to have any effect on outcomes in this trial

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: In response to a request for further details on sequence generation, an author of this study explained that, "Three classes of 7th standard girls from the schools were randomly assigned to either of the two intervention groups or control group by the statistician", and that a "Lottery method

		was used to allocate a class to any one of the three treatments." Comment: it seems likely that the allocation sequence was generated using a truly random method
Allocation concealment (selection bias)	Unclear risk	Quote: N/A Comment: insufficient details available to make a judgement
Blinding of participants (performance bias) All outcomes	Unclear risk	Quote: "Control group did not receive placebo but was unaware of the supplemented group." Comment: it is unclear how measured outcomes might be influenced by a lack of placebo
Blinding of personnel (performance bias) All outcomes	Unclear risk	Quote: "Control group did not receive placebo but was unaware of the supplemented group." Comment: it is unclear how measured outcomes might be influenced by a lack of placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The measurement team (both pretest and posttest observations) was blinded as to whether each girl was a member of one of the intervention groups or the control group." Comment: sufficient blinding seems likely
Incomplete outcome data (attrition bias) All outcomes	Low risk	% Missing: 6 Reasons/details: in the zinc group: 1 participant was "excluded because of religious fasting" that she observed during the study period. In the control group: 4 participants were excluded because they were absent on the day of outcome measurement Comment: 6% of the randomised participants eligible for our review had data missing; this 6% missing figure includes all groups except the "zinc- and micronutrient-rich food supplements" group, since this group is not included in any meta-analyses in this review. In addition, this 6% missing figure only includes participants who were less than 13 years of age at baseline. Though it is unclear whether being absent on the day of testing might bias re-

		sults, the amount of missing data seems too minimal to impact results
Selective reporting (reporting bias)	Unclear risk	Comment: prevalence of zinc deficiency and prevalence of anaemia were reported, but were not pre-specified in the protocol for this study; though the related outcomes of plasma zinc concentration and haemoglobin concentration were pre-specified in the protocol for this study
Other bias	Low risk	Comment: appears to be free of other bias

Uckardes 2009

Methods	CRCT?: IRCT; Cross-over?: non-cross-over
Participants	Country: Turkey; Setting: Ankara; Urbanicity: urban Inclusion criteria: 3rd grade student Exclusion criteria: any chronic systemic disease which could affect their neuropsychological performance and zinc metabolism *Baseline characteristics* Avg age (mo): 102; Min age (mo): 89; Max age (mo): 140; % Female: 50.5 Avg HAZ: N/A; Stunting: unclear; Avg height (cm): 127.45; Avg zinc concentration (μg/dL): 119.7 Total N: 226; Group 1 N: 113; Group 2 N: 113
Interventions	*Group 1:* zinc Formulation: solution; Compound: sulfate; Frequency: 5 days/wk; Duration (mo): 2.5; Dose (mg): 15; Co-intervention(s): N/A *Group 2*: no zinc Placebo given; Co-intervention(s): N/A
Outcomes	Serum or plasma zinc concentration, prevalence of zinc deficiency Time point (wk): 10
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Children in each class were randomized to one of the research groups." "Randomization was made simply by dividing the class student list into two as study and control groups." Comment: insufficient details available to

		make a judgement as to whether or not an allocation sequence was generated using a truly random method
Allocation concealment (selection bias)	Unclear risk	Quote: N/A Comment: insufficient details available to make a judgement
Blinding of participants (performance bias) All outcomes	Low risk	Quote: "Double-blind...placebo controlled trial." "The placebo was also manufactured by the company with same appearance." Comment: sufficient blinding seems likely
Blinding of personnel (performance bias) All outcomes	Low risk	Quote: "Double-blind... placebo controlled trial...The investigators and teachers were blind until the end of the analysis." ("Zinc and placebo syrups were given by the teachers at school..." So, the teachers were the providers of the syrups.) "The placebo was also manufactured by the company with same appearance." Comment: sufficient blinding seems likely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Double-blind... placebo controlled trial...The investigators. ..were blind until the end of the analysis. " "The placebo was also manufactured by the company with same appearance." Comment: sufficient blinding seems likely
Incomplete outcome data (attrition bias) All outcomes	Low risk	% Missing: 4 Reasons/details: "Four children from the zinc group and four from the placebo group left the study because family moved to another district (n = 4), school absenteeism (n = 2) and vomiting (n = 2)." Comment: missing data seem too minimal to impact results
Selective reporting (reporting bias)	Unclear risk	Comment: though side effects "were monitored by teachers daily at school", "side effects were not collected numerically from all subjects" and "only the teachers' of 2 classes (45 case, 45 placebo) had documented data." No trial protocol referenced by the study

Other bias	Unclear risk	Comment: "Serum zinc level was measured…Caloric spectrophotometery was used instead of atomic absorption spectrophotometer due to the limited budget of the study. This method may not be as sensitive as atomic absorption spectrophotometery for measuring serum zinc levels or there may be a systematic error in our chemical methodology. Although we could not detect any children with zinc deficiency in our participants most probably due to the methodology, other studies from our region demonstrate a prevalence of zinc deficiency around 20%." Thus, an insensitive instrument for measuring prevalence of zinc deficiency may have been used, and this could have lead to an under-estimation of the number of participants with zinc deficiency and/or the effect of zinc supplementation on zinc deficiency prevalence

Udomkesmalee 1992

Methods	CRCT?: IRCT; Cross-over?: non-cross-over
Participants	Country: Thailand; Setting: Pana District, Ubon Province, Northeast Thailand; Urbanicity: rural Inclusion criteria: serum concentration of retinol < 1.05 μmol/L; serum concentration of zinc <12.2 μmol/L Exclusion criteria: N/A *Baseline characteristics* Avg age (mo): 112; Min age (mo): 72; Max age (mo): 156; % Female: 42 Avg HAZ: N/A; Stunting: both - separate data not given; Avg height (cm): N/A; Avg zinc concentration (μg/dL): 85.8 Total N: 133; Group 1 N: 33; Group 2 N: 35; Group 3 N: 32; Group 4 N: 33
Interventions	*Group 1:* zinc Formulation: capsule; Compound: gluconate; Frequency: 5 days/wk; Duration (mo): 6; Dose (mg): 25; Co-intervention(s): N/A *Group 2*: no zinc Placebo given; Co-intervention(s): N/A *Group 3:* zinc Co-intervention(s): 1500 RE vitamin A per day *Group 4*: no zinc Placebo given; Co-intervention(s): 1500 RE vitamin A per day
Outcomes	Serum or plasma zinc concentration Time point (wk): 24

Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "They were then randomly assigned…" Comment: insufficient details available to make a judgement as to whether or not an allocation sequence was generated using a truly random method
Allocation concealment (selection bias)	Unclear risk	Quote: "The capsule code was revealed after all analyses were completed." Comment: despite this statement, the method of allocation concealment is not described in sufficient detail to allow a definite judgement
Blinding of participants (performance bias) All outcomes	Low risk	Quote: "...double-blind study…All supplementary capsules were similar in appearance…The capsule code was revealed after all analyses were completed." Comment: sufficient blinding seems likely
Blinding of personnel (performance bias) All outcomes	Low risk	Quote: "...double-blind study…All supplementary capsules were similar in appearance…The capsule code was revealed after all analyses were completed." Comment: sufficient blinding seems likely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "...double-blind study…All supplementary capsules were similar in appearance…The capsule code was revealed after all analyses were completed." Comment: sufficient blinding seems likely
Incomplete outcome data (attrition bias) All outcomes	Low risk	% Missing: 5 Reasons/details: "One subject withdrew toward the end of study period; six subjects were identified with thalassemia according to abnormal blood cell morphology." Comment: missing data seem too minimal to impact results

Udomkesmalee 1992 (*Continued*)

Selective reporting (reporting bias)	High risk	Comment: height and weight were measured, but are not reported in a way that can be meta-analysed. Prevalence of anaemia may have been measured as an outcome, but is not reported in a way that can be meta-analysed
Other bias	Low risk	Comment: appears to be free of other bias

Udomkesmalee 1992 (2)

Methods	
Participants	
Interventions	
Outcomes	Serum or plasma zinc concentration
Notes	As Udomkesmalee 1992 above

Umeta 2000

Methods	CRCT?: IRCT; Cross-over?: non-cross-over
Participants	Country: Ethiopia; Setting: Dodota Sire district, Arsi zone, central Ethiopia; Urbanicity: rural Inclusion criteria: apparently healthy; looked well; exclusively breastfed for the first 4 months of life; free from intestinal parasites Exclusion criteria: N/A *Baseline characteristics* Avg age (mo): 9.4; Min age (mo): 6; Max age (mo): 12; % Female: 50 Avg HAZ: -1.7; Stunting: both - separate data given; Avg height (cm): 67.2; Avg zinc concentration (μg/dL): N/A Total N: 200; Group 1 N: 100; Group 2 N: 100
Interventions	*Group 1:* zinc Formulation: solution; Compound: sulfate; Frequency: 6 days/wk; Duration (mo): 6; Dose (mg): 10; Co-intervention(s): N/A *Group 2*: no zinc Placebo given; Co-intervention(s): N/A
Outcomes	Incidence of all-cause diarrhoea, height, weight, weight-to-height ratio, serum or plasma zinc concentration Time point (wk): 24
Notes	

Umeta 2000 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: Participants were "randomly assigned to receive the zinc supplement or placebo." Comment: insufficient details available to make a judgement as to whether or not an allocation sequence was generated using a truly random method
Allocation concealment (selection bias)	Unclear risk	Quote: N/A Comment: insufficient details available to make a judgement
Blinding of participants (performance bias) All outcomes	Low risk	Quote: "…double-blind, placebo-controlled trial…The supplement and placebo were indistinguishable in colour and the slight metallic taste of the supplement was acceptable to the infants." Comment: the "slight metallic taste of the supplement" does not seem likely to influence outcomes. Sufficient blinding seems likely
Blinding of personnel (performance bias) All outcomes	Low risk	Quote: "…double-blind, placebo-controlled trial…The supplement and placebo were indistinguishable in colour and the slight metallic taste of the supplement was acceptable to the infants...Neither the field assistants nor the investigator knew the codes. The codes were revealed only after the study was completed and the data analysis was finalised." Comment: sufficient blinding seems likely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "…double-blind, placebo-controlled trial…The supplement and placebo were indistinguishable in colour and the slight metallic taste of the supplement was acceptable to the infants...Neither the field assistants nor the investigator knew the codes. The codes were revealed only after the study was completed and the data analysis was finalised." Comment: sufficient blinding seems likely

Umeta 2000 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	% Missing: 8 Reasons/details: N/A Comment: no reasons for dropout were reported. However, the same amount of data was missing from the zinc group and the placebo group, and missing data seem too minimal to impact results
Selective reporting (reporting bias)	Unclear risk	Comment: no trial protocol referenced by the study
Other bias	Low risk	Comment: appears to be free of other bias

Vakili 2009

Methods	CRCT?: IRCT; Cross-over?: non-cross-over
Participants	Country: Iran; Setting: Altimor, a suburb of Mashhad in north east Iran; Urbanicity: peri-urban Inclusion criteria: free of chronic diseases, such as sickle cell disease or protein-energy malnutrition Exclusion criteria: N/A *Baseline characteristics* Avg age (mo): 93.4; Min age (mo): 78; Max age (mo): 120; % Female: 50 Avg HAZ: N/A; Stunting: unclear; Avg height (cm): N/A; Avg zinc concentration (μg/dL): N/A Total N: 200; Group 1 N: 100; Group 2 N: 100
Interventions	*Group 1:* zinc Formulation: pill/tablet; Compound: sulfate; Frequency: 6 days/wk; Duration (mo): 5; Dose (mg): 10; Co-intervention(s): N/A *Group 2*: no zinc Placebo given; Co-intervention(s): N/A
Outcomes	No outcomes of interest reported in a way that can be meta-analysed
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "The study was a randomized…intervention trial…A total of 200 children…were randomly assigned…" Comment: insufficient details available to make a judgement as to whether or not an allocation sequence was generated using a

Vakili 2009 (*Continued*)

		truly random method
Allocation concealment (selection bias)	Unclear risk	Quote: N/A Comment: insufficient details available to make a judgement
Blinding of participants (performance bias) All outcomes	Unclear risk	Quote: "The study was a…double-blind…intervention trial…" Comment: insufficient details available to make a judgement
Blinding of personnel (performance bias) All outcomes	Unclear risk	Quote: "The study was a…double-blind…intervention trial…" Comment: insufficient details available to make a judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "The study was a…double-blind…intervention trial…" Comment: insufficient details available to make a judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	% Missing: 0 Reasons/details: N/A Comment: N/A
Selective reporting (reporting bias)	Unclear risk	Comment: no trial protocol referenced by the study
Other bias	Low risk	Comment: appears to be free of other bias

Veenemans 2011

Methods	CRCT?: IRCT; Cross-over?: non-cross-over
Participants	Country: Tanzania; Setting: Segera and Kwedizinga wards in Handeni District of Northern Tanzania; Urbanicity: rural Inclusion criteria: N/A Exclusion criteria: height-for-age z-score > -1.5 SD; weight-for-height z-score < -3 SD; haemoglobin concentration < 70 g/L; unlikely to remain permanently resident or comply with interventions; signs of severe or chronic disease *Baseline characteristics* Avg age (mo): 32.5; Min age (mo): 6; Max age (mo): 60; % Female:51 Avg HAZ: -2.43; Stunting: both - separate data not given; Avg height (cm): N/A; Avg zinc concentration (μg/dL): N/A Total N: 612; Group 1 N: 153; Group 2 N: 153; Group 3 N: 151; Group 4 N: 155
Interventions	*Group 1:* zinc Formulation: capsule; Compound: gluconate; Frequency: daily; Duration (mo): 11; Dose

	(mg): 10; Co-intervention(s): N/A *Group 2*: no zinc Placebo given; Co-intervention(s): N/A *Group 3:* zinc Co-intervention(s): multi-nutrients (including iron) *Group 4*: no zinc Placebo given; Co-intervention(s): multi-nutrients (including iron)
Outcomes	All-cause mortality, all-cause hospitalisation, incidence of all-cause diarrhoea, incidence of LRTI, incidence of malaria, serum or plasma zinc concentration, prevalence of zinc deficiency, blood haemoglobin concentration, prevalence of anaemia, serum or plasma ferritin concentration, prevalence of iron deficiency Time point (wk): 36 (biochemical outcomes), 47.3 (morbidity and mortality outcomes)
Notes	- Participants were enrolled between February and August 2008, and "Supplementation and follow-up continued for all children until 12 March 2009, when the trial was stopped. " The primary analysis of malaria episodes had a median follow-up duration of 331 days - "Those with Plasmodium infection at baseline were treated with artemether-lumefantrine."

