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# Oral zinc for treating diarrhoea in children (Review)

Lazzerini M, Wanzira H

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[Intervention Review]

# Oral zinc for treating diarrhoea in children

Marzia Lazzerini[1], Humphrey Wanzira[1]

[1]WHO Collaborating Centre for Maternal and Child Health, Institute for Maternal and Child Health IRCCS Burlo Garofolo, Trieste, Italy

**Contact:** Marzia Lazzerini, WHO Collaborating Centre for Maternal and Child Health, Institute for Maternal and Child Health IRCCS Burlo Garofolo, Via dell'Istria 65/1, 34137, Trieste, Italy. marzia.lazzerini@burlo.trieste.it.

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## ABSTRACT

### Background

In developing countries, diarrhoea causes around 500,000 child deaths annually. Zinc supplementation during acute diarrhoea is currently recommended by the World Health Organization (WHO) and the United Nations Children's Fund (UNICEF).

### Objectives

To evaluate oral zinc supplementation for treating children with acute or persistent diarrhoea.

### Search methods

We searched the Cochrane Infectious Diseases Group Specialized Register, CENTRAL (the Cochrane Library 2016, Issue 5), MEDLINE, Embase, LILACS, CINAHL, *m*RCT, and reference lists up to 30 September 2016. We also contacted researchers.

### Selection criteria

Randomized controlled trials (RCTs) that compared oral zinc supplementation with placebo in children aged one month to five years with acute or persistent diarrhoea, including dysentery.

### Data collection and analysis

Both review authors assessed trial eligibility and risk of bias, extracted and analysed data, and drafted the review. The primary outcomes were diarrhoea duration and severity. We summarized dichotomous outcomes using risk ratios (RR) and continuous outcomes using mean differences (MD) with 95% confidence intervals (CI). Where appropriate, we combined data in meta-analyses (using either a fixed-effect or random-effects model) and assessed heterogeneity.

We assessed the certainty of the evidence using the GRADE approach.

### Main results

Thirty-three trials that included 10,841 children met our inclusion criteria. Most included trials were conducted in Asian countries that were at high risk of zinc deficiency.

*Acute diarrhoea*

There is currently not enough evidence from well-conducted RCTs to be able to say whether zinc supplementation during acute diarrhoea reduces death or number of children hospitalized (*very low certainty evidence*).

In children older than six months of age, zinc supplementation may shorten the average duration of diarrhoea by around half a day (MD −11.46 hours, 95% CI −19.72 to −3.19; 2581 children, 9 trials, *low certainty evidence*), and probably reduces the number of children whose diarrhoea persists until day seven (RR 0.73, 95% CI 0.61 to 0.88; 3865 children, 6 trials, *moderate certainty evidence*). In children with signs of malnutrition the effect appears greater, reducing the duration of diarrhoea by around a day (MD −26.39 hours, 95% CI −36.54 to −16.23; 419 children, 5 trials, *high certainty evidence*).

Conversely, in children younger than six months of age, the available evidence suggests zinc supplementation may have no effect on the mean duration of diarrhoea (MD 5.23 hours, 95% CI −4.00 to 14.45; 1334 children, 2 trials, *low certainty evidence*), or the number of children who still have diarrhoea on day seven (RR 1.24, 95% CI 0.99 to 1.54; 1074 children, 1 trial, *low certainty evidence*).

None of the included trials reported serious adverse events. However, zinc supplementation increased the risk of vomiting in both age groups (children greater than six months of age: RR 1.57, 95% CI 1.32 to 1.86; 2605 children, 6 trials, *moderate certainty evidence*; children less than six months of age: RR 1.54, 95% CI 1.05 to 2.24; 1334 children, 2 trials, *moderate certainty evidence*).

*Persistent diarrhoea*

In children with persistent diarrhoea, zinc supplementation probably shortens the average duration of diarrhoea by around 16 hours (MD −15.84 hours, 95% CI −25.43 to −6.24; 529 children, 5 trials, *moderate certainty evidence*).

**Authors' conclusions**

In areas where the prevalence of zinc deficiency or the prevalence of malnutrition is high, zinc may be of benefit in children aged six months or more. The current evidence does not support the use of zinc supplementation in children less six months of age, in well-nourished children, and in settings where children are at low risk of zinc deficiency.

12 April 2019

Up to date

All studies incorporated from most recent search

All eligible published studies found in the last search (30 Sep, 2016) were included and two ongoing studies have been identified (see 'Characteristics of ongoing studies' section)

## PLAIN LANGUAGE SUMMARY

### Oral zinc supplementation for treating diarrhoea in children

In low- and middle-income countries, millions of children suffer from severe diarrhoea every year and many die from dehydration. Giving fluids by mouth (using an oral rehydration solution (ORS)) has been shown to save children's lives, but it has no effect on the length of time the children suffer with diarrhoea. Zinc supplementation could help reduce the duration and the severity of diarrhoea, and therefore have an additional benefit over ORS in reducing children mortality.

### What is oral zinc and how may it shorten the duration and severity of diarrhoea

Zinc is usually given as zinc sulphate, zinc acetate, or zinc gluconate, which are all water-soluble compounds. The World Health Organization (WHO) and the United Nations Children's Fund (UNICEF) recommend 10 mg to 20 mg of zinc per day for children with diarrhoea. There are several mechanism of action of zinc on acute diarrhoea, some of which are specific to the gastrointestinal system: zinc restores mucosal barrier integrity and enterocyte brush-border enzyme activity, it promotes the production of antibodies and circulating lymphocytes against intestinal pathogens, and has a direct effect on ion channels, acting as a potassium channel blocker of adenosine 3-5-cyclic monophosphate-mediated chlorine secretion. Cochrane researchers examined the evidence available up to 30 September 2016.

### What the evidence in the review suggests

Thirty-three trials that included 10,841 children met the inclusion criteria of this review.

Among children with acute diarrhoea, we don't know if treating children with zinc has an effect on death or number of children hospitalized (*very low certainty evidence*). In children older than six months, zinc supplementation may shorten the average duration of diarrhoea by around half a day (*low certainty evidence*), and probably reduces the number of children whose diarrhoea persists until day seven (*moderate certainty evidence*). In children with signs of malnutrition the effect appears greater, reducing the duration of diarrhoea by around a day (*high certainty evidence*). Conversely, in children younger than six months, the available evidence suggests zinc supplementation may have no effect on the mean duration of diarrhoea (*low certainty evidence*), or the number of children who still have diarrhoea on day seven

(*low certainty evidence*). Zinc supplementation increased the risk of vomiting in both age groups (*moderate certainty evidence*). No other adverse effects were reported.

Among children with persistent diarrhoea, zinc supplementation probably shortens the average duration of diarrhoea by around 16 hours (*moderate certainty*) but it probably increases the risk of vomiting (*moderate certainty evidence*).

In areas where the prevalence of zinc deficiency or the prevalence of malnutrition is high, zinc may be of benefit in children aged six months or more. The current evidence does not support the use of zinc supplementation in children less six months of age, in well-nourished children, and in settings where children are at low risk of zinc deficiency.

## SUMMARY OF FINDINGS

### Summary of findings for the main comparison. 'Summary of findings' table 1

**Zinc compared to placebo for children more than 6 months of age with acute diarrhoea**

**Patient or population:** children with acute diarrhoea
**Settings:** all countries
**Intervention:** zinc
**Comparison:** placebo

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | Number of participants (trials) | Certainty of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | | |
| | Placebo | Zinc | | | | |
| **Duration of diarrhoea** | **All trials** | | **MD −11.46** (−19.72 to −3.19) | 2581 (9 trials) | ⊕⊕⊖⊖ **low** [1,2] | No comment |
| | The mean duration of diarrhoea among placebo ranged from **31.2 to 169.5 hours** | The mean duration of diarrhoea among zinc ranged from **28.8 to 147.6 hours** | | | | |
| | **Trials limited to children with signs of malnutrition** | | **MD −26.39** (−36.54 to −16.23) | 419 (5 trials) | ⊕⊕⊕⊕ **high** | No comment |
| | The mean duration of diarrhoea among placebo ranged from **103.4 to 146.4 hours** | The mean duration of diarrhoea among zinc ranged from **70.4 to 120.0 hours** | | | | |
| **Diarrhoea on day 7** | **128 per 1000** | **93 per 1000** (78 to 113) | **RR 0.73** (0.61 to 0.88) | 3865 (6 trials) | ⊕⊕⊕⊖ **moderate** [3] | No comment |
| **Number of children hospitalized** (community trials only) | — | — | — | 276 (1 trial) | ⊕⊖⊖⊖ **very low** [4,5] | No events |
| **Death** | **5 per 1000** | **1 per 1000** (0 to 11) | **RR 0.29** (0.04 to 2.20) | 1134 (4 trials) | ⊕⊖⊖⊖ **very low** [6,7] | Few events |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Adverse events (vomiting)** | **119 per 1000** | **188 per 1000** (173 to 242) | **RR 1.57** (1.32 to 1.86) | 2605 (6 trials) | ⊕⊕⊕⊖ **moderate** [8] | No comment |

*The basis for the **assumed risk** (for example, the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
Abbreviations: **CI:** confidence interval; **MD:** mean difference; **RR:** risk ratio.

GRADE Working Group grades of evidence
**High certainty:** further research is very unlikely to change our confidence in the estimate of effect.
**Moderate certainty:** further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low certainty:** 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 certainty:** we are very uncertain about the estimate.

[1]Downgraded by 1 for indirectness: all trials were conducted in Asia.
[2]Downgraded by 1 for serious imprecision: wide CI.
[3]Downgraded by 1 for serious indirectness: these trials were all conducted in Asia in countries at high risk of zinc deficiency.
[4]Downgraded by 1 for serious indirectness: only one small community trial reported on number of children hospitalized.
[5]Downgraded by 2 for very serious imprecision: no hospitalizations occurred in this trial.
[6]Downgraded by 1 for serious indirectness: the included trials were mostly conducted in hospitals and are therefore likely to underestimate death at the community level.
[7]Downgraded by 2 for very serious imprecision: only three deaths occurred in these two trials, consequently the trials are significantly underpowered to detect or exclude an effect.
[8]Downgraded by 1 for serious risk of bias: two trials reported no details on sequence generation, allocation concealment, blinding, and incomplete outcome data, while one did not give any details regarding allocation concealment.

## Summary of findings 2. 'Summary of findings' table 2

**Zinc compared to placebo for children aged less than 6 months with acute diarrhoea**

**Patient or population:** children aged less than 6 months with acute diarrhoea
**Settings:** all countries
**Intervention:** zinc
**Comparison:** placebo

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | Number of participants (trials) | Certainty of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | | |
| | Placebo | Zinc | | | | |
| **Duration of diarrhoea** | The mean duration of diarrhoea among place- | The mean duration of diarrhoea among zinc ranged from **105.6 to 133.2 hours** | **MD 5.23** (−4.00 to 14.45) | 1334 (2 trials) | ⊕⊕⊖⊖ **low** [1,2] | No comment |

| | | | | | | |
|---|---|---|---|---|---|---|
| | bo ranged from **97.9 to 133.2 hours** | | | | | |
| **Diarrhoea on day 7** | **203 per 1000** | **252 per 1000** (201 to 313) | **RR 1.24** (0.99 to 1.54) | 1074 (1 trial) | ⊕⊕⊖⊖ **low** [3,4] | No comment |
| **Number of children hospitalized** (community trials only) | — | — | — | 1074 (1 trial) | ⊕⊖⊖⊖ **very low** [5,6] | No events |
| **Death** | **2 per 1000** | **2 per 1000** (0 to 32) | **RR 1.00** (0.06 to 15.89) | 1334 (2 trials) | ⊕⊖⊖⊖ **very low** [7,8] | Only 1 event in each treatment group |
| **Adverse events (vomiting)** | **64 per 1000** | **104 per 1000** (67 to 143) | **RR 1.54** (1.05 to 2.24) | 1334 (2 trials) | ⊕⊕⊕⊖ **moderate** [9] | No comment |

*The basis for the **assumed risk** (for example, the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
Abbreviations: **CI:** confidence interval; **MD:** mean difference; **RR:** risk ratio.

GRADE Working Group grades of evidence
**High certainty:** further research is very unlikely to change our confidence in the estimate of effect.
**Moderate certainty:** further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low certainty:** 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 certainty:** we are very uncertain about the estimate.

[1]Downgraded by 1 for inconsistency: only two trials were done and both had inconsistent results.
[2]Downgraded by 1 for imprecision: large CI.
[3]Downgraded by 1 for inconsistency: different results in the subgroups.
[4]Downgraded by 1 for indirectness: only one trial (although multi-country) as it is not possible to generalize these results.
[5]Downgraded by 2 for imprecision: only one hospitalization was recorded in 1074 participants. Much larger trials would be necessary to prove or exclude an effect.
[6]Downgraded by 1 for imprecision: the result is not statistically significant.
[7]Downgraded by 1 for indirectness: most of this data is from Asia and may not be applicable elsewhere.
[8]Downgraded by 2 for imprecision: in these two trials deaths were very rare, and consequently these trials are significantly underpowered to detect or exclude an effect on mortality.
[9]Downgraded by 1 under consistency because only two trials were done.