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "We used stratified block randomisation to allocate interventions. A colleague not otherwise involved in the trial used tables with random numbers to generate the allocation sequence consisting of randomly permuted blocks with random size (4 or 8) within each of six strata defined by Plasmodium infection (yes/no infected) and age class (6-17 months, 18-35 months, and 36-60 months)." Comment: N/A
Allocation concealment (selection bias)	Low risk	Quote: "A colleague not otherwise involved in the trial used tables with random numbers to generate the allocation sequence…Interventions were indicated by colour code on paper slips in opaque, consecutively numbered envelopes that were prepared in advance, in excess of the expected number required…This code was not revealed to researchers, field staff, or participants, who therefore did not know who received what intervention…At the end of each screening day, when eligibility had been fully established, children

		were individually allocated in order of their screening number to intervention groups by drawing successive envelopes from a box corresponding to the infection- and age-specific stratum for that child. The number of the envelope was then recorded on a list before the envelope was opened." Comment: indicates central randomisation (i.e. randomisation by someone not involved with enrolling patients) and sequentially numbered, opaque, sealed envelopes to conceal allocation
Blinding of participants (performance bias) All outcomes	Low risk	Quote: "Intervention group was indicated by colour code, but neither participants…knew who received what intervention…This code was not revealed to…participants, who therefore did not know who received what intervention…All types of powder had similar appearance, smell, and taste…The randomisation code was not revealed to…participants until data collection was completed and the database had been finalised and sent to the Trial Oversight Committee." Comment: sufficient blinding seems likely
Blinding of personnel (performance bias) All outcomes	Low risk	Quote: "Intervention group was indicated by colour code, but neither…nor field staff knew who received what intervention…This code was not revealed to…field staff…who therefore did not know who received what intervention…All types of powder had similar appearance, smell, and taste…The randomisation code was not revealed to…field workers…until data collection was completed and the database had been finalised and sent to the Trial Oversight Committee." Comment: sufficient blinding seems likely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Intervention group was indicated by colour code, but neither…researchers, nor…knew who received what intervention…This code was not revealed to researchers…, who therefore did not know who received what intervention…All types of powder had similar appearance, smell, and taste…The randomisation code was

		not revealed to researchers…until data collection was completed and the database had been finalised and sent to the Trial Oversight Committee…It should be noted also that the clinical outcome assessors were blinded to what intervention had been assigned to individual children." Comment: sufficient blinding seems likely
Incomplete outcome data (attrition bias) All outcomes	Low risk	% Missing: 3 Reasons/details: in the zinc group: 5 participants emigrated from the study area, and 1 was "withdrawn by parents." In the placebo group: 4 participants emigrated from the study area. In the multi-nutrients with zinc group, 3 participants emigrated from the study area, 1 was "withdrawn by parents", and 1 died. In the multi-nutrients without zinc group, 3 participants emigrated from the study area and 2 died Comment: reasons for, and amount of, missing data were similar between study groups. Migration was the most common reason for missing data, and this reason is unlikely to bias results. Missing data seem too minimal to impact results
Selective reporting (reporting bias)	High risk	Comment: anthropometric indices, including height-for-age z-score, were pre-specified as a secondary outcome in the protocol for this study and were measured, but are not reported as outcomes. Hospitalisations due to malaria were measured, but were not pre-specified in the protocol for this study, and are not reported in a way that can be meta-analysed. Malaria prevalence and LRTI incidence were reported, but were not pre-specified in the protocol for this study Protocol identifier: NCT00623857 Online web appendix obtained from http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1001125
Other bias	Low risk	Comment: appears to be free of other bias

Veenemans 2011 (2)

Methods	
Participants	
Interventions	
Outcomes	All-cause mortality, all-cause hospitalisation, incidence of all-cause diarrhoea, incidence of LRTI, incidence of malaria, serum or plasma zinc concentration, prevalence of zinc deficiency, blood haemoglobin concentration, prevalence of anaemia, serum or plasma ferritin concentration, prevalence of iron deficiency
Notes	As Veenemans 2011 above

Walravens 1983

Methods	CRCT?: IRCT; Cross-over?: non-cross-over
Participants	Country: United States of America; Setting: Denver, Colorado; Urbanicity: urban Inclusion criteria: height-for-age below the 10th percentile on the National Center for Health Statistics grids; nutritional or biochemical evidence of zinc deficiency; products of term pregnancies; birth measurements appropriate for gestation age; 2 or more of the following: calculated dietary zinc intake < 2/3 of the Recommended Dietary Allowance, plasma zinc < 68 µg/dL or hair zinc < 105 µg/g Exclusion criteria: detectable medical reasons for poor growth *Baseline characteristics* Avg age (mo): 50; Min age (mo): 24; Max age (mo): 72; % Female: 35 Avg HAZ: -2.07; Stunting: both - separate data not given; Avg height (cm): N/A; Avg zinc concentration (μg/dL): 72 Total N: 57; Group 1 N: N/A; Group 2 N: N/A
Interventions	*Group 1:* zinc Formulation: solution; Compound: sulfate; Frequency: Twice daily; Duration (mo): 12; Dose (mg): 5; Co-intervention(s): N/A *Group 2*: no zinc Placebo given; Co-intervention(s): N/A
Outcomes	Height, weight, weight-to-height ratio, serum or plasma zinc concentration, serum or plasma copper concentration Time point (wk): 52
Notes	This was a "pair-matched" study, and at the end of the study, 20 participants remained in the zinc group and 20 participants in the placebo group. So, there might have been approximately equal numbers of participants randomised to the zinc group and the placebo group, but the exact number of participants randomised to each group was not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Random sequence generation (selection bias)	Unclear risk	Quote: "These subjects were pair-matched as closely as possible...The first member of a pair was assigned randomly to either the zinc supplement or a placebo." Comment: insufficient details available to make a judgement as to whether or not an allocation sequence was generated using a truly random method
Allocation concealment (selection bias)	Low risk	Quote: "These subjects were pair-matched as closely as possible...by one of the investigators who was not involved with the clinical management of the children, and had no knowledge of the progress of the participants during the course of treatment period. The first member of a pair was assigned randomly to either the zinc supplement or a placebo." Comment: indicates central randomisation (i.e. randomisation by someone not involved with enrolling patients) to conceal allocation
Blinding of participants (performance bias) All outcomes	Low risk	Quote: "…double blind…study…The two syrups were indistinguishable in appearance and were prepared at the pharmacy of the University of Colorado Medical Center, where the code was kept...Test or control assignment was unknown to the children and their families..." Comment: sufficient blinding seems likely
Blinding of personnel (performance bias) All outcomes	Low risk	Quote: "…double blind…study…The two syrups were indistinguishable in appearance and were prepared at the pharmacy of the University of Colorado Medical Center, where the code was kept...Test or control assignment was unknown to... the members of the investigating team who were responsible for clinical care, anthropometry, diet, or laboratory analysis." Comment: sufficient blinding seems likely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "…double blind…study…The two syrups were indistinguishable in appearance and were prepared at the pharmacy of the University of Colorado Medical Center, where the code was kept...Test or control assignment was unknown to...

Walravens 1983 (*Continued*)

		the members of the investigating team who were responsible for clinical care, anthropometry, diet, or laboratory analysis." Comment: sufficient blinding seems likely
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	% Missing: 30 Reasons/details: "Of the 17 (30%) who failed to complete the study, 11 moved from the area and six withdrew." Comment: a large proportion of the data is missing and the amount of missing data was not reported separately for each study group
Selective reporting (reporting bias)	Unclear risk	Comment: no trial protocol referenced by the study
Other bias	Low risk	Comment: appears to be free of other bias

Walravens 1989

Methods	CRCT?: IRCT; Cross-over?: non-cross-over
Participants	Country: United States of America; Setting: Denver, Colorado; Urbanicity: urban Inclusion criteria: for children whose initial growth was not in the 10 lower percentiles: documented decline of 20 or more percentiles in weight-for-age resulting in a weight below the 10th percentile. For children whose initial growth was in the 10 lower percentiles: a decline in weight percentiles; documented decline of 20 or more percentiles in weight for height Exclusion criteria: malabsorption, chronic infections, other known causes of growth failure, families with previous problems of neglect, disturbed family dynamics, language barriers precluding adequate communication *Baseline characteristics* Avg age (mo): 15.2; Min age (mo): 8; Max age (mo): 27; % Female: 48 Avg HAZ: -1.35; Stunting: unclear; Avg height (cm): 74.61; Avg zinc concentration (μg/dL): 70 Total N: N/A; Group 1 N: N/A; Group 2 N: N/A
Interventions	*Group 1:* zinc Formulation: solution; Compound: sulfate; Frequency: unclear; Duration (mo): 6; Dose (mg): 25; Co-intervention(s): N/A *Group 2*: no zinc Placebo given; Co-intervention(s): N/A
Outcomes	Height, weight, serum or plasma zinc concentration Time point (wk): 24

Notes	Number of participants randomised to each study group was not reported. Instead, the following was reported: "87 families were approached regarding the zinc supplementation study. The families of 30 infants either refused participation after the introductory screening or refused to continue in the study after starting it. The remaining 57 infants completed the supplementation project...The final matching included 13 male and 12 female pairs and seven unmatched infants." It is unclear how many of the 87 infants approached were randomised to each study group, because it is unclear how many of the 30 infants who refused did so before randomisation versus after randomisation

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Pair matching was done by an investigator (K.M.H.) not involved in the clinical management of the children...The first member of a pair was randomly assigned to receive either the zinc supplement or the placebo." Comment: insufficient details available to make a judgement as to whether or not an allocation sequence was generated using a truly random method
Allocation concealment (selection bias)	Unclear risk	Quote: N/A Comment: insufficient details available to make a judgement
Blinding of participants (performance bias) All outcomes	Low risk	Quote: "…double-blind, controlled study…The two syrups were indistinguishable in appearance...Test or control assignment was unknown to the families..." Comment: sufficient blinding seems likely
Blinding of personnel (performance bias) All outcomes	Low risk	Quote: "…double-blind, controlled study…The two syrups were indistinguishable in appearance...Test or control assignment was unknown to the. ..investigators involved in clinical care, anthropometry, or dietary analysis." Comment: sufficient blinding seems likely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "…double-blind, controlled study…The two syrups were indistinguishable in appearance...Test or control assignment was unknown to the. ..investigators involved in clinical care, an-

Walravens 1989 (*Continued*)

		thropometry, or dietary analysis." Comment: sufficient blinding seems likely
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	% Missing: N/A Reasons/details: "The families of 30 infants either refused participation after the introductory screening or refused to continue in the study after starting it." Comment: the following were not reported: number of participants randomised, number of participants randomised to each group, amount of missing data for each group
Selective reporting (reporting bias)	Unclear risk	Comment: no trial protocol referenced by the study
Other bias	Low risk	Comment: appears to be free of other bias

Wessells 2012b

Methods	CRCT?: IRCT; Cross-over?: non-cross-over
Participants	Country: Burkina Faso; Setting: the catchment area of the governmental health clinic located in Toussiana; Urbanicity: rural Inclusion criteria: currently breastfeeding; haemoglobin level $\geq$ 60 g/L; no fever or diarrhoea (> 3 liquid or semi-liquid stools in a 24-hour period) reported in the past week Exclusion criteria: currently consuming vitamin or mineral supplements or zinc-fortified infant formulas; demonstrated bipedal oedema or other serious medical conditions; had a twin enrolled in the study *Baseline characteristics* Avg age (mo): 13.7; Min age (mo): 6; Max age (mo): 23; % Female: 49 Avg HAZ: -1.5; Stunting: unclear; Avg height (cm): 72.5; Avg zinc concentration (μg/dL): 62.9 Total N: 451; Group 1 N: 300; Group 2 N: 151
Interventions	*Group 1:* zinc Formulation: solution or dispersible tablets; Compound: sulfate; Frequency: daily; Duration (mo): 0.75; Dose (mg): 5; Co-intervention(s): N/A *Group 2*: no zinc Placebo given; Co-intervention(s): N/A
Outcomes	Serum or plasma zinc concentration, prevalence of zinc deficiency, serum or plasma copper concentration Time point (wk): 3

Notes	150 participants were randomised to receive dispersible zinc tablets, 150 participants were randomised to receive liquid zinc supplements, and 151 participants were randomised to receive liquid placebo supplements