### Summary of findings 3. 'Summary of findings' table 3

| **Zinc compared to placebo for children with persistent diarrhoea** |
|---|

**Patient or population:** children with persistent diarrhoea
**Settings:** all countries
**Intervention:** zinc
**Comparison:** placebo

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | Number of participants (trials) | Certainty of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | | |
| | Placebo | Zinc | | | | |
| **Duration of diarrhoea** | The mean duration of diarrhoea among placebo ranged from **84 to 132** | The mean duration of diarrhoea among zinc ranged from **69.4 to 122.4 hours** | **MD −15.84** (−25.43 to −6.24) | 529 (5 trials) | ⊕⊕⊕⊖ **moderate** [1] | No comment |
| **Diarrhoea on day 7** | **191 per 1000** | **99 per 1000** (52 to 195) | **RR 0.52** (0.27 to 1.02) | 221 (2 trials) | ⊕⊕⊖⊖ **low** [1,2] | No comment |
| **Hospitalization** | — | — | — | 275 (1 trial) | ⊕⊖⊖⊖ **very low** [1,3] | No events |
| **Death** | — | — | — | 402 (3 trials) | ⊕⊖⊖⊖ **very low** [1,4] | No events |
| **Adverse events (vomiting)** | **8 per 1000** | **16 per 1000** (3 to 85) | **RR 1.97** (0.37 to 10.59) | 505 (4 trials) | ⊕⊖⊖⊖ **very low** [1,5] | No comment |

*The basis for the **assumed risk** (for example, the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
**Abbreviations: CI:** confidence interval; **MD:** mean difference; **RR:** risk ratio.

GRADE Working Group grades of evidence
**High certainty:** further research is very unlikely to change our confidence in the estimate of effect.
**Moderate certainty:** further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low certainty:** 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 certainty:** we are very uncertain about the estimate.

[1]Downgraded by 1 for indirectness: most of this data is from Asia and may not be applicable elsewhere.
[2]Downgraded by 1 for imprecision: the result does not reach statistically significance, and the number of recorded events is low.
[3]Downgraded by 2 for imprecision: no hospitalizations were recorded. Much larger trials would be necessary to prove or exclude an effect.
[4]Downgraded by 2 for imprecision: in these three trials deaths were very rare, and consequently these trials are significantly underpowered to detect or exclude an effect on mortality.

[5]Downgraded by 2 for imprecision: vomiting was very uncommon in these trials.

# BACKGROUND

## Description of the condition

Despite improving trends in mortality rates, diarrhoea still causes nearly 10% of all deaths in children under five years of age and accounts for about 500,000 child deaths in developing countries every year (Liu 2015a; Liu 2015b). The incidence of diarrhoea decreased from 3.4 episodes per child-year in 1990 to 2.9 episodes per child-year in 2010. However, it still remains one of the most common reasons of hospital admission, with an estimated 1731 million episodes of childhood diarrhoea reported in 2011 of which 2% progressed to severe disease (Das 2014). Diarrhoea is also an important cause of malnutrition, particularly when it is prolonged (Brown 2003).

Zinc deficiency is mainly due to inadequate dietary intake and is estimated to be common in many countries, especially in children (IZiNCG 2004; Wagstaff 2004; Hess 2009). According to recent estimates, 17.3% of the world's population is currently at risk of inadequate zinc intake (Wessells 2012). The regional estimated prevalence of inadequate zinc intake ranges from 7.5% in high-income regions to 30% in South Asia (Wessells 2012). Foods more rich in zinc are 'expensive foods', such as meat and fish (IZiNCG 2004). Zinc is also present in nuts, seeds, legumes, and wholegrain cereal, but the high phytate content of these foods interferes with its absorption (IZiNCG 2004). Zinc cannot be stored in the body, and nearly 50% of zinc excretion takes place through the gastrointestinal tract and is increased during episodes of diarrhoea (IZiNCG 2004). Zinc requirement varies with age and is highest in children due to their rapid rates of growth. As a consequence, young children who are regularly exposed to gastrointestinal pathogens and have diets low in animal products and high in phytate-rich foods are most at risk of zinc deficiency (IZiNCG 2004).

## Description of the intervention

Treatment of diarrhoea with oral rehydration solution (ORS) reduces mortality due to dehydration (Liu 2015a; Liu 2015b). In addition to ORS, the World Health Organization (WHO) and United Nations Children's Fund (UNICEF) recommend for children under five years of age with diarrhoea a supplementation with 10 to 20 mg of zinc per day, at least twice the recommended daily allowance (WHO/UNICEF 2004). Zinc is usually given as zinc sulphate, zinc acetate, or zinc gluconate, which are all water-soluble compounds (IZiNCG 2004).

## How the intervention might work

There are several different mechanism of action of zinc on acute diarrhoea (Berni Canani 2010; Krebs 2014). Zinc influences the activity of over 300 enzymes, some of which are responsible for DNA replication and transcription (IZiNCG 2004). Zinc promotes immunity, skin and mucosal resistance to infection, growth, and development of the nervous system (MacDonald 2000; Prasad 2008; Hess 2009). It is also an important antioxidant and preserves cellular membrane integrity (O'Dell 2000; Powell 2000; Prasad 2014). At the level of gastrointestinal system, zinc restores mucosal barrier integrity and enterocyte brush-border enzyme activity (Roy 1992; Shankar 1998), it promotes the production of antibodies and circulating lymphocytes against intestinal pathogens (Sazawal 1997b; Albert 2003; Raqib 2004), and has a direct effect on ion channels, acting as a potassium channel blocker of adenosine 3-5-cyclic monophosphate-mediated chlorine secretion (Hoque 2005; Hoque 2009).

Zinc supplementation may have different effects according to the level of zinc deficiency in the country and in the individual. It is important to verify whether zinc supplementation is effective in countries with high, or even medium or low risk of zinc deficiency (IZiNCG 2004). Despite an accurate estimation of the prevalence of zinc deficiency in populations is hampered by the lack of reliable indicators or biomarkers (Wieringa 2015), indirect indicators such as the prevalence of stunting or anaemia, and the absorbable zinc content of the national food supply are currently used at to estimate the prevalence of zinc deficiency in populations (IZiNCG 2004). Zinc requirements are higher in malnourished children because nutritional zinc deficiency is considered more severe in these children (IZiNCG 2004). However, infants have lower requirements (IZiNCG 2004), as healthy normal birthweight infants have adequate zinc levels at birth from maternal sources even if maternal stores are suboptimal (Iqbal 2001). Infants may also be able to mobilize hepatic stores accumulated during gestation (Zlotkin 1988), and are less likely to have had a zinc-depleting illness. Breastfeeding will provide zinc supplementation and protective immune factors against infections (Krebs 1999).