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Eligible study participants were randomly assigned to 1 of 3 treatment groups by using an independently generated block randomization scheme, with a varied block length of 3 or 6...Tables of random permutation…" Comment: N/A
Allocation concealment (selection bias)	Low risk	Quote: "Eligible study participants were randomly assigned to 1 of 3 treatment groups by using an independently generated block randomization scheme…" Comment: indicates central randomisation (i.e. randomisation by someone not involved with enrolling patients) to conceal allocation
Blinding of participants (performance bias) All outcomes	Unclear risk	Quote: "...partially-masked, placebo-controlled trial…Zn and placebo syrups were indistinguishable in appearance, flavor, and packaging...Treatment groups remained masked until all statistical analyses were completed." Comment: though the zinc and placebo syrups were indistinguishable, there was no placebo for the zinc tablets that some participants received. Thus, people involved in the study would not have been blind to the group assignment of the zinc tablet group
Blinding of personnel (performance bias) All outcomes	Unclear risk	Quote: "...partially-masked, placebo-controlled trial…Zn and placebo syrups were indistinguishable in appearance, flavor, and packaging...Treatment groups remained masked until all statistical analyses were completed." Comment: though the zinc and placebo syrups were indistinguishable, there was no placebo for the zinc tablets that some participants received. Thus, people involved in

		the study would not have been blind to the group assignment of the zinc tablet group
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "...partially-masked, placebo-controlled trial…Zn and placebo syrups were indistinguishable in appearance, flavor, and packaging...Treatment groups remained masked until all statistical analyses were completed." Comment: though the zinc and placebo syrups were indistinguishable, there was no placebo for the zinc tablets that some participants received. Thus, people involved in the study would not have been blind to the group assignment of the zinc tablet group
Incomplete outcome data (attrition bias) All outcomes	Low risk	% Missing: 4 Reasons/details: in the zinc group (comprised of participants who received liquid zinc supplements and participants who received zinc tablets): 11 withdrew consent, 3 moved from the study area, and 2 withdrew due to illness. In the placebo group: 3 withdrew consent and 1 withdrew due to illness. In addition, there were 5 blood draw failures in the zinc group Comment: reasons for missing data were similar between study groups. Missing data seem too minimal to impact results
Selective reporting (reporting bias)	Unclear risk	Comment: prevalence of LRTI was measured, but is not reported. Prevalence of diarrhoea was measured, but is not reported in a way that can be meta-analysed. Neither LRTI nor diarrhoea prevalence was pre-specified in the protocol for this study. However, based on email contact with an author of this study, it seems likely that there was probably not sufficient time to allow for detectable differences in morbidity and that morbidity outcomes were included in the measurements simply to control for any baseline differences or possible confounding Protocol identifier: NCT00944853
Other bias	Low risk	Comment: appears to be free of other bias

Wuehler 2008

Methods	CRCT?: IRCT; Cross-over?: non-cross-over
Participants	Country: Ecuador; Setting: El Carmen, a small town in the coastal plains, and the communities surrounding it; Latacunga, a medium-sized town in the Andean highlands, and several surrounding rural communities; and 2 shantytowns in the hills adjacent to the capital city of Quito, also in the Andean highlands; Urbanicity: multiple Inclusion criteria: LAZ < -1.3 for children 12 to 20 mo old and < -1.5 for children 21 to 29 mo old, assessed by comparison with the WHO/NCHS international reference data; haemoglobin ≥ 10.5 g/dL, adjusted for altitude; absence of chronic disease or congenital defects that restrict normal growth Exclusion criteria: N/A *Baseline characteristics* Avg age (mo): 20.9; Min age (mo): 12; Max age (mo): 30; % Female: 46.9 Avg HAZ: -2.3; Stunting: both - separate data not given; Avg height (cm): 77.3; Avg zinc concentration (μg/dL): 71.9 Total N: 503; Group 1 N: 376; Group 2 N: 127
Interventions	*Group 1:* zinc Formulation: solution; Compound: sulfate; Frequency: daily; Duration (mo): 6; Dose (mg): 6.7 on average (among participants who received 3, 7, or 10 mg/day of zinc); Co-intervention(s): N/A *Group 2*: no zinc Placebo given; Co-intervention(s): N/A
Outcomes	Incidence of all-cause diarrhoea, height, weight, weight-to-height ratio, serum or plasma zinc concentration, blood haemoglobin concentration, serum or plasma ferritin concentration, serum or plasma copper concentration Time point (wk): 24
Notes	127, 124, 126, 126, and 128 participants were randomised to receive placebo, 3 mg zinc/day, 7 mg zinc/day, 10 mg zinc/day, and 10 mg zinc/day + 0.5 mg copper/day, respectively. Baseline characteristics reported in this table are weighted averages of all groups except the zinc + copper group, since the zinc + copper group is not included in any meta-analyses in this review

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "The randomization lists…were generated…by using a fixed block randomization procedure." "Participants were assigned a study number...The numbers were previously assigned to one of the five study groups by computer randomization by the study's statistician." Comment: N/A

Allocation concealment (selection bias)	Low risk	Quote: "The randomization lists…were generated independently…" Comment: indicates central randomisation (i.e. randomisation by someone not involved with enrolling patients) to conceal allocation
Blinding of participants (performance bias) All outcomes	Low risk	Quote: "...double-masked intervention trial...blinding of...participants to treatment group…" "There was no color or other method of distinguishing between supplements…The flavor of the zinc and copper were masked by the preservative that was added to all syrups." Comment: sufficient blinding seems likely
Blinding of personnel (performance bias) All outcomes	Low risk	Quote: "...double-masked intervention trial...blinding of investigators...to treatment group…" "There was no color or other method of distinguishing between supplements…The flavor of the zinc and copper were masked by the preservative that was added to all syrups." Comment: sufficient blinding seems likely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "...double-masked intervention trial...blinding of investigators...to treatment group…" "There was no color or other method of distinguishing between supplements…The flavor of the zinc and copper were masked by the preservative that was added to all syrups." Comment: sufficient blinding seems likely
Incomplete outcome data (attrition bias) All outcomes	Low risk	% Missing: 10.7 Reasons/details: participants "moved out of the study area", "refused to continue supplement consumption", "refused blood draws", or "withdrew consent without a specified reason". "Moved out of the study area" was the most common reason for missing data Comment: 10.7% of the randomised participants eligible for our review had data missing; this 10.7% missing figure includes all groups except the zinc + copper group, since the zinc + copper group is not included in any meta-analyses in this re-

		view. "There were no significant differences in rates of attrition by treatment group... nor any significant differences between the baseline characteristics of the children who left the study prematurely and those of children who completed the full 6-mo intervention." Migration was the most common reason for missing data and this reason is unlikely to bias results
Selective reporting (reporting bias)	High risk	Comment: diarrhoea prevalence and LRTI prevalence were measured, but are not reported in a way that can be meta-analysed
Other bias	Low risk	Comment: appears to be free of other bias

What follows is an explanation of what is meant by the various abbreviations in the Characteristics of included studies, Characteristics of studies awaiting classification, and Characteristics of ongoing studies tables.

- Unclear: it is not clear how this study should be classified for this characteristic; N/A: data not available (i.e. not reported) or not applicable.
- CRCT?: is this study cluster-randomised (i.e. a CRCT) or individually randomised (i.e. an IRCT)?
- Cross-over?: is this study a non-cross-over trial or a cross-over trial?
- Urbanicity: was the study conducted in a rural, urban, or peri-urban area? "Multiple" means that the study was conducted in more than one such area (e.g. in both urban and rural areas).
- Avg: average; (mo): months; Min: minimum; Max: maximum; HAZ: height-for-age z-score.
- Stunting: 'Stunted' means that all study participants were stunted. 'Non-stunted' means that none of the study participants were stunted. 'Both' means that some of the study participants were stunted, and some were non-stunted. 'Separate data given' means that the trial reported at least some data separately for stunted participants or non-stunted participants.
- N: sample size; Clusters: number of clusters in a CRCT study or study group.
- Dose: the actual dose of zinc given at each administration of the supplement, not a daily dose equivalent.
- Co-intervention(s): co-interventions administered along with zinc or placebo. The frequency and duration of co-intervention administration is the same as that of zinc or placebo unless stated otherwise.
- Placebo (not) given: whether or not a placebo substitute for zinc was administered.
- Time point (wk): how long (in weeks) after randomisation were reported outcomes observed?
- % Missing: approximate % of study participants with missing data for non-mortality outcomes.

Other abbreviations

d: day; GH: growth hormone; IFA: iron + folic acid; IU: international units; LAZ: length-for-age z score; LRTI: lower respiratory tract infection; LTFU: lost to follow-up; MM: micronutrient mix; MV: multivitamin; NCHS: National Center for Health Statistics; SD: standard deviation; wk: week; WLZ: weight-for-length z score

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ahmed 2009b	Non-RCT.
Bates 1993	Non-RCT.
Behrens 1990	Therapeutic supplementation.
Berger 2006	Wrong age range.
Bobat 2005	Condition of HIV.
Brooks 2005	Wrong age range.
Campos 2004	Non-RCT.
Cuevas 2002	No eligible comparison.
Duggan 2003	Fortification/sprinkles.
Fahmida 2007	Wrong age range.
Hashemipour 2009	Condition of obesity.
Heinig 2006	Wrong age range.
Hess 2011	Acceptability study randomising order of administration.
Imamoglu 2005	Non-RCT.
Kordas 2005	Therapeutic supplementation.
Osendarp 2002	Wrong age range.
Payne-Robinson 1991	Severe protein-energy malnutrition.
Perrone 1999	No eligible comparison.
Ronaghy 1969	Wrong age range.
Ronaghy 1974	Wrong age range.
Roxas 1980	Non-RCT.
Shingwekar 1979	Non-RCT.

(*Continued*)

Shrivastava 1993	Non-RCT.
Walravens 1992	Wrong age range.
Wasantwisut 2006	Wrong age range.
Yanfeng 1997	No eligible comparison.
Zeba 2008	No eligible comparison.
Zimmermann 2013	Intervention not eligible (LifeStraw with or without zinc).

RCT: randomised controlled trial

Characteristics of studies awaiting assessment *[ordered by study ID]*

Arabaci 2010

Methods	CRCT?: N/A; Cross-over?: N/A
Participants	Country: N/A; Setting: N/A; Urbanicity: N/A Inclusion criteria: haemoglobin < 11 g/dL and ferritin < 12 ng/mL Exclusion criteria: N/A *Baseline characteristics* Avg age (mo): N/A; Min age (mo): 6; Max age (mo): 72; % Female: N/A Avg HAZ: N/A; Stunting: N/A; Avg height (cm): N/A; Avg zinc concentration (μg/dL): N/A Total N: 53; Group 1 N: 27; Group 2 N: 26
Interventions	*Group 1:* zinc Formulation: N/A; Compound: N/A; Frequency: N/A; Duration (mo): 3; Dose (mg): N/A; Co-intervention(s): N/A *Group 2*: no zinc Unclear whether or not placebo given; Co-intervention(s): N/A
Outcomes	Time point (wk): N/A
Notes	A full-text trial report exists for this study, but could not be obtained

Chicourel 2001

Methods	CRCT?: N/A; Cross-over?: N/A
Participants	Country: Brazil; Setting: municipality of Juiz de Fora; Urbanicity: unclear Inclusion criteria: N/A Exclusion criteria: N/A *Baseline characteristics* Avg age (mo): N/A; Min age (mo): 49; Max age (mo): 82; % Female: N/A Avg HAZ: N/A; Stunting: unclear; Avg height (cm): N/A; Avg zinc concentration (μg/dL): N/A Total N: 59; Group 1 N: 30; Group 2 N: 29
Interventions	*Group 1:* zinc Formulation: N/A; Compound: N/A; Frequency: N/A; Duration (mo): unclear; Dose (mg): 10; Co-intervention(s) : N/A *Group 2*: no zinc Placebo given; Co-intervention(s): N/A
Outcomes	Time point (wk): N/A
Notes	In addition to the study groups mentioned in this table, there was a group of 31 participants who received iron supplementation (30 mg) A full-text trial report exists for this study, but could not be obtained

Jimenez 2000

Methods	CRCT?: N/A; Cross-over?: N/A
Participants	Country: N/A; Setting: N/A; Urbanicity: N/A Inclusion criteria: recently recovered from persistent diarrhoea Exclusion criteria: N/A *Baseline characteristics* Avg age (mo): N/A; Min age (mo): N/A; Max age (mo): N/A; % Female: N/A Avg HAZ: N/A; Stunting: N/A; Avg height (cm): N/A; Avg zinc concentration (μg/dL): N/A Total N: N/A; Group 1 N: N/A; Group 2 N: N/A
Interventions	*Group 1:* zinc Formulation: N/A; Compound: sulfate; Frequency: N/A; Duration (mo): N/A; Dose (mg): 10 mg/day; Co-intervention(s): N/A *Group 2*: no zinc Placebo given; Co-intervention(s): N/A
Outcomes	Height, weight, blood haemoglobin concentration Time point (wk): N/A
Notes	Not enough information was available in the trial report to determine study eligibility (e.g. that participants met the age criteria for this review)

Mitter 2009

Methods	CRCT?: IRCT; Cross-over?: non-cross-over
Participants	Country: Brazil; Setting: a favela in northeast Brazil; Urbanicity: urban Inclusion criteria: below median height-for-age z-score Exclusion criteria: N/A *Baseline characteristics* Avg age (mo): N/A; Min age (mo): N/A; Max age (mo): N/A; % Female: N/A Avg HAZ: N/A; Stunting: unclear; Avg height (cm): N/A; Avg zinc concentration (μg/dL): N/A Total N: 213; Group 1 N: N/A; Group 2 N: N/A; Group 3 N: N/A; Group 4 N: N/A; Group 5 N: N/A; Group 6 N: N/A; Group 7 N: N/A; Group 8 N: N/A
Interventions	*Group 1:* zinc Formulation: unclear; Compound: unclear; Frequency: 2 days/wk; Duration (mo): 12; Dose (mg): 40; Co-intervention(s): N/A *Group 2*: no zinc Unclear whether or not placebo given; Co-intervention(s): N/A *Group 3:* zinc Formulation: unclear; Compound: unclear; Frequency: 2 days/wk; Duration (mo): 12; Dose (mg): 40; Co-intervention(s): 200,000 IU retinol every 4 months *Group 4*: no zinc Unclear whether or not placebo given; Co-intervention(s): 200,000 IU retinol every 4 months *Group 5:* zinc Formulation: unclear; Compound: unclear; Frequency: 2 days/wk; Duration (mo): 12; Dose (mg): 40; Co-intervention(s): 16 g of glutamine for 10 days *Group 6*: no zinc Unclear whether or not placebo given; Co-intervention(s): 16 g of glutamine for 10 days *Group 7:* zinc Formulation: unclear; Compound: unclear; Frequency: 2 days/wk; Duration (mo): 12; Dose (mg): 40; Co-intervention(s): 200,000 IU retinol every 4 months; 16 g of glutamine for 10 days *Group 8*: no zinc Unclear whether or not placebo given; Co-intervention(s): 200,000 IU retinol every 4 months; 16 g of glutamine for 10 days
Outcomes	Time point (wk): N/A
Notes	Not enough information was available in the trial report to determine study eligibility (e.g. that participants met the age criteria for this review)

Smith 1985

Methods	CRCT?: IRCT; Cross-over?: non-cross-over
Participants	Country: Australia; Setting: 5 communities in the Kimberley region of Western Australia; Urbanicity: unclear Inclusion criteria: N/A Exclusion criteria: N/A *Baseline characteristics* Avg age (mo): N/A; Min age (mo): 60; Max age (mo): 180; % Female: N/A Avg HAZ: N/A; Stunting: unclear; Avg height (cm): N/A; Avg zinc concentration (μg/dL): N/A Total N: N/A; Group 1 N: N/A; Group 2 N: N/A

Interventions	*Group 1:* zinc Formulation: unclear; Compound: acetate; Frequency: 5 days/wk; Duration (mo): N/A; Dose (mg): 20 mg to children aged 5 to 8 years, 40 mg to children aged 9 to 15 years; Co-intervention(s): N/A *Group 2*: no zinc Placebo given; Co-intervention(s): N/A
Outcomes	Serum or plasma zinc concentration Time point (wk): N/A
Notes	It was reported that, "Pairs of children…were randomised to receive oral zinc or placebo", and that "102 pairs…completed the trial." However, number of children randomised was not reported Not enough information was available in the trial report to determine study eligibility (e.g. that participants met the age criteria for this review)

Avg: average; CRCT: cluster-randomised controlled trial; HAZ: height-for-age z-score; IRCT: individually randomised controlled trial; IU: international units; mo: month; wk: week

Characteristics of ongoing studies *[ordered by study ID]*

CTRI/2010/091/001417

Trial name or title	'A clinical trial to study the effect of zinc sulfate in reducing the incidence of diarrhea, acute respiratory tract infections and in promoting growth in infants of 6-11 months of age'
Methods	CRCT?: N/A; Cross-over?: N/A
Participants	Country: India; Setting: N/A; Urbanicity: unclear Inclusion criteria: apparently healthy Exclusion criteria: receiving zinc supplement currently or in past 3 months; child who is severely malnourished, immunodeficient or on steroid therapy, severely ill requiring hospitalisation; children of families who are not likely to stay in the study area until completion of the study *Baseline characteristics* Avg age (mo): N/A; Min age (mo): 6; Max age (mo): 11; % Female: N/A Avg HAZ: N/A; Stunting: N/A; Avg height (cm): N/A; Avg zinc concentration (μg/dL): N/A Total N: 220 (target sample size); Group 1 N: N/A; Group 2 N: N/A
Interventions	*Group 1:* zinc Formulation: solution; Compound: sulfate; Frequency: daily; Duration (mo): 0.5; Dose (mg): 20; Co-intervention(s): N/A *Group 2*: no zinc Placebo given; Co-intervention(s): N/A
Outcomes	Primary outcomes: incidence of diarrhoea, acute respiratory tract infections, height, weight Secondary outcomes: "Nil" Time point (wk): 20

CTRI/2010/091/001417 (*Continued*)

Starting date	
Contact information	Akash Malik (drakashmalik28@gmail.com). EMW emailed 30 January 2013
Notes	COMPLETED

NCT00133406

Trial name or title	'Long-term Impact and Intervention for Diarrhea in Brazil'
Methods	CRCT?: N/A; Cross-over?: N/A
Participants	Country: Brazil; Setting: a favela; Urbanicity: urban Inclusion criteria: height-for-age Z-score (HAZ) less than the median for the Parque Universitario community; resident in Brazilian favela Exclusion criteria: exclusively breastfed; participated in the "hospital study" or any other study with in the past 2 years; fever at time of screening; systemic disease at the time of screening including but not limited to: shock, meningitis, sepsis, pneumonia, tuberculosis, varicella; on antibiotics during screening; siblings from the same household enrolled in this study *Baseline characteristics* Avg age (mo): N/A; Min age (mo): 2; Max age (mo): 8; % Female: N/A Avg HAZ: N/A; Stunting: N/A; Avg height (cm): N/A; Avg zinc concentration (μg/dL): N/A Total N: 280 or 321 (target sample size); Group 1 N: N/A; Group 2 N: N/A; Group 3 N: N/A; Group 4 N: N/A
Interventions	*Group 1:* zinc Formulation: N/A; Compound: N/A; Frequency: 2 days/wk; Duration (mo): 12; Dose (mg): 40; Co-intervention(s): N/A *Group 2*: no zinc Placebo given; Co-intervention(s): N/A *Group 3:* zinc Formulation: N/A; Compound: N/A; Frequency: 2 days/wk; Duration (mo): 12; Dose (mg): 40; Co-intervention(s): 100,000 IU vitamin A for children under 12 months of age, 200,000 IU for children at least 12 months of age, "both q months for 1 year at 0, 4 and 8 months" *Group 4*: no zinc Placebo given; Co-intervention(s): 100,000 IU vitamin A for children under 12 months of age, 200,000 IU for children at least 12 months of age, "both q months for 1 year at 0, 4 and 8 months"
Outcomes	Number of episodes of diarrhoea, number of days of diarrhoea, height-for-age Z Score (HAZ), blood zinc level Time point (wk): 144
Starting date	June 2006 (date of first enrolment)
Contact information	Richard Guerrant (rlg9a@virginia.edu). EMW emailed 20 January 2013

NCT00133406 (*Continued*)

Notes	There is also a sub-study to determine if 10 days of glutamine delivered as an oral bolus improves the health of the digestive system

NCT00228254

Trial name or title	'Vitamin A and zinc: Prevention of Pneumonia (VAZPOP) Study'
Methods	CRCT?: N/A; Cross-over?: N/A
Participants	Country: Ecuador; Setting: Quito; Urbanicity: urban Inclusion criteria: residence of 1 year or longer in the neighbourhood Exclusion criteria: recent vitamin or micronutrient use; clinical evidence of zinc or vitamin A deficiency; severe malnutrition such as weight < or = to 60% of expected weight *Baseline characteristics* Avg age (mo): N/A; Min age (mo): 6; Max age (mo): 36; % Female: N/A Avg HAZ: N/A; Stunting: N/A; Avg height (cm): N/A; Avg zinc concentration (μg/dL): N/A Total N: 2,582; Group 1 N: N/A; Group 2 N: N/A; Group 3 N: N/A; Group 4 N: N/A
Interventions	*Group 1:* zinc Formulation: N/A; Compound: N/A; Frequency: N/A; Duration (mo): N/A; Dose (mg): 12.5; Co-intervention(s): 10,000 IU per week *Group 2*: no zinc Placebo given; Co-intervention(s): 10,000 IU per week
Outcomes	Primary outcomes: incidence of acute lower respiratory infection (pneumonia), growth Secondary outcomes: incidence of diarrhoeal disease, incidence of other respiratory infections Time point (wk): N/A
Starting date	January 2000
Contact information	Jeffrey K Griffiths (jeffrey.griffiths@tufts.edu). EMW emailed 20 January 2013
Notes	

NCT00374023

Trial name or title	'A Study on Immunological Effect of Vitamin A and Zinc in a Placebo Controlled 4 Cell Trial'
Methods	
Participants	
Interventions	
Outcomes	
Starting date	

NCT00374023 (*Continued*)

Contact information	Swapan K Roy
Notes	Estimated completion 1995

NCT00421668

Trial name or title	
Methods	
Participants	
Interventions	
Outcomes	
Starting date	
Contact information	Christopher Duggan (christopher.duggan@childrens.harvard.edu). EMW emailed 21 January 2013
Notes	COMPLETED

NCT00589264

Trial name or title	'Zinc and Biobehavioral Development in Early Childhood'
Methods	CRCT?: N/A; Cross-over?: N/A
Participants	Country: Peru; Setting: Lima; Urbanicity: N/A Inclusion criteria: born at term of non-low birth weight; free of major malformations, genetic abnormalities, or health problems associated with developmental delays; planning to remain in study area for 1 year; in good general health Exclusion criteria: low birth weight; non-term delivery; vision or hearing problems; anaemia *Baseline characteristics* Avg age (mo): 6; Min age (mo): 6; Max age (mo): 6; % Female: N/A Avg HAZ: N/A; Stunting: N/A; Avg height (cm): N/A; Avg zinc concentration (μg/dL): N/A Total N: N/A; Group 1 N: N/A; Group 2 N: N/A
Interventions	*Group 1:* zinc Formulation: N/A; Compound: N/A; Frequency: daily; Duration (mo): 6; Dose (mg): 10; Co-intervention (s): 10 mg iron and 1/2 mg copper *Group 2*: no zinc Placebo given; Co-intervention(s): 10 mg iron and 1/2 mg copper
Outcomes	Growth Time point (wk): N/A

NCT00589264 (*Continued*)

Starting date	July 2004
Contact information	Laura E Caulfield (lcaulfie@jhsph.edu). EMW emailed 21 January 2013
Notes	COMPLETED

NCT00944359

Trial name or title	'Impact of Preventive and Therapeutic Zinc Supplementation Programs Among Young Children'
Methods	CRCT?: CRCT; Cross-over?: N/A
Participants	Country: Burkina Faso; Setting: N/A; Urbanicity: N/A Inclusion criteria: plan to remain in study area for 1 year Exclusion criteria: evidence of congenital abnormalities and chronic infection; severe anaemia and severe acute malnutrition; consumption of micronutrient supplementation including zinc *Baseline characteristics* Avg age (mo): N/A; Min age (mo): 6; Max age (mo): 27; % Female: N/A Avg HAZ: N/A; Stunting: N/A; Avg height (cm): N/A; Avg zinc concentration (μg/dL): N/A Total N: N/A; Group 1 N: N/A; Group 2 N: N/A
Interventions	*Group 1:* zinc Formulation: N/A; Compound: N/A; Frequency: daily; Duration (mo): 12; Dose (mg): 7; Co-intervention (s): N/A *Group 2*: no zinc Placebo given; Co-intervention(s): N/A
Outcomes	Primary outcomes: change in length and length-for-age Z-score, change in weight and weight-for-age, incidence of diarrhoea and laboratory-confirmed malaria, change in plasma zinc concentration Secondary outcomes: incidence of stunting, change in haemoglobin and iron status Time point (wk): 52
Starting date	December 2010
Contact information	Kenneth H Brown (khbrown@ucdavis.edu). EMW emailed 23 January 2013
Notes	

NCT00967551

Trial name or title	Micronutrient Sprinkles in a Daycare Center
Methods	
Participants	
Interventions	

NCT00967551 (*Continued*)

Outcomes	
Starting date	
Contact information	Conrad Cole (Conrad.Cole@cchmc.org). EMW emailed 30 January 2013
Notes	COMPLETED

NCT00980421

Trial name or title	'Safety of Various Mode of Delivery of Iron Supplement on Iron Toxicity Markers in Preschool Children'
Methods	CRCT?: N/A; Cross-over?: N/A
Participants	Country: India; Setting: Sangam Vihar, Delhi; Urbanicity: N/A Inclusion criteria: willing to stay in the study area for 6 months Exclusion criteria: severely malnourished or ill requiring hospitalisation *Baseline characteristics* Avg age (mo): N/A; Min age (mo): 24; Max age (mo): 36; % Female: N/A Avg HAZ: N/A; Stunting: N/A; Avg height (cm): N/A; Avg zinc concentration (μg/dL): N/A Total N: 120; Group 1 N: 120; Group 2 N: 120
Interventions	*Group 1:* zinc Formulation: pill/tablet; Compound: sulfate; Frequency: daily; Duration (mo): 6; Dose (mg): 10; Co-intervention(s): 12.5 mg/day of iron *Group 2*: no zinc Placebo given; Co-intervention(s): 12.5 mg/day of iron
Outcomes	Mortality, incidence of disease requiring hospitalisation, iron status Time point (wk): 24
Starting date	October 2009
Contact information	Venugopal P Menon (biocmr@sify.com) and Jitender Kumar (cmrdelhi@airtelmail.in). EMW emailed 21 January 2013
Notes	In addition to the study groups mentioned in this table, there is a group of 60 participants that receives biscuits fortified with iron (IB), and a group of 60 participants that receives placebo tablets