Zinc can cause vomiting because of its metallic taste (Fontaine 2001). In high doses, zinc can also cause epigastric pain, lethargy, and fatigue (IZiNCG 2004). One small study suggested a possible increase in mortality in malnourished children supplemented with 6 mg/kg/day of zinc compared to those supplemented with 1.5 mg/kg/day (Doherty 1998). Copper deficiency with zinc supplementation can occur although usually only when zinc is consumed in very high doses (100 to 300 mg/day for adults) over a long period of time (IZiNCG 2004), and malnourished children are at particularly high risk of this due to lower basal copper levels.

Iron and zinc deficiencies often co-exist. These two compounds may compete for the same absorptive pathways, and iron may interfere with zinc utilization (Gunshin 1997; Kordas 2004). A review of combined supplementation showed that giving zinc with iron resulted in a lower increase in iron levels compared to giving iron alone; iron supplementation alone had no effect on zinc status (Fischer Walker 2005). A trial that assessed combined supplementation on diarrhoea and malaria morbidity showed that zinc combined with iron reduced zinc's protective effect against diarrhoea (Richard 2006). Several trials have also reported a negative interaction of the combined supplementation on physical growth and development (Rosado 1997; Dijkhuizen 2001; Zlotkin 2003; Lind 2004; Bhandari 2007). Some protocols suggest supplementing malnourished children also with copper because these children are also prone to copper deficiency (Beshgetoor 1998).

## Why it is important to do this review

Previous meta-analysis and systematic reviews have indicated that zinc supplementation in diarrhoea is effective (Bhutta 2000b; Lukacik 2008; Patro 2008; Haider 2009; Liberato 2015; Zou 2015; Lazzerini 2016). This Cochrane Review will have an up-to-date extensive search for trials, will explore more outcome measures of interest, and will report on more possible sources of heterogeneity. This Cochrane Review updates the last published version of this review (Lazzerini 2013).

## OBJECTIVES

To evaluate oral zinc supplementation for treating children with acute or persistent diarrhoea.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

Randomized controlled trials (RCTs).

#### Types of participants

Children between one month and five years of age with acute or persistent diarrhoea, including dysentery.

We excluded trials of infants below one month of age and studies that exclusively enrolled children with particular conditions, such preterm or low birthweight infants and children with HIV.

Acute diarrhoea is usually defined as three or more loose stools in a 24-hour period. Persistent diarrhoea is defined as diarrhoea lasting more than 14 days. Dysentery is a diarrhoeal illness in which blood is observed in the stool. The final day of diarrhoea is usually defined as the last day meeting the above definition followed by 48 hours without diarrhoea.

#### Types of interventions

##### *Intervention*

Oral zinc supplementation of any zinc salt at doses of 5 mg/day or more for any duration.

##### *Control*

Placebo.

Concurrent supplementation of other minerals and vitamins are eligible only if administered to both the intervention and control groups.

We excluded ORS plus zinc and food fortification interventions (such as milk fortification) as the amount of ORS/food consumed, and hence the zinc intake, would be less certain.

#### Types of outcome measures

##### *Primary outcomes*

###### Measures of diarrhoea duration

- Diarrhoea duration.
- Diarrhoea at 3, 5, and 7 days after starting the intervention.

###### Measures of diarrhoea severity

- Stool frequency.
- Stool output.

##### *Secondary outcomes*

- Hospitalization (number of children hospitalized).
- Death (from any cause and diarrhoea specific).

###### Adverse events

- Serious adverse events (life-threatening or requiring hospitalization).
- Any adverse event that results in the discontinuation of treatment.
- Other adverse events, such as vomiting and reduced copper levels.

### Search methods for identification of studies

We attempted to identify all relevant trials regardless of language or publication status (published, unpublished, in press, and in progress).

#### Electronic searches

We searched the following databases using the search terms and strategy described in Table 1: the Cochrane Infectious Diseases Group Specialized Register (30 September 2016); Cochrane Central Register of Controlled Trials (CENTRAL), published in the Cochrane Library (2016, Issue 9); MEDLINE (1966 to 30 September 2016); Embase (1974 to 30 September 2016); LILACS (1982 to 30 September 2016); CINAHL (1982 to 30 September 2016), the *meta*Register of Current Controlled Trials (*m*RCT; 30 September 2016), ClinicalTrials.gov (30 September 2016), and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (30 September 2016).

#### Searching other resources

##### *Researchers and organizations*

For unpublished and ongoing trials, we contacted individual researchers working in the field, including researchers at the WHO.

##### *Reference lists*

We checked the reference lists of all studies identified by the above methods.

### Data collection and analysis

#### Selection of studies

Both review authors screened all trials identified by the search strategy by title/abstract, and we retrieved the full-text articles of all potentially relevant trials. Both review authors independently applied the inclusion criteria to the full-text reports using a pilot-tested data extraction form, and scrutinized publications to ensure we included each trial only once. We contacted the trial authors for clarification if necessary, and resolved any disagreements through discussion and consensus after referring to the protocol; we recorded and reported their solutions. We listed studies excluded after full-text assessment and their reasons for exclusion in a 'Characteristics of excluded studies' table. We constructed a PRISMA flow diagram to illustrate the study selection process.

#### Data extraction and management

Both review authors independently extracted data using a pilot-tested data extraction form and entered the data into Review Manager 5 (RevMan 5) (Review Manager 5). When data were missing or unclear, we contacted the trial authors for clarification. For dichotomous outcomes, we recorded the number of participants that experienced the event and the number of participants assessed in each group. For continuous outcomes, we extracted the

arithmetic mean values, standard deviation (SD) values, and the number of participants assessed in each group. If a trial reported continuous data using geometric means, we extracted the SD values on the log scale; we extracted median and range values and reported these in a table.

### Assessment of risk of bias in included studies

Both review authors independently assessed the risk of bias for each trial using the Cochrane 'Risk of bias' assessment tool (Higgins 2011). We categorized our judgments as either at low, high, or unclear risk of bias, and we used this information to guide our interpretation of the results. Where the judgement for efficacy trials was 'unclear' we attempted to contact the trial authors for clarification and we resolved any differences of opinion through discussion. If data were missing or unclear, we contacted the trial authors for further information.

### Measures of treatment effect

For dichotomous data, we reported outcome measures using the risk ratio (RR). For continuous data summarized by arithmetic means and SDs, we used the mean difference (MD) values to combine the results in a meta-analysis. We presented continuous data summarized using other summary statistics that we could not combine in a meta-analysis in a table. We calculated the geometric mean ratios and transformed them in the log scale for analysis, and presented them on the natural scale

### Unit of analysis issues

There were no cluster RCTs.