NCT01306097

Trial name or title	'Zinc Supplementation and Severe and Recurrent Diarrhea'
Methods	
Participants	

NCT01306097 (*Continued*)

Interventions	
Outcomes	
Starting date	
Contact information	Bandar Abbas, Hormozgan, Iran
Notes	COMPLETED

NCT01616693

Trial name or title	'Zinc and/or Probiotic Supplementation of Rotavirus and Oral Polio Virus Vaccines'
Methods	
Participants	
Interventions	
Outcomes	
Starting date	
Contact information	Gagandeep Kang (gkang@cmcvellore.ac.in) and Jacob John (jacob@cmcsph.org)
Notes	Currently recruiting

Avg: average; CRCT: cluster-randomised controlled trial; HAZ: height-for-age z-score; IU: international units; mo: month; wk: week

DATA AND ANALYSES

Comparison 1. Zinc versus no zinc

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	14	138302	Risk Ratio (Fixed, 95% CI)	0.95 [0.86, 1.05]
2 Mortality due to all-cause diarrhoea	4	132321	Risk Ratio (Fixed, 95% CI)	0.95 [0.69, 1.31]
3 Mortality due to LRTI	3	132063	Risk Ratio (Fixed, 95% CI)	0.86 [0.64, 1.15]
4 Mortality due to malaria	2	42818	Risk Ratio (Fixed, 95% CI)	0.90 [0.77, 1.06]
5 All-cause hospitalisation	9	92872	Risk Ratio (Fixed, 95% CI)	1.04 [0.97, 1.11]
6 Incidence of all-cause diarrhoea	35	15042	Risk Ratio (Fixed, 95% CI)	0.87 [0.85, 0.89]
7 Prevalence of all-cause diarrhoea	15	8519	Risk Ratio (Fixed, 95% CI)	0.88 [0.86, 0.90]
8 Hospitalisation due to all-cause diarrhoea	5	74039	Risk Ratio (Fixed, 95% CI)	1.03 [0.87, 1.22]
9 Incidence of severe diarrhoea	7	4982	Risk Ratio (Fixed, 95% CI)	0.89 [0.84, 0.95]
10 Incidence of persistent diarrhoea	9	6216	Risk Ratio (Fixed, 95% CI)	0.73 [0.62, 0.85]
11 Prevalence of persistent diarrhoea	2	665	Risk Ratio (Fixed, 95% CI)	0.70 [0.64, 0.76]
12 Incidence of LRTI	18	9610	Risk Ratio (Fixed, 95% CI)	1.00 [0.94, 1.07]
13 Prevalence of LRTI	4	1955	Risk Ratio (Fixed, 95% CI)	1.20 [1.10, 1.30]
14 Hospitalisation due to LRTI	4	74743	Risk Ratio (Fixed, 95% CI)	1.10 [0.93, 1.30]
15 Incidence of malaria	6	2407	Risk Ratio (Fixed, 95% CI)	1.05 [0.95, 1.15]
16 Prevalence of malaria	1	661	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.47, 1.64]
17 Height	59	13669	Std. Mean Difference (Fixed, 95% CI)	-0.09 [-0.13, -0.06]
18 Weight	52	12305	Std. Mean Difference (Fixed, 95% CI)	-0.10 [-0.14, -0.07]
19 Weight-to-height ratio	29	7901	Std. Mean Difference (IV, Fixed, 95% CI)	-0.05 [-0.10, -0.01]
20 Prevalence of stunting	9	3838	Risk Ratio (Fixed, 95% CI)	0.94 [0.86, 1.02]
21 Serum or plasma zinc concentration	56	9810	Std. Mean Difference (Fixed, 95% CI)	-0.62 [-0.67, -0.58]
22 Prevalence of zinc deficiency	21	5434	Risk Ratio (Fixed, 95% CI)	0.49 [0.45, 0.53]
23 Study withdrawal	6	4263	Risk Ratio (M-H, Fixed, 95% CI)	1.75 [0.93, 3.32]
24 Participants with ≥ 1 side effect	3	850	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [1.00, 1.27]
25 Vomiting episodes	6	4095	Risk Ratio (Fixed, 95% CI)	1.68 [1.61, 1.75]
26 Participants with ≥ 1 vomiting episode	5	35192	Risk Ratio (Fixed, 95% CI)	1.29 [1.14, 1.46]
27 Blood haemoglobin concentration	36	6024	Std. Mean Difference (Fixed, 95% CI)	0.05 [-0.00, 0.10]
28 Prevalence of anaemia	19	4287	Risk Ratio (Fixed, 95% CI)	1.00 [0.95, 1.06]
29 Serum or plasma ferritin concentration	25	4474	Std. Mean Difference (Fixed, 95% CI)	-0.07 [-0.13, -0.00]
30 Prevalence of iron deficiency	15	3149	Risk Ratio (Fixed, 95% CI)	0.99 [0.89, 1.10]
31 Serum or plasma copper concentration	13	3071	Std. Mean Difference (Fixed, 95% CI)	0.22 [0.14, 0.29]
32 Prevalence of copper deficiency	3	1337	Risk Ratio (Fixed, 95% CI)	2.64 [1.28, 5.42]

Comparison 2. Zinc versus zinc plus iron

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	1	323	Risk Ratio (Fixed, 95% CI)	0.33 [0.01, 8.39]
2 All-cause hospitalisation	1	399	Risk Ratio (Fixed, 95% CI)	0.92 [0.45, 1.89]
3 Incidence of all-cause diarrhoea	5	1530	Risk Ratio (Fixed, 95% CI)	1.10 [1.03, 1.18]
4 Prevalence of all-cause diarrhoea	1	399	Risk Ratio (Fixed, 95% CI)	0.90 [0.76, 1.06]
5 Incidence of severe diarrhoea	1	323	Risk Ratio (Fixed, 95% CI)	0.78 [0.59, 1.04]
6 Hospitalisation due to all-cause diarrhoea	1	399	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.25, 3.88]
7 Incidence of LRTI	3	1065	Risk Ratio (Fixed, 95% CI)	0.93 [0.83, 1.04]
8 Incidence of malaria	1	419	Risk Ratio (Fixed, 95% CI)	0.86 [0.59, 1.24]
9 Height	5	1517	Std. Mean Difference (IV, Fixed, 95% CI)	0.06 [-0.04, 0.16]
10 Weight	4	910	Std. Mean Difference (IV, Fixed, 95% CI)	0.12 [-0.01, 0.25]
11 Weight-to-height ratio	4	933	Std. Mean Difference (IV, Fixed, 95% CI)	0.06 [-0.07, 0.19]
12 Prevalence of stunting	2	462	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.85, 0.99]
13 Serum or plasma zinc concentration	8	1337	Std. Mean Difference (IV, Fixed, 95% CI)	0.16 [0.05, 0.27]
14 Prevalence of zinc deficiency	3	350	Risk Ratio (M-H, Fixed, 95% CI)	1.42 [0.75, 2.68]
15 Study withdrawal	2	557	Risk Ratio (M-H, Fixed, 95% CI)	1.41 [0.91, 2.18]
16 Blood haemoglobin concentration	8	1341	Std. Mean Difference (IV, Fixed, 95% CI)	-0.23 [-0.34, -0.12]
17 Serum or plasma ferritin concentration	6	945	Std. Mean Difference (IV, Fixed, 95% CI)	-1.78 [-1.99, -1.56]
18 Prevalence of iron deficiency	2	248	Risk Ratio (M-H, Fixed, 95% CI)	0.12 [0.04, 0.32]
19 Prevalence of anaemia	3	482	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.67, 0.92]
20 Serum or plasma copper concentration	2	353	Std. Mean Difference (IV, Fixed, 95% CI)	0.06 [-0.15, 0.27]

Comparison 3. Zinc versus no zinc: subgroup analyses

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality: age subgroup analysis	15	155782	Risk Ratio (Fixed, 95% CI)	0.93 [0.85, 1.02]
1.1 6 months to < 1 year	6	29879	Risk Ratio (Fixed, 95% CI)	1.06 [0.88, 1.27]
1.2 1 to < 5 years	10	125903	Risk Ratio (Fixed, 95% CI)	0.89 [0.80, 0.99]
2 All-cause mortality: dose subgroup analysis	17	156372	Risk Ratio (Fixed, 95% CI)	0.93 [0.84, 1.02]
2.1 0 to < 5 mg	2	717	Risk Ratio (Fixed, 95% CI)	0.72 [0.08, 6.47]
2.2 5 to < 10 mg	1	274	Risk Ratio (Fixed, 95% CI)	3.04 [0.32, 28.90]
2.3 10 to < 15 mg	11	152062	Risk Ratio (Fixed, 95% CI)	0.93 [0.84, 1.02]
2.4 20 mg or more	3	3319	Risk Ratio (Fixed, 95% CI)	0.14 [0.01, 2.78]
3 All-cause mortality: duration subgroup analysis	15	155517	Risk Ratio (Fixed, 95% CI)	0.93 [0.84, 1.02]

3.1 0 to < 6 months	2	2817	Risk Ratio (Fixed, 95% CI)	0.59 [0.07, 5.15]
3.2 6 to < 12 months	7	3898	Risk Ratio (Fixed, 95% CI)	0.68 [0.37, 1.25]
3.3 12 months or more	6	148802	Risk Ratio (Fixed, 95% CI)	0.93 [0.85, 1.03]
4 All-cause mortality: iron co-interventions subgroup analysis	15	164227	Risk Ratio (Fixed, 95% CI)	0.93 [0.85, 1.02]
4.1 Iron co-intervention	4	99242	Risk Ratio (Fixed, 95% CI)	0.99 [0.86, 1.15]
4.2 No iron co-intervention	11	64985	Risk Ratio (Fixed, 95% CI)	0.89 [0.79, 1.00]
5 All-cause mortality: formulation subgroup analysis	15	155517	Risk Ratio (Fixed, 95% CI)	0.93 [0.84, 1.02]
5.1 Solution	5	3639	Risk Ratio (Fixed, 95% CI)	0.99 [0.25, 3.91]
5.2 Pill/Tablet	8	149854	Risk Ratio (Fixed, 95% CI)	0.93 [0.85, 1.02]
5.3 Capsule	1	306	Risk Ratio (Fixed, 95% CI)	0.51 [0.05, 5.60]
5.4 Powder	1	1718	Risk Ratio (Fixed, 95% CI)	0.71 [0.27, 1.86]
6 Incidence of all-cause diarrhoea: age subgroup analysis	34	14788	Risk Ratio (Fixed, 95% CI)	0.87 [0.86, 0.89]
6.1 6 months to < 1 year	14	5576	Risk Ratio (Fixed, 95% CI)	0.88 [0.85, 0.90]
6.2 1 to < 5 years	19	8370	Risk Ratio (Fixed, 95% CI)	0.87 [0.84, 0.90]
6.3 5 to < 13 years	2	842	Risk Ratio (Fixed, 95% CI)	0.90 [0.81, 0.98]
7 Incidence of all-cause diarrhoea: dose subgroup analysis	35	15274	Risk Ratio (Fixed, 95% CI)	0.87 [0.85, 0.89]
7.1 0 to < 5 mg	7	1784	Risk Ratio (Fixed, 95% CI)	0.95 [0.89, 1.01]
7.2 5 to < 10 mg	6	2630	Risk Ratio (Fixed, 95% CI)	0.73 [0.64, 0.83]
7.3 10 to < 15 mg	13	5452	Risk Ratio (Fixed, 95% CI)	0.96 [0.92, 0.99]
7.4 15 to < 20 mg	3	477	Risk Ratio (Fixed, 95% CI)	0.61 [0.58, 0.65]
7.5 20 mg or more	8	4931	Risk Ratio (Fixed, 95% CI)	0.90 [0.87, 0.94]
8 Incidence of all-cause diarrhoea: duration subgroup analysis	35	15042	Risk Ratio (Fixed, 95% CI)	0.87 [0.85, 0.89]
8.1 0 to < 6 months	8	4190	Risk Ratio (Fixed, 95% CI)	0.89 [0.85, 0.93]
8.2 6 to < 12 months	18	8971	Risk Ratio (Fixed, 95% CI)	0.86 [0.84, 0.89]
8.3 12 months or more	9	1881	Risk Ratio (Fixed, 95% CI)	0.88 [0.82, 0.95]
9 Incidence of all-cause diarrhoea: iron co-interventions subgroup analysis	35	15643	Risk Ratio (Fixed, 95% CI)	0.87 [0.85, 0.89]
9.1 Iron co-intervention	10	4299	Risk Ratio (Fixed, 95% CI)	1.00 [0.96, 1.05]
9.2 No iron co-intervention	26	11344	Risk Ratio (Fixed, 95% CI)	0.82 [0.80, 0.84]
10 Incidence of all-cause diarrhoea: formulation subgroup analysis	33	14937	Risk Ratio (Fixed, 95% CI)	0.87 [0.85, 0.89]
10.1 Solution	25	10768	Risk Ratio (Fixed, 95% CI)	0.84 [0.82, 0.86]
10.2 Pill/tablet	4	1696	Risk Ratio (Fixed, 95% CI)	0.90 [0.81, 0.99]
10.3 Capsule	2	612	Risk Ratio (Fixed, 95% CI)	0.78 [0.60, 1.01]
10.4 Powder	2	1861	Risk Ratio (Fixed, 95% CI)	1.04 [0.98, 1.09]
11 Prevalence of all-cause diarrhoea: age subgroup analysis	15	8519	Risk Ratio (Fixed, 95% CI)	0.88 [0.86, 0.90]
11.1 6 months to < 1 year	8	3714	Risk Ratio (Fixed, 95% CI)	0.96 [0.93, 1.00]
11.2 1 to < 5 years	8	4805	Risk Ratio (Fixed, 95% CI)	0.85 [0.83, 0.87]
12 Prevalence of all-cause diarrhoea: dose subgroup analysis	15	8519	Risk Ratio (Fixed, 95% CI)	0.88 [0.86, 0.90]
12.1 0 to < 5 mg	3	1200	Risk Ratio (Fixed, 95% CI)	1.00 [0.92, 1.08]
12.2 5 to < 10 mg	1	274	Risk Ratio (Fixed, 95% CI)	1.17 [0.60, 2.28]
12.3 10 to < 15 mg	6	3434	Risk Ratio (Fixed, 95% CI)	0.93 [0.90, 0.96]

12.4 15 to < 20 mg	1	258	Risk Ratio (Fixed, 95% CI)	0.61 [0.54, 0.69]
12.5 20 mg or more	4	3353	Risk Ratio (Fixed, 95% CI)	0.85 [0.82, 0.87]
13 Prevalence of all-cause diarrhoea: duration subgroup analysis	15	8519	Risk Ratio (Fixed, 95% CI)	0.88 [0.86, 0.90]
13.1 0 to < 6 months	4	3353	Risk Ratio (Fixed, 95% CI)	0.85 [0.82, 0.87]
13.2 6 to < 12 months	10	4957	Risk Ratio (Fixed, 95% CI)	0.92 [0.89, 0.95]
13.3 12 months or more	1	209	Risk Ratio (Fixed, 95% CI)	0.88 [0.74, 1.03]
14 Prevalence of all-cause diarrhoea: iron co-interventions subgroup analysis	15	8519	Risk Ratio (Fixed, 95% CI)	0.88 [0.86, 0.90]
14.1 Iron co-intervention	3	1024	Risk Ratio (Fixed, 95% CI)	0.96 [0.88, 1.05]
14.2 No iron co-intervention	12	7495	Risk Ratio (Fixed, 95% CI)	0.88 [0.86, 0.90]
15 Prevalence of all-cause diarrhoea: formulation subgroup analysis	15	8519	Risk Ratio (Fixed, 95% CI)	0.88 [0.86, 0.90]
15.1 Solution	9	4657	Risk Ratio (Fixed, 95% CI)	0.88 [0.85, 0.90]
15.2 Pill/tablet	5	2144	Risk Ratio (Fixed, 95% CI)	0.86 [0.81, 0.92]
15.3 Powder	1	1718	Risk Ratio (Fixed, 95% CI)	1.03 [0.95, 1.12]
16 Incidence of LRTI: age subgroup analysis	21	9232	Risk Ratio (Fixed, 95% CI)	1.01 [0.95, 1.08]
16.1 6 months to < 1 year	8	3566	Risk Ratio (Fixed, 95% CI)	0.97 [0.88, 1.07]
16.2 1 to < 5 years	11	4830	Risk Ratio (Fixed, 95% CI)	1.05 [0.96, 1.16]
16.3 5 to < 13 years	2	836	Risk Ratio (Fixed, 95% CI)	1.00 [0.72, 1.40]
17 Incidence of LRTI: dose subgroup analysis	18	9610	Risk Ratio (Fixed, 95% CI)	1.00 [0.94, 1.07]
17.1 0 to < 5 mg	3	845	Risk Ratio (Fixed, 95% CI)	0.94 [0.78, 1.13]
17.2 10 to < 15 mg	8	4045	Risk Ratio (Fixed, 95% CI)	1.00 [0.91, 1.10]
17.3 20 mg or more	7	4720	Risk Ratio (Fixed, 95% CI)	1.02 [0.92, 1.13]
18 Incidence of LRTI: duration subgroup analysis	18	9610	Risk Ratio (Fixed, 95% CI)	1.00 [0.94, 1.07]
18.1 0 to < 6 months	3	3148	Risk Ratio (Fixed, 95% CI)	1.03 [0.92, 1.14]
18.2 6 to < 12 months	11	5114	Risk Ratio (Fixed, 95% CI)	0.98 [0.90, 1.06]
18.3 12 months or more	4	1348	Risk Ratio (Fixed, 95% CI)	1.08 [0.83, 1.42]
19 Incidence of LRTI: iron co-interventions subgroup analysis	18	9610	Risk Ratio (Fixed, 95% CI)	1.00 [0.94, 1.07]
19.1 Iron co-intervention	6	2896	Risk Ratio (Fixed, 95% CI)	0.99 [0.87, 1.12]
19.2 No iron co-intervention	12	6714	Risk Ratio (Fixed, 95% CI)	1.01 [0.93, 1.08]
20 Incidence of LRTI: formulation subgroup analysis	18	9610	Risk Ratio (Fixed, 95% CI)	1.00 [0.94, 1.07]
20.1 Solution	14	7007	Risk Ratio (Fixed, 95% CI)	0.98 [0.91, 1.05]
20.2 Pill/tablet	1	686	Risk Ratio (Fixed, 95% CI)	1.19 [0.93, 1.51]
20.3 Capsule	2	612	Risk Ratio (Fixed, 95% CI)	1.12 [0.84, 1.51]
20.4 Powder	1	1305	Risk Ratio (Fixed, 95% CI)	1.25 [0.75, 2.09]
21 Height: country income level subgroup analysis	59	13669	Std. Mean Difference (Fixed, 95% CI)	-0.09 [-0.13, -0.06]
21.1 Low- or middle-income	53	13385	Std. Mean Difference (Fixed, 95% CI)	-0.09 [-0.13, -0.06]
21.2 High-income	6	284	Std. Mean Difference (Fixed, 95% CI)	-0.17 [-0.40, 0.06]
22 Height: age subgroup analysis	56	13334	Std. Mean Difference (Fixed, 95% CI)	-0.03 [-0.06, 0.00]
22.1 6 months to < 1 year	13	3730	Std. Mean Difference (Fixed, 95% CI)	0.26 [0.19, 0.33]
22.2 1 to < 5 years	27	6155	Std. Mean Difference (Fixed, 95% CI)	-0.09 [-0.14, -0.04]
22.3 5 to < 13 years	17	3449	Std. Mean Difference (Fixed, 95% CI)	-0.25 [-0.32, -0.18]

23 Height: stunting subgroup analysis	13	931	Std. Mean Difference (Fixed, 95% CI)	-0.21 [-0.34, -0.08]
23.1 Stunted	10	712	Std. Mean Difference (Fixed, 95% CI)	-0.25 [-0.40, -0.10]
23.2 Non-stunted	4	219	Std. Mean Difference (Fixed, 95% CI)	-0.09 [-0.36, 0.17]
24 Height: dose subgroup analysis	55	13407	Std. Mean Difference (Fixed, 95% CI)	-0.08 [-0.11, -0.05]
24.1 0 to < 5 mg	7	1170	Std. Mean Difference (Fixed, 95% CI)	-0.02 [-0.13, 0.10]
24.2 5 to < 10 mg	11	2978	Std. Mean Difference (Fixed, 95% CI)	-0.29 [-0.37, -0.22]
24.3 10 to < 15 mg	25	4344	Std. Mean Difference (Fixed, 95% CI)	-0.06 [-0.12, -0.00]
24.4 15 to < 20 mg	3	240	Std. Mean Difference (Fixed, 95% CI)	0.01 [-0.24, 0.26]
24.5 20 mg or more	11	4675	Std. Mean Difference (Fixed, 95% CI)	0.01 [-0.05, 0.07]
25 Height: duration subgroup analysis	59	13669	Std. Mean Difference (Fixed, 95% CI)	-0.09 [-0.13, -0.06]
25.1 0 to < 6 months	13	4475	Std. Mean Difference (Fixed, 95% CI)	0.01 [-0.04, 0.07]
25.2 6 to < 12 months	30	6479	Std. Mean Difference (Fixed, 95% CI)	-0.17 [-0.22, -0.12]
25.3 12 months or more	16	2715	Std. Mean Difference (Fixed, 95% CI)	-0.10 [-0.17, -0.02]
26 Height: iron co-interventions subgroup analysis	58	13439	Std. Mean Difference (Fixed, 95% CI)	-0.09 [-0.13, -0.06]
26.1 Iron co-intervention	12	2929	Std. Mean Difference (Fixed, 95% CI)	-0.01 [-0.08, 0.07]
26.2 No iron co-intervention	46	10510	Std. Mean Difference (Fixed, 95% CI)	-0.12 [-0.16, -0.08]
27 Height: formulation subgroup analysis	53	13220	Std. Mean Difference (Fixed, 95% CI)	-0.09 [-0.13, -0.06]
27.1 Solution	38	9030	Std. Mean Difference (Fixed, 95% CI)	-0.12 [-0.16, -0.07]
27.2 Pill/tablet	12	3868	Std. Mean Difference (Fixed, 95% CI)	-0.02 [-0.09, 0.04]
27.3 Capsule	3	322	Std. Mean Difference (Fixed, 95% CI)	-0.31 [-0.59, -0.03]
28 Weight: country income level subgroup analysis	52	12305	Std. Mean Difference (Fixed, 95% CI)	-0.10 [-0.14, -0.07]
28.1 Low- or middle-income	47	12034	Std. Mean Difference (Fixed, 95% CI)	-0.10 [-0.14, -0.07]
28.2 High-income	5	271	Std. Mean Difference (Fixed, 95% CI)	-0.16 [-0.40, 0.07]
29 Weight: age subgroup analysis	49	11949	Std. Mean Difference (Fixed, 95% CI)	0.01 [-0.03, 0.04]
29.1 6 months to < 1 year	13	3730	Std. Mean Difference (Fixed, 95% CI)	0.31 [0.25, 0.38]
29.2 1 to < 5 years	23	5565	Std. Mean Difference (Fixed, 95% CI)	-0.06 [-0.11, -0.01]
29.3 5 to < 13 years	14	2654	Std. Mean Difference (Fixed, 95% CI)	-0.28 [-0.36, -0.20]
30 Weight: stunting subgroup analysis	11	854	Std. Mean Difference (Fixed, 95% CI)	-0.19 [-0.32, -0.05]
30.1 Stunted	8	635	Std. Mean Difference (Fixed, 95% CI)	-0.25 [-0.40, -0.09]
30.2 Non-stunted	4	219	Std. Mean Difference (Fixed, 95% CI)	-0.01 [-0.27, 0.26]
31 Weight: dose subgroup analysis	49	12064	Std. Mean Difference (Fixed, 95% CI)	-0.10 [-0.13, -0.06]
31.1 0 to < 5 mg	7	1170	Std. Mean Difference (Fixed, 95% CI)	-0.00 [-0.12, 0.11]
31.2 5 to < 10 mg	10	2766	Std. Mean Difference (Fixed, 95% CI)	-0.27 [-0.35, -0.20]
31.3 10 to < 15 mg	22	3969	Std. Mean Difference (Fixed, 95% CI)	-0.11 [-0.17, -0.04]
31.4 15 to < 20 mg	3	240	Std. Mean Difference (Fixed, 95% CI)	0.20 [-0.06, 0.45]
31.5 20 mg or more	9	3919	Std. Mean Difference (Fixed, 95% CI)	-0.01 [-0.08, 0.05]
32 Weight: duration subgroup analysis	52	12305	Std. Mean Difference (Fixed, 95% CI)	-0.10 [-0.14, -0.07]
32.1 0 to < 6 months	12	4417	Std. Mean Difference (Fixed, 95% CI)	-0.05 [-0.11, 0.00]
32.2 6 to < 12 months	25	5289	Std. Mean Difference (Fixed, 95% CI)	-0.20 [-0.26, -0.15]
32.3 12 months or more	15	2599	Std. Mean Difference (Fixed, 95% CI)	0.01 [-0.07, 0.09]
33 Weight: iron co-interventions subgroup analysis	52	12305	Std. Mean Difference (Fixed, 95% CI)	-0.10 [-0.14, -0.07]
33.1 Iron co-intervention	10	2494	Std. Mean Difference (Fixed, 95% CI)	-0.06 [-0.14, 0.02]
33.2 No iron co-intervention	42	9811	Std. Mean Difference (Fixed, 95% CI)	-0.12 [-0.16, -0.08]