### Dealing with missing data

We planned to conduct an analysis so that we included all individuals with a recorded outcome in the analysis. If there was missing information or we needed more details on reported measures, we sought further clarification from the trial authors. To take into account the participants for whom there was no outcome data available, we also conducted an intention-to-treat (ITT) analysis for worst-case/best-case scenarios.

### Assessment of heterogeneity

We assessed heterogeneity between trials by visually inspecting the forest plot, using the $Chi^2$ test for heterogeneity with a 5% level of statistical significance, and the $I^2$ statistic with a value of 50% representing a moderate level of heterogeneity. If we detected significant heterogeneity but considered it was appropriate to pool data, we used the random-effects model.

### Assessment of reporting biases

We constructed funnel plots to look for evidence of publication bias for the outcome duration of diarrhoea and diarrhoea at day 7.

### Data synthesis

We analysed the data using RevMan 5 (Review Manager 5). We presented all results with 95% confidence intervals (CIs).

#### *Quality of the evidence*

We assessed the certainty of the evidence using the GRADE approach (GRADEpro GDT 2014). We used GRADEpro Guideline Development Tool (GDT) software to construct the 'Summary of findings' tables (GRADEpro GDT 2014). The GRADE system considers 'certainty' to be a judgment of the extent to which we can be confident that the estimates of effect are correct. The level of 'certainty' is judged on a four-point scale. Evidence from RCTs is initially graded as high and downgraded by either 1, 2, or 3 levels after full consideration of: any limitations in the design of the studies, the directness (or applicability) of the evidence, the consistency and precision of the results, and the possibility of publication bias.

We have displayed the estimates of effect, and the GRADE assessments of our confidence in these estimates in 'Summary of findings tables' for the main comparisons. Where we have downgraded the evidence our reasons for doing so are displayed in footnotes.

When making conclusions about the relative effects of the interventions we used language that reflected the GRADE assessments and our confidence in the estimates, that is if the evidence was of high certainty we said "zinc reduces"; if it was of moderate certainty we stated "zinc probably reduces"; it was of low certainty we used "zinc may reduce"; and where the evidence was of very low certainty we did not draw conclusions.

### Subgroup analysis and investigation of heterogeneity

We stratified the analyses for acute diarrhoea or persistent diarrhoea as these are different conditions. We also stratified the results by age (children aged less than and greater than six months) because we observed a clear difference in zinc effect according to the age of children enrolled and significant heterogeneity if we pooled all the trials together. We explored the following potential sources of heterogeneity using subgroup analyses: nutritional status (malnourished children versus well-nourished plus moderate malnourished); geographical region (by continent and by high versus medium estimated risk of zinc deficiency as defined by the International Zinc Nutrition Consultative Group (IZiNCG) (IZiNCG 2004)); zinc dose (less than versus greater than 20 mg/day); zinc salt (zinc sulphate versus zinc acetate versus zinc gluconate versus other type); concomitant copper or iron supplementation; and trial setting (hospital versus community trials). We also explored the effect of sex, although we did not specify this in the original Cochrane Protocol (Lazzerini 2005).

### Sensitivity analysis

We conducted a sensitivity analysis in which we limited the analyses to those trials with adequate allocation concealment, blinding (excluded those trials classified as unclear), and those that included an adequate number of randomized participants in the analysis (excluded those trials classified as inadequate or unclear). To take into account the participants for whom no outcome data were available, we also conducted an ITT analysis for worst-case/best-case scenarios.

## RESULTS

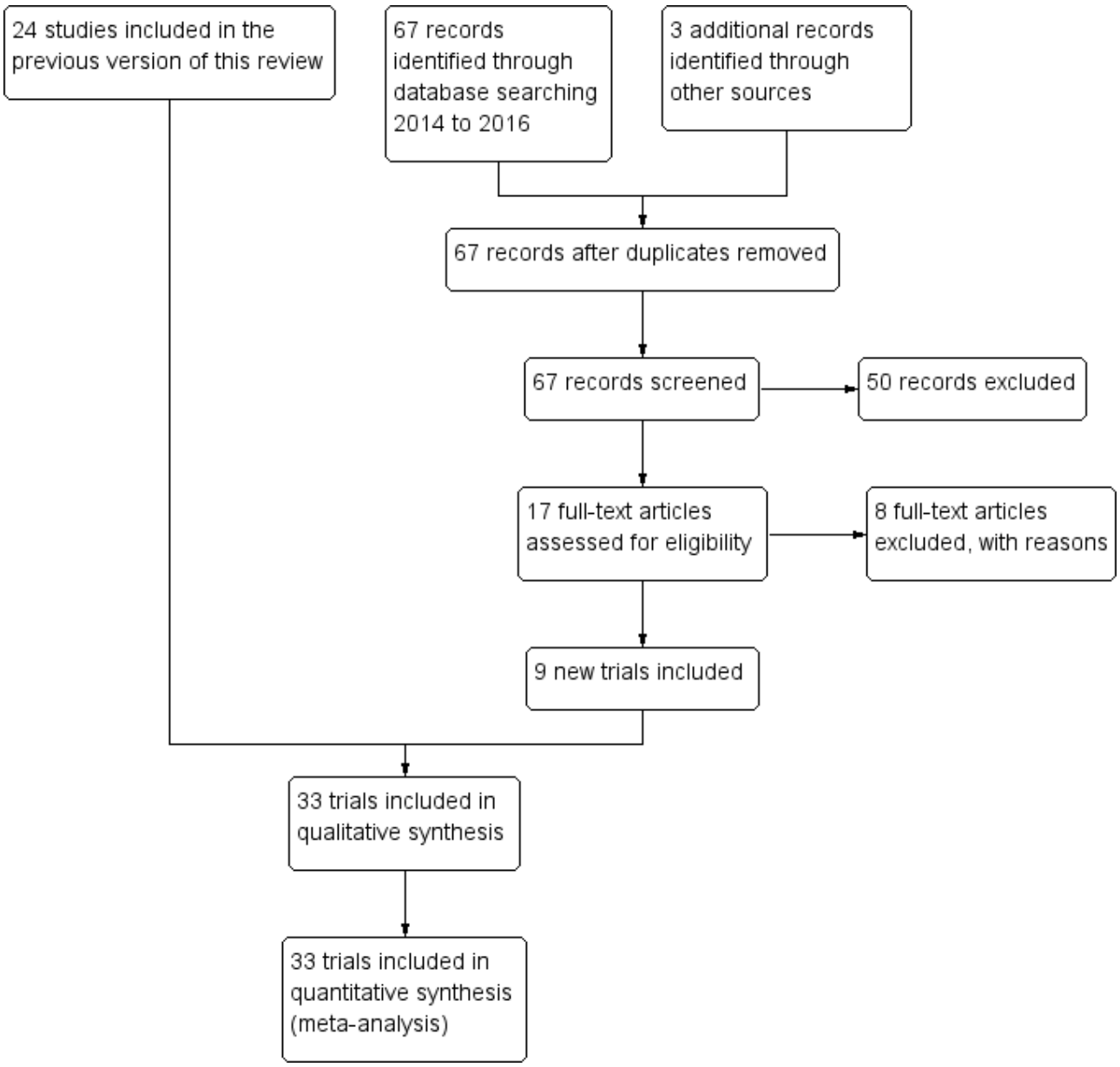
## Description of studies

### Results of the search

In the previous version of this review, Lazzerini 2013, 24 trials met the inclusion criteria. We updated the literature search to 30 September 2016 and identified 68 records after removal of duplicates. After screening the articles by title and abstract, we