34 Weight: formulation subgroup analysis	48	12107	Std. Mean Difference (Fixed, 95% CI)	-0.11 [-0.14, -0.07]
34.1 Solution	34	8147	Std. Mean Difference (Fixed, 95% CI)	-0.14 [-0.19, -0.10]
34.2 Pill/tablet	11	3656	Std. Mean Difference (Fixed, 95% CI)	-0.01 [-0.08, 0.06]
34.3 Capsule	3	304	Std. Mean Difference (Fixed, 95% CI)	-0.41 [-0.71, -0.12]
35 Weight-to-height ratio: country income level subgroup analysis	29	7901	Std. Mean Difference (IV, Fixed, 95% CI)	-0.05 [-0.10, -0.01]
35.1 Low- or middle-income	27	7801	Std. Mean Difference (IV, Fixed, 95% CI)	-0.05 [-0.09, -0.01]
35.2 High-income	2	100	Std. Mean Difference (IV, Fixed, 95% CI)	-0.14 [-0.53, 0.25]
36 Weight-to-height ratio: age subgroup analysis	28	7718	Std. Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.07, 0.02]
36.1 6 months to < 1 year	9	2559	Std. Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.11, 0.04]
36.2 1 to < 5 years	14	4302	Std. Mean Difference (IV, Fixed, 95% CI)	-0.02 [-0.08, 0.05]
36.3 5 to < 13 years	6	857	Std. Mean Difference (IV, Fixed, 95% CI)	-0.07 [-0.20, 0.06]
37 Weight-to-height ratio: dose subgroup analysis	28	8059	Std. Mean Difference (IV, Fixed, 95% CI)	-0.05 [-0.10, -0.01]
37.1 0 to < 5 mg	5	671	Std. Mean Difference (IV, Fixed, 95% CI)	-0.07 [-0.22, 0.08]
37.2 5 to < 10 mg	6	1229	Std. Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.12, 0.10]
37.3 10 to < 15 mg	11	2389	Std. Mean Difference (IV, Fixed, 95% CI)	-0.08 [-0.16, 0.01]
37.4 15 to < 20 mg	2	194	Std. Mean Difference (IV, Fixed, 95% CI)	0.22 [-0.06, 0.50]
37.5 20 mg or more	6	3576	Std. Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.13, 0.00]
38 Weight-to-height ratio: duration subgroup analysis	29	7901	Std. Mean Difference (IV, Fixed, 95% CI)	-0.05 [-0.10, -0.01]
38.1 0 to < 6 months	6	3337	Std. Mean Difference (IV, Fixed, 95% CI)	-0.07 [-0.14, -0.00]
38.2 6 to < 12 months	18	4212	Std. Mean Difference (IV, Fixed, 95% CI)	-0.05 [-0.11, 0.01]
38.3 12 months or more	5	352	Std. Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.11, 0.31]
39 Weight-to-height ratio: iron co-interventions subgroup analysis	28	7671	Std. Mean Difference (IV, Fixed, 95% CI)	-0.05 [-0.09, -0.00]
39.1 Iron co-intervention	8	1409	Std. Mean Difference (IV, Fixed, 95% CI)	-0.14 [-0.24, -0.03]
39.2 No iron co-intervention	20	6262	Std. Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.08, 0.02]
40 Weight-to-height ratio: formulation subgroup analysis	28	7671	Std. Mean Difference (IV, Fixed, 95% CI)	-0.05 [-0.09, -0.00]
40.1 Solution	22	6019	Std. Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.12, -0.01]
40.2 Pill/tablet	6	1652	Std. Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.08, 0.11]
41 Serum or plasma zinc concentration: country income level subgroup analysis	56	9810	Std. Mean Difference (Fixed, 95% CI)	-0.62 [-0.67, -0.58]
41.1 Low- or middle-income	50	9581	Std. Mean Difference (Fixed, 95% CI)	-0.63 [-0.68, -0.59]
41.2 High-income	6	229	Std. Mean Difference (Fixed, 95% CI)	-0.23 [-0.49, 0.03]
42 Serum or plasma zinc concentration: age subgroup analysis	53	9328	Std. Mean Difference (Fixed, 95% CI)	-0.61 [-0.65, -0.57]
42.1 6 months to < 1 year	11	2042	Std. Mean Difference (Fixed, 95% CI)	-0.46 [-0.55, -0.37]
42.2 1 to < 5 years	22	4911	Std. Mean Difference (Fixed, 95% CI)	-0.75 [-0.81, -0.69]
42.3 5 to < 13 years	21	2375	Std. Mean Difference (Fixed, 95% CI)	-0.47 [-0.55, -0.38]
43 Serum or plasma zinc concentration: dose subgroup analysis	52	9472	Std. Mean Difference (Fixed, 95% CI)	-0.62 [-0.67, -0.58]
43.1 0 to < 5 mg	6	855	Std. Mean Difference (Fixed, 95% CI)	-0.35 [-0.49, -0.21]
43.2 5 to < 10 mg	8	1762	Std. Mean Difference (Fixed, 95% CI)	-0.49 [-0.59, -0.40]
43.3 10 to < 15 mg	23	4596	Std. Mean Difference (Fixed, 95% CI)	-0.62 [-0.68, -0.56]
43.4 15 to < 20 mg	8	535	Std. Mean Difference (Fixed, 95% CI)	-0.76 [-0.94, -0.58]

43.5 20 mg or more	9	1724	Std. Mean Difference (Fixed, 95% CI)	-0.88 [-0.98, -0.78]
44 Serum or plasma zinc concentration: duration subgroup analysis	56	9810	Std. Mean Difference (Fixed, 95% CI)	-0.62 [-0.67, -0.58]
44.1 0 to < 6 months	17	3079	Std. Mean Difference (Fixed, 95% CI)	-0.81 [-0.88, -0.73]
44.2 6 to < 12 months	28	4347	Std. Mean Difference (Fixed, 95% CI)	-0.52 [-0.58, -0.46]
44.3 12 months or more	11	2384	Std. Mean Difference (Fixed, 95% CI)	-0.59 [-0.67, -0.50]
45 Serum or plasma zinc concentration: iron co-interventions subgroup analysis	56	9810	Std. Mean Difference (Fixed, 95% CI)	-0.62 [-0.67, -0.58]
45.1 Iron co-intervention	17	3231	Std. Mean Difference (Fixed, 95% CI)	-0.47 [-0.54, -0.39]
45.2 No iron co-intervention	39	6579	Std. Mean Difference (Fixed, 95% CI)	-0.70 [-0.75, -0.65]
46 Serum or plasma zinc concentration: Formulation subgroup analysis	52	9810	Std. Mean Difference (Fixed, 95% CI)	-0.64 [-0.68, -0.59]
46.1 Solution	31	4741	Std. Mean Difference (Fixed, 95% CI)	-0.78 [-0.84, -0.72]
46.2 Pill/tablet	13	3553	Std. Mean Difference (Fixed, 95% CI)	-0.42 [-0.49, -0.35]
46.3 Capsule	8	1115	Std. Mean Difference (Fixed, 95% CI)	-1.07 [-1.21, -0.94]
46.4 Powder	1	401	Std. Mean Difference (Fixed, 95% CI)	0.06 [-0.14, 0.25]
47 Prevalence of zinc deficiency: age subgroup analysis	22	5544	Risk Ratio (Fixed, 95% CI)	0.49 [0.45, 0.53]
47.1 6 months to < 1 year	2	549	Risk Ratio (Fixed, 95% CI)	0.62 [0.54, 0.70]
47.2 1 to < 5 years	12	3761	Risk Ratio (Fixed, 95% CI)	0.41 [0.37, 0.47]
47.3 5 to < 13 years	8	1234	Risk Ratio (Fixed, 95% CI)	0.31 [0.20, 0.49]
48 Prevalence of zinc deficiency: dose subgroup analysis	22	5544	Risk Ratio (Fixed, 95% CI)	0.49 [0.45, 0.53]
48.1 5 to < 10 mg	3	1181	Risk Ratio (Fixed, 95% CI)	0.34 [0.27, 0.44]
48.2 10 to < 15 mg	11	2890	Risk Ratio (Fixed, 95% CI)	0.57 [0.52, 0.63]
48.3 15 to < 20 mg	2	194	Risk Ratio (Fixed, 95% CI)	0.46 [0.24, 0.89]
48.4 20 mg or more	6	1279	Risk Ratio (Fixed, 95% CI)	0.14 [0.10, 0.19]
49 Prevalence of zinc deficiency: duration subgroup analysis	22	5544	Risk Ratio (Fixed, 95% CI)	0.49 [0.45, 0.53]
49.1 0 to < 6 months	9	2554	Risk Ratio (Fixed, 95% CI)	0.22 [0.18, 0.27]
49.2 6 to < 12 months	7	1043	Risk Ratio (Fixed, 95% CI)	0.59 [0.53, 0.67]
49.3 12 months or more	6	1947	Risk Ratio (Fixed, 95% CI)	0.55 [0.48, 0.64]
50 Prevalence of zinc deficiency: iron co-interventions subgroup analysis	22	5544	Risk Ratio (Fixed, 95% CI)	0.49 [0.45, 0.53]
50.1 Iron co-intervention	6	1704	Risk Ratio (Fixed, 95% CI)	0.62 [0.55, 0.69]
50.2 No iron co-intervention	16	3840	Risk Ratio (Fixed, 95% CI)	0.37 [0.33, 0.42]
51 Prevalence of zinc deficiency: formulation subgroup analysis	22	5690	Risk Ratio (Fixed, 95% CI)	0.49 [0.45, 0.53]
51.1 Solution	12	2415	Risk Ratio (Fixed, 95% CI)	0.49 [0.44, 0.54]
51.2 Pill/tablet	7	2392	Risk Ratio (Fixed, 95% CI)	0.59 [0.50, 0.68]
51.3 Capsule	4	883	Risk Ratio (Fixed, 95% CI)	0.29 [0.23, 0.37]
52 Blood haemoglobin concentration: age subgroup analysis	34	5810	Std. Mean Difference (Fixed, 95% CI)	-0.00 [-0.06, 0.05]
52.1 6 months to < 1 year	11	2192	Std. Mean Difference (Fixed, 95% CI)	0.04 [-0.05, 0.12]
52.2 1 to < 5 years	14	2332	Std. Mean Difference (Fixed, 95% CI)	-0.04 [-0.12, 0.04]
52.3 5 to < 13 years	9	1286	Std. Mean Difference (Fixed, 95% CI)	-0.01 [-0.13, 0.11]

53 Blood haemoglobin concentration: dose subgroup analysis	36	6113	Std. Mean Difference (Fixed, 95% CI)	-0.02 [-0.07, 0.03]
53.1 0 to < 5 mg	6	966	Std. Mean Difference (Fixed, 95% CI)	-0.01 [-0.14, 0.12]
53.2 5 to < 10 mg	2	306	Std. Mean Difference (Fixed, 95% CI)	0.01 [-0.21, 0.23]
53.3 10 to < 15 mg	20	3452	Std. Mean Difference (Fixed, 95% CI)	-0.01 [-0.08, 0.06]
53.4 15 to < 20 mg	5	364	Std. Mean Difference (Fixed, 95% CI)	0.04 [-0.17, 0.24]
53.5 20 mg or more	5	1025	Std. Mean Difference (Fixed, 95% CI)	-0.10 [-0.22, 0.02]
54 Blood haemoglobin concentration: duration subgroup analysis	36	6011	Std. Mean Difference (Fixed, 95% CI)	-0.01 [-0.07, 0.04]
54.1 0 to < 6 months	8	672	Std. Mean Difference (Fixed, 95% CI)	-0.17 [-0.33, -0.01]
54.2 6 to < 12 months	18	3738	Std. Mean Difference (Fixed, 95% CI)	0.01 [-0.06, 0.08]
54.3 12 months or more	10	1601	Std. Mean Difference (Fixed, 95% CI)	-0.01 [-0.11, 0.09]
55 Blood haemoglobin concentration: iron co-interventions subgroup analysis	36	6011	Std. Mean Difference (Fixed, 95% CI)	-0.01 [-0.07, 0.04]
55.1 Iron co-intervention	17	3098	Std. Mean Difference (Fixed, 95% CI)	0.01 [-0.07, 0.08]
55.2 No iron co-intervention	19	2913	Std. Mean Difference (Fixed, 95% CI)	-0.04 [-0.11, 0.04]
56 Blood haemoglobin concentration: formulation subgroup analysis	36	6011	Std. Mean Difference (Fixed, 95% CI)	-0.01 [-0.07, 0.04]
56.1 Solution	20	2990	Std. Mean Difference (Fixed, 95% CI)	-0.01 [-0.08, 0.06]
56.2 Pill/tablet	9	1605	Std. Mean Difference (Fixed, 95% CI)	-0.01 [-0.12, 0.09]
56.3 Capsule	6	989	Std. Mean Difference (Fixed, 95% CI)	-0.07 [-0.20, 0.06]
56.4 Powder	1	427	Std. Mean Difference (Fixed, 95% CI)	0.07 [-0.12, 0.26]
57 Prevalence of anaemia: age subgroup analysis	19	4287	Risk Ratio (Fixed, 95% CI)	1.00 [0.95, 1.06]
57.1 6 months to < 1 year	8	1726	Risk Ratio (Fixed, 95% CI)	1.01 [0.95, 1.08]
57.2 1 to < 5 years	8	2161	Risk Ratio (Fixed, 95% CI)	0.99 [0.88, 1.12]
57.3 5 to < 13 years	3	400	Risk Ratio (Fixed, 95% CI)	0.73 [0.47, 1.12]
58 Prevalence of anaemia: dose subgroup analysis	19	4287	Risk Ratio (Fixed, 95% CI)	1.00 [0.95, 1.06]
58.1 0 to < 5 mg	3	616	Risk Ratio (Fixed, 95% CI)	1.01 [0.94, 1.09]
58.2 5 to < 10 mg	1	208	Risk Ratio (Fixed, 95% CI)	0.94 [0.47, 1.87]
58.3 10 to < 15 mg	12	3069	Risk Ratio (Fixed, 95% CI)	1.01 [0.92, 1.11]
58.4 15 to < 20 mg	2	181	Risk Ratio (Fixed, 95% CI)	0.76 [0.40, 1.46]
58.5 20 mg or more	1	213	Risk Ratio (Fixed, 95% CI)	0.17 [0.06, 0.46]
59 Prevalence of anaemia: duration subgroup analysis	19	4287	Risk Ratio (Fixed, 95% CI)	1.00 [0.95, 1.06]
59.1 0 to < 6 months	2	325	Risk Ratio (Fixed, 95% CI)	0.18 [0.06, 0.48]
59.2 6 to < 12 months	9	1989	Risk Ratio (Fixed, 95% CI)	1.01 [0.94, 1.08]
59.3 12 months or more	8	1973	Risk Ratio (Fixed, 95% CI)	1.00 [0.90, 1.12]
60 Prevalence of anaemia: iron co-interventions subgroup analysis	19	4287	Risk Ratio (Fixed, 95% CI)	1.00 [0.95, 1.06]
60.1 Iron co-intervention	10	2755	Risk Ratio (Fixed, 95% CI)	1.00 [0.91, 1.09]
60.2 No iron co-intervention	9	1532	Risk Ratio (Fixed, 95% CI)	1.00 [0.93, 1.08]
61 Prevalence of anaemia: formulation subgroup analysis	19	4287	Risk Ratio (Fixed, 95% CI)	1.00 [0.95, 1.06]
61.1 Solution	6	1115	Risk Ratio (Fixed, 95% CI)	0.90 [0.78, 1.04]
61.2 Pill/tablet	8	1958	Risk Ratio (Fixed, 95% CI)	1.02 [0.95, 1.10]
61.3 Capsule	4	886	Risk Ratio (Fixed, 95% CI)	1.00 [0.88, 1.13]

61.4 Powder	1	328	Risk Ratio (Fixed, 95% CI)	1.19 [0.81, 1.73]
62 Serum or plasma ferritin concentration: country income level subgroup analysis	25	4474	Std. Mean Difference (Fixed, 95% CI)	0.13 [0.07, 0.19]
62.1 Low- or middle-income	24	4427	Std. Mean Difference (Fixed, 95% CI)	0.12 [0.06, 0.19]
62.2 High-income	1	47	Std. Mean Difference (Fixed, 95% CI)	0.88 [0.29, 1.47]
63 Serum or plasma ferritin concentration: age subgroup analysis	24	4416	Std. Mean Difference (Fixed, 95% CI)	0.14 [0.08, 0.20]
63.1 6 months to < 1 year	6	1166	Std. Mean Difference (Fixed, 95% CI)	0.14 [0.03, 0.26]
63.2 1 to < 5 years	11	2716	Std. Mean Difference (Fixed, 95% CI)	0.16 [0.08, 0.24]
63.3 5 to < 13 years	7	534	Std. Mean Difference (Fixed, 95% CI)	0.05 [-0.15, 0.24]
64 Serum or plasma ferritin concentration: dose subgroup analysis	25	4586	Std. Mean Difference (Fixed, 95% CI)	0.13 [0.07, 0.19]
64.1 0 to < 5 mg	4	371	Std. Mean Difference (Fixed, 95% CI)	0.07 [-0.14, 0.28]
64.2 5 to < 10 mg	1	78	Std. Mean Difference (Fixed, 95% CI)	0.15 [-0.34, 0.63]
64.3 10 to < 15 mg	14	3171	Std. Mean Difference (Fixed, 95% CI)	0.20 [0.13, 0.28]
64.4 15 to < 20 mg	4	314	Std. Mean Difference (Fixed, 95% CI)	0.14 [-0.08, 0.36]
64.5 20 mg or more	4	652	Std. Mean Difference (Fixed, 95% CI)	-0.17 [-0.33, -0.02]
65 Serum or plasma ferritin concentration: duration subgroup analysis	24	4416	Std. Mean Difference (Fixed, 95% CI)	0.14 [0.08, 0.20]
65.1 0 to < 6 months	8	902	Std. Mean Difference (Fixed, 95% CI)	-0.06 [-0.20, 0.07]
65.2 6 to < 12 months	10	1735	Std. Mean Difference (Fixed, 95% CI)	0.07 [-0.03, 0.17]
65.3 12 months or more	6	1779	Std. Mean Difference (Fixed, 95% CI)	0.34 [0.24, 0.45]
66 Serum or plasma ferritin concentration: iron co-interventions subgroup analysis	25	4474	Std. Mean Difference (Fixed, 95% CI)	0.13 [0.07, 0.19]
66.1 Iron co-intervention	14	2765	Std. Mean Difference (Fixed, 95% CI)	0.05 [-0.02, 0.13]
66.2 No iron co-intervention	11	1709	Std. Mean Difference (Fixed, 95% CI)	0.27 [0.17, 0.38]
67 Serum or plasma ferritin concentration: formulation subgroup analysis	23	4369	Std. Mean Difference (Fixed, 95% CI)	0.13 [0.07, 0.20]
67.1 Solution	14	2043	Std. Mean Difference (Fixed, 95% CI)	-0.01 [-0.10, 0.08]
67.2 Pill/tablet	3	1070	Std. Mean Difference (Fixed, 95% CI)	0.16 [0.04, 0.29]
67.3 Capsule	5	939	Std. Mean Difference (Fixed, 95% CI)	0.54 [0.38, 0.69]
67.4 Powder	1	317	Std. Mean Difference (Fixed, 95% CI)	0.18 [-0.04, 0.40]
68 Prevalence of iron deficiency: age subgroup analysis	16	3248	Risk Ratio (Fixed, 95% CI)	0.99 [0.89, 1.10]
68.1 6 months to < 1 year	5	905	Risk Ratio (Fixed, 95% CI)	0.92 [0.82, 1.05]
68.2 1 to < 5 years	7	1992	Risk Ratio (Fixed, 95% CI)	1.16 [0.94, 1.44]
68.3 5 to < 13 years	4	351	Risk Ratio (Fixed, 95% CI)	1.12 [0.61, 2.04]
69 Prevalence of iron deficiency: dose subgroup analysis	16	3248	Risk Ratio (Fixed, 95% CI)	0.99 [0.89, 1.10]
69.1 0 to < 5 mg	1	144	Risk Ratio (Fixed, 95% CI)	0.78 [0.61, 1.00]
69.2 10 to < 15 mg	10	2634	Risk Ratio (Fixed, 95% CI)	1.03 [0.91, 1.16]
69.3 15 to < 20 mg	2	194	Risk Ratio (Fixed, 95% CI)	1.07 [0.52, 2.18]
69.4 20 mg or more	3	276	Risk Ratio (Fixed, 95% CI)	2.16 [0.72, 6.44]
70 Prevalence of iron deficiency: Duration subgroup analysis	16	3248	Risk Ratio (Fixed, 95% CI)	0.99 [0.89, 1.10]
70.1 0 to < 6 months	3	276	Risk Ratio (Fixed, 95% CI)	2.16 [0.72, 6.44]

70.2 6 to < 12 months	5	981	Risk Ratio (Fixed, 95% CI)	0.88 [0.73, 1.05]
70.3 12 months or more	8	1991	Risk Ratio (Fixed, 95% CI)	1.04 [0.91, 1.18]
71 Prevalence of iron deficiency: Iron co-interventions subgroup analysis	16	3248	Risk Ratio (Fixed, 95% CI)	0.99 [0.89, 1.10]
71.1 Iron co-intervention	10	2301	Risk Ratio (Fixed, 95% CI)	1.02 [0.89, 1.17]
71.2 No iron co-intervention	6	947	Risk Ratio (Fixed, 95% CI)	0.94 [0.79, 1.11]
72 Prevalence of iron deficiency: formulation subgroup analysis	16	3248	Risk Ratio (Fixed, 95% CI)	0.99 [0.89, 1.10]
72.1 Solution	8	1163	Risk Ratio (Fixed, 95% CI)	0.90 [0.75, 1.08]
72.2 Pill/tablet	4	1199	Risk Ratio (Fixed, 95% CI)	1.05 [0.91, 1.20]
72.3 Capsule	4	886	Risk Ratio (Fixed, 95% CI)	0.88 [0.56, 1.37]
73 Serum or plasma copper concentration: country income level subgroup analysis	13	3071	Std. Mean Difference (Fixed, 95% CI)	0.22 [0.14, 0.29]
73.1 Low- or middle-income	12	3031	Std. Mean Difference (Fixed, 95% CI)	0.22 [0.15, 0.30]
73.2 High-income	1	40	Std. Mean Difference (Fixed, 95% CI)	-0.38 [-0.99, 0.23]
74 Serum or plasma copper concentration: age subgroup analysis	13	3071	Std. Mean Difference (Fixed, 95% CI)	0.22 [0.14, 0.29]
74.1 6 months to < 1 year	5	865	Std. Mean Difference (Fixed, 95% CI)	0.11 [-0.02, 0.24]
74.2 1 to < 5 years	8	2206	Std. Mean Difference (Fixed, 95% CI)	0.26 [0.17, 0.35]
75 Serum or plasma copper concentration: dose subgroup analysis	13	3169	Std. Mean Difference (Fixed, 95% CI)	0.20 [0.13, 0.27]
75.1 0 to < 5 mg	4	410	Std. Mean Difference (Fixed, 95% CI)	0.08 [-0.12, 0.27]
75.2 5 to < 10 mg	2	519	Std. Mean Difference (Fixed, 95% CI)	0.31 [0.13, 0.49]
75.3 10 to < 15 mg	8	1310	Std. Mean Difference (Fixed, 95% CI)	0.01 [-0.10, 0.12]
75.4 20 mg or more	1	930	Std. Mean Difference (Fixed, 95% CI)	0.46 [0.33, 0.59]
76 Serum or plasma copper concentration: duration subgroup analysis	13	3071	Std. Mean Difference (Fixed, 95% CI)	0.22 [0.14, 0.29]
76.1 0 to < 6 months	2	1355	Std. Mean Difference (Fixed, 95% CI)	0.44 [0.33, 0.55]
76.2 6 to < 12 months	7	1168	Std. Mean Difference (Fixed, 95% CI)	0.08 [-0.04, 0.20]
76.3 12 months or more	4	548	Std. Mean Difference (Fixed, 95% CI)	-0.06 [-0.24, 0.11]
77 Serum or plasma copper concentration: iron co-interventions subgroup analysis	13	3071	Std. Mean Difference (Fixed, 95% CI)	0.22 [0.14, 0.29]
77.1 Iron co-intervention	4	650	Std. Mean Difference (Fixed, 95% CI)	0.10 [-0.05, 0.25]
77.2 No iron co-intervention	9	2421	Std. Mean Difference (Fixed, 95% CI)	0.25 [0.17, 0.33]
78 Serum or plasma copper concentration: Formulation subgroup analysis	13	2929	Std. Mean Difference (Fixed, 95% CI)	0.46 [0.38, 0.53]
78.1 Solution	11	2490	Std. Mean Difference (Fixed, 95% CI)	0.37 [0.29, 0.46]
78.2 Pill/Tablet	3	439	Std. Mean Difference (Fixed, 95% CI)	0.83 [0.65, 1.01]

CONTRIBUTIONS OF AUTHORS

JJ, EMW, AI, SD, and ZB contributed to the background. EMW and JJ were primarily responsible for the methods. JJ, EMW, and AI developed the search strategy with Margaret Anderson. JJ executed the first literature search, and EMW and AI executed the update. JJ, EMW, AI, EC, and AI reviewed citations for inclusion. Disagreements were resolved through consultation with a third author. JJ, EMW, AI, SD, XHC, and AJ extracted data. JJ and EMW entered outcome data into RevMan, analysed the data, and made the tables. 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.

DECLARATIONS OF INTEREST

Evan Mayo-Wilson - none known.

Jean Junior - none known.

Aamer Imdad has published previous reviews about zinc.

Sohni Dean - none known.

Xin Hui Chan - none known.

Evelyn Chan - none known.

Aneil Jaswal - none known.

Zulfiqar A Bhutta was involved in some of the included trials. Zulfiqar was not involved in data extraction of these studies. Zulfiqar has published previous reviews about zinc.

SOURCES OF SUPPORT

Internal sources

- Aga Khan University, Pakistan.

Aamer Imdad, Sohni Dean, and Zulfiqar A Bhutta are supported by Aga Khan University, Karachi, Pakistan

- The Centre for Evidence-Based Intervention, UK.

Jean Junior and Evan Mayo-Wilson are supported by the Centre for Evidence-Based Intervention, University of Oxford

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

1. We eliminated hospitalisation due to severe diarrhoea and hospitalisation due to persistent diarrhoea as outcomes. (Studies only reported hospitalisation due to all-cause diarrhoea, undifferentiated by level of severity or persistence. However, if a child was hospitalised for a diarrhoea episode, this episode would likely be severe and/or persistent.)

2. We re-specified the "Side effects (for example, abdominal pain, nausea, vomiting, diarrhoea)" outcome to be: Study withdrawal, participants with one or more side effect, vomiting episodes, and participants with one or more vomiting episode. Participants with one or more vomiting episode is included in the 'Summary of findings' table.

3. We did not include incidence of severe diarrhoea and incidence of persistent diarrhoea in the 'Summary of findings' table.

4. Given the large number of excluded studies, we did not search all excluded study reference lists to identify additional studies.

5. We changed the age subgroup analysis from, "children six months to under five years versus five years to 13 years" to "children six months to under one year, versus one to under five years, versus five years to under 13 years."

6. We clarified the exclusion of mixed micronutrients and added "powder" as a category to the subgroup analysis for formulation.

7. We added an additional comparison to include zinc versus zinc plus iron.

8. We did not undertake a sensitivity analysis excluding studies from the primary analysis for risk of bias due to incomplete outcome data. Effects were more likely to be underestimated than overestimated as a result of dropout, so we consider the primary result to be a conservative estimate.