excluded 48 articles and assessed 20 articles for eligibility. Nine new trials met the inclusion criteria of the review and thus we included 33 trials (10,841 children) in this review update. We have presented a PRISMA study flow diagram in Figure 1 and we have reported the trial selection process in Table 2.

**Figure 1. Study flow diagram.**




### Included studies

Thirty-three trials in total met the inclusion criteria of this review. We have listed the details of the included trials in the 'Characteristics of included studies' table. Three included trials presented results divided in two or more subgroups, and specifically: one trial presented two intervention groups of zinc 20 mg and zinc 5 mg, and one control group (Brooks 2005a); one trial presented data for three different study sites (Fischer Walker 2006); one trial presented the results as children with low and normal zinc serum levels (Polat 2003). For these three trials there was no way to combine mean values and standard deviation (SD) values, and thus we entered the data separately as Brooks 2005a (20 mg), Brooks 2005a (5 mg), Fischer Walker 2006 ETH, Fischer Walker 2006 IND, Fischer Walker 2006 PAK, Polat 2003 (low Zn), and Polat 2003 (normal Zn).

#### *Type of diarrhoea*

Most trials included children with acute diarrhoea only. Of these, 13 used the definition for acute diarrhoea that we used in this Cochrane Review (Faruque 1999; Dutta 2000; Strand 2002; Al-Sonboli 2003; Polat 2003; Bhatnagar 2004a; Brooks 2005a; Fischer Walker 2006; Boran 2006; Dutta 2011; Crisinel 2015; Passariello 2015; Tran 2015), two trials defined diarrhoea as the presence of either four (Sazawal 1995), or five (Bahl 2002), unformed stools in 24

hours, one trial defined diarrhoea as acute onset of change in stool frequency and consistency (Karamyyar 2013), one shigellosis trial included participants with bloody mucoid diarrhoea (dysentery) or febrile diarrhoea less than five days' duration (Roy 2008a).

Three trials enrolled only children with rotavirus infection (Dalgic 2011; Jin 2013; Jiang 2016).

Eight trials did not report the definition of acute diarrhoea (Sachdev 1988; Roy 1997; Larson 2005;Fajolu 2008; Shimelis 2008; Patel 2009; Patro 2010; Jiang 2016).

Five trials were on children with persistent diarrhoea (Sachdev 1990; Roy 1998; Bhutta 1999; Penny 1999; Khatun 2001).

#### *Age*

Two trials only enrolled children under six months of age (Brooks 2005a; Fischer Walker 2006). Seventeen trials only enrolled children over six months of age (Sachdev 1988; Sachdev 1990; Sazawal 1995; Bhutta 1999; Faruque 1999; Penny 1999; Khatun 2001; Bahl 2002; Strand 2002; Boran 2006; Roy 2008a; Fajolu 2008; Patel 2009; Dutta 2011; Karamyyar 2013; Passariello 2015; Tran 2015). Fourteen trials included children of different ages greater than one month (Roy 1997; Roy 1998; Dutta 2000; Al-Sonboli 2003; Polat 2003; Bhatnagar 2004a; Larson 2005; Shimelis 2008; Patro 2010; Dalgic 2011; Jin 2013; Crisinel 2015; Patel 2015; Jiang 2016).

#### *Nutritional status*

Eight trials only enrolled malnourished children (Roy 1997; Roy 1998; Bhutta 1999; Dutta 2000; Khatun 2001; Polat 2003; Roy 2008a; Passariello 2015). Two trials included well-nourished children (Boran 2006; Patro 2010), and one trial enrolled children regardless of their nutritional status (Larson 2005), while the remaining 20 trials enrolled children who were well nourished or with mild or moderate malnutrition. No trials included only severe malnourished children. Two trials did not mention the nutritional status of children (Jin 2013; Jiang 2016). There was some variability between trials regarding the definition of malnutrition (most used 'weight/age'; only some used 'weight/height'); therefore we were unable to follow the definition of malnutrition proposed in our protocol (Lazzerini 2005).

#### *Sex*

Four trials only included males (Dutta 2000; Bhatnagar 2004a; Brooks 2005a; Dutta 2011), while the remaining 29 trials enrolled children of both sexes.

#### *Geographical region*

Most included trials were conducted in Asia. Only three trials were conducted in Europe (Patro 2010; Crisinel 2015; Passariello 2015), two in South America (Al-Sonboli 2003; Penny 1999), two in Africa (Fajolu 2008; Shimelis 2008), one multicentre trial in Asia and Africa (Fischer Walker 2006), and one trial in Australia (Tran 2015). Thus, participants were from Bangladesh (Roy 1997; Roy 1998; Faruque 1999; Khatun 2001; Brooks 2005a; Larson 2005; Roy 2008a), India (Sachdev 1988; Sachdev 1990; Sazawal 1995; Dutta 2000; Bahl 2002; Bhatnagar 2004a; Fischer Walker 2006 IND; Patel 2009; Patel 2015), Pakistan (Bhutta 1999; Fischer Walker 2006 PAK), Nepal (Strand 2002), China (Jin 2013; Jiang 2016), Turkey (Polat 2003; Boran 2006; Dalgic 2011), Brazil (Al-Sonboli 2003), Peru (Penny 1999), Ethiopia (Fischer Walker 2006 ETH; Shimelis 2008), Nigeria (Fajolu 2008), Poland (Patro 2010), Italy (Passariello 2015), Switzerland (Crisinel 2015), and Australia (Tran 2015).

#### *Risk of zinc deficiency*

Most trials were conducted in countries ranked as at high risk of zinc deficiency (IZiNCG 2004). Nine trials were conducted in countries at medium risk: Nepal (Strand 2002); Turkey (Polat 2003; Boran 2006, Dalgic 2011); Brazil (Al-Sonboli 2003), China (Jin 2013), Iran (Karamyyar 2013), Nigeria (Fajolu 2008), and Ethiopia (Shimelis 2008). Four trials were conducted in countries where zinc deficiency is considered rare: Poland (Patro 2010), Italy (Passariello 2015), Switzerland (Crisinel 2015), and Australia (Tran 2015).

#### *Zinc dose*

The most frequent zinc dose was 20 mg/day. Only three trials administered higher zinc doses: 40 mg/day (Dutta 2000); 22 or 45 mg/day (Al-Sonboli 2003); 20 and 40 mg respectively in children under and above six months of age (Passariello 2015). Two trials, of which one was of children aged less than six months only, gave 10 mg/day zinc (Fischer Walker 2006; Roy 2008a).

Seven trials used different dosages based on the age of children (under and above six months of age): 5 mg and 10 mg (Boran 2006), 10 mg and 20 mg (Fajolu 2008; Patro 2010; Crisinel 2015; Jiang 2016 ), 20 and 40 mg (Passariello 2015;); one trial used zinc at two different dosages (5 mg and 20 mg) in children aged less than six months (Brooks 2005a),

Seven trials used different doses depending on age (zinc < 20 mg in infants and ≥ 20 mg in older children), but they did not report results separately for each treatment group (Faruque 1999; Bahl 2002; Strand 2002; Bhatnagar 2004a; Boran 2006; Crisinel 2015; Passariello 2015). We classified these trials as 'not assignable' and could not include them in the sensitivity analysis for zinc dose.

Three trials reported a per kilo dose: 1 mg/kg/day (Karamyyar 2013); 2 mg/kg/day (Bhutta 1999); 3 mg/kg/day (Patel 2009). We were unable to include these trials in the subgroup analyses.

#### *Type of zinc salt*

Eight trials used zinc acetate (Roy 1997; Roy 1998; Faruque 1999; Khatun 2001; Strand 2002; Brooks 2005a; Roy 2008a; Dalgic 2011), five used zinc gluconate (Sazawal 1995; Penny 1999; Bahl 2002; Jin 2013; Jiang 2016), and three did not specify (Shimelis 2008; Dutta 2011; Passariello 2015), while all the remaining trials used zinc sulphate.

#### *Concomitant copper or iron supplementation*

One trial compared zinc alone versus zinc and copper versus placebo (Patel 2009).

#### *Study setting*

Most trials were conducted in hospitals, with the exception of six community-based trials (Penny 1999; Bahl 2002; Strand 2002; Fischer Walker 2006; Boran 2006; Passariello 2015), and one trial was held in both hospital and community settings (Larson 2005).

***Treatment regimen***

**Treatment duration**

About half of trials administered zinc for two weeks. Of the remaining trials, one gave zinc for a total of four days (Tran 2015), three gave zinc for seven days after recovery (Bahl 2002; Strand 2002; Polat 2003), four gave zinc until recovery (Al-Sonboli 2003; Brooks 2005a; Karamyyar 2013; Passariello 2015), one trial gave zinc for seven days (Khatun 2001), and three trials gave zinc for 10 days (Patro 2010; Crisinel 2015; Jiang 2016). Five trials were unclear in respect of duration of zinc supplementation (Sachdev 1988; Sachdev 1990; Sazawal 1995; Dutta 2000; Dalgic 2011). One trial on adverse events administered only one dose of zinc (Larson 2005).

**Formulation**

Most included trials administered zinc as syrup. Seven used dispersible tablets (Al-Sonboli 2003; Larson 2005; Fischer Walker 2006; Shimelis 2008; Jin 2013; Crisinel 2015: Jiang 2016), four used powder (Sachdev 1988; Sachdev 1990; Penny 1999; Dalgic 2011), two mixed it with ORS (Passariello 2015; Tran 2015), and one did not specify (Fajolu 2008; Patel 2015).

**Dose frequency**

Zinc was administered once a day in most of the included trials. It was administered twice a day in five trials (Sachdev 1988; Sachdev 1990; Khatun 2001; Roy 2008a; Patro 2010), three times a day in six trials (Roy 1997; Roy 1998; Dutta 2000; Polat 2003; Bhatnagar 2004a), and together with ORS depending on stool frequency in two trials (Passariello 2015; Tran 2015). One trial administered zinc twice a day to infants, and a single dose to children over six months (Dalgic 2011). Three trials did not specify the dose frequency (Fajolu 2008; Patel 2009, Patel 2015).

**Additional treatment**

Most trials administered zinc alone. Seven trials used zinc and multivitamin, which did not contain iron (Sazawal 1995; Roy 1997; Roy 1998; Bhutta 1999; Khatun 2001; Bhatnagar 2004a; Roy 2008a). One trial used zinc and vitamin A (Faruque 1999). One trial used concomitant copper (Patel 2009).

**Excluded studies**

For this review update we excluded 11 studies after full-text assessment. We have provided the total results of the study selection (that is, for the previous versions of this review plus this update) in Table 2, and listed the reasons for exclusion of studies after full-text assessment in the 'Characteristics of excluded studies' table.

## Risk of bias in included studies

See Figure 2 and Figure 3 for the risk of bias in the included trials.

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

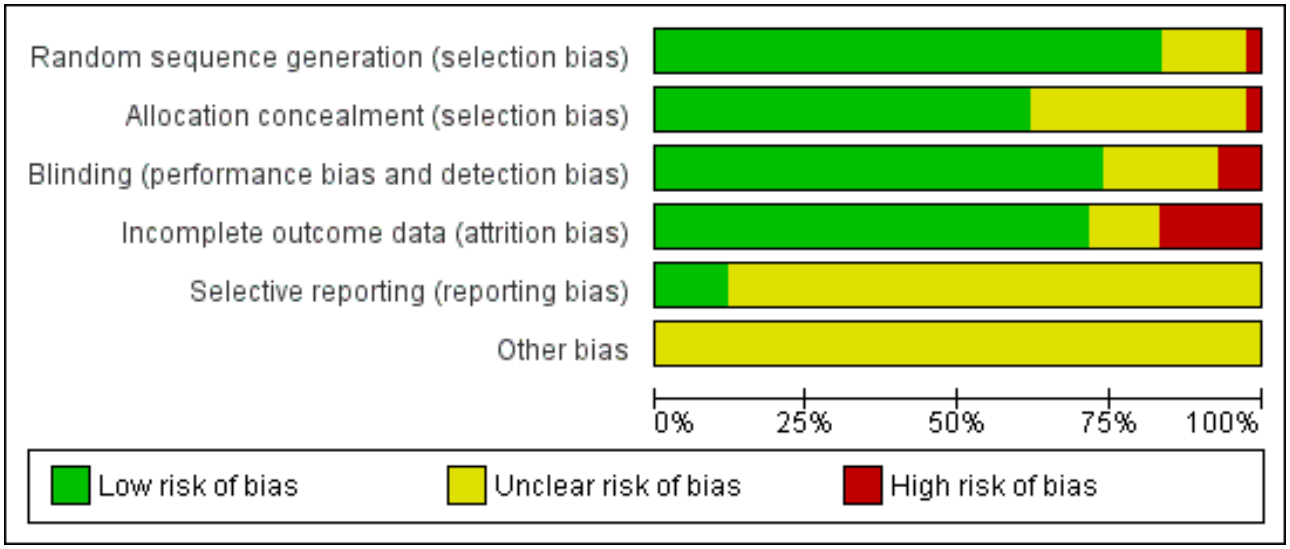


**Figure 3. 'Risk of bias' summary: review authors' judgements about each 'Risk of bias' item for each included trial.**

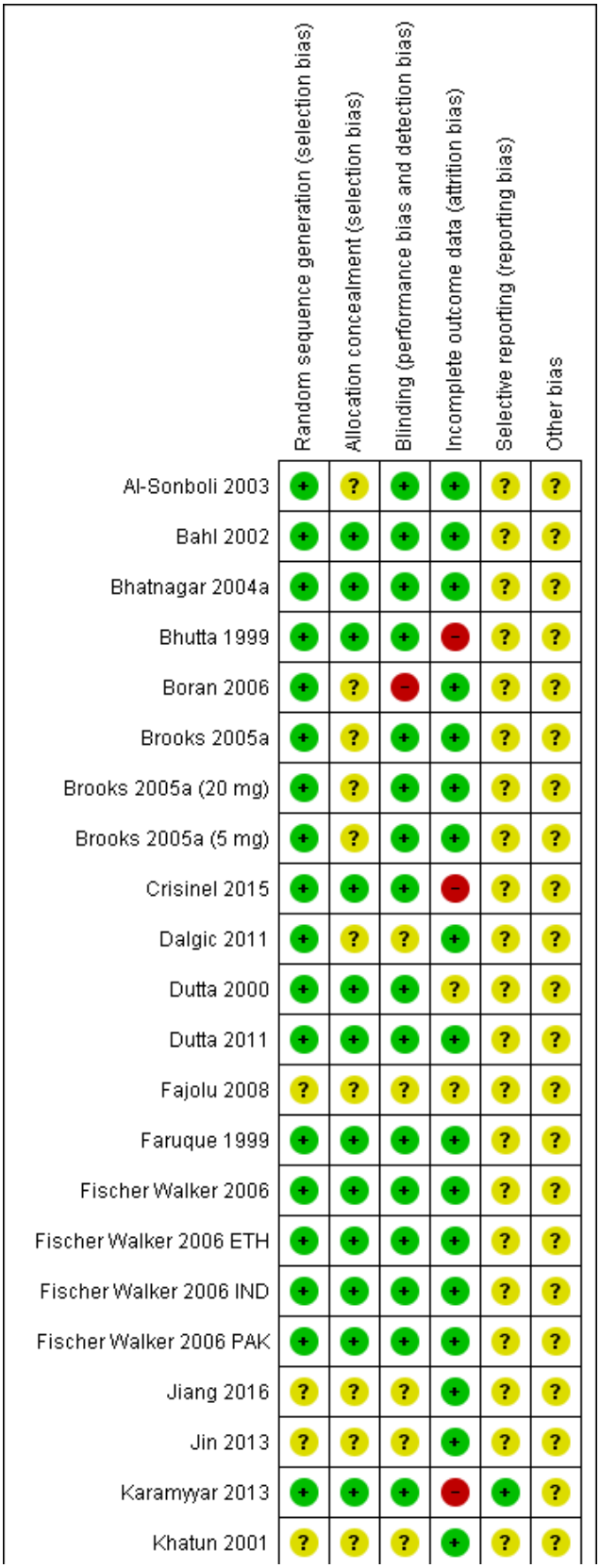
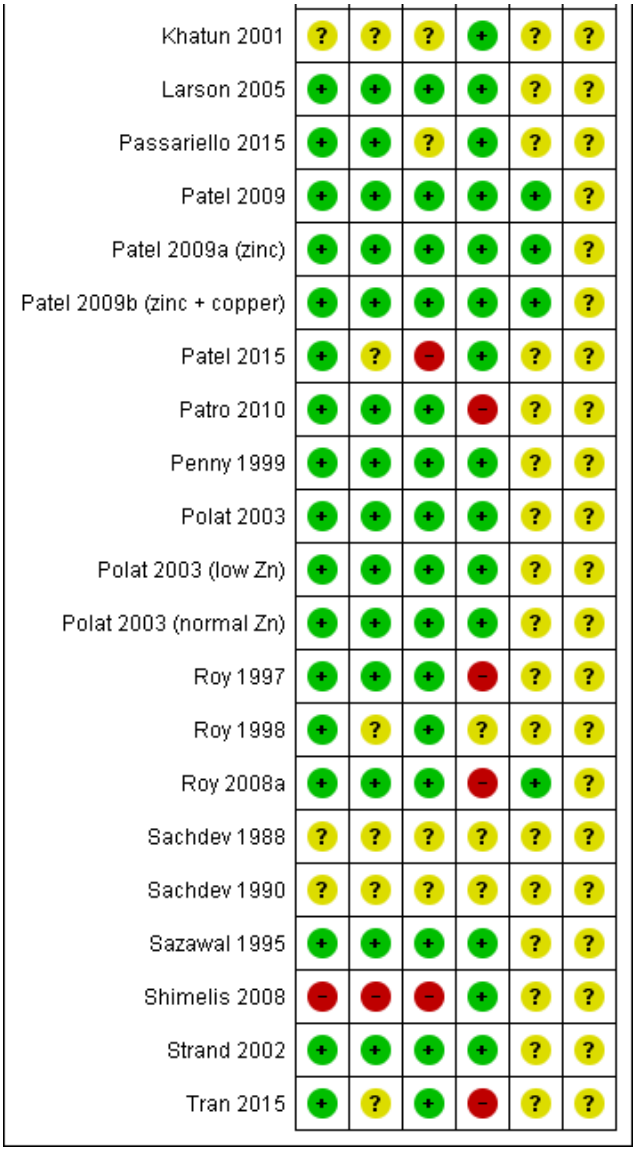


**Figure 3. (Continued)**




### Allocation

Twenty-six trials used adequate methods to generate the allocation sequence. The methods used in the other trials was either at unclear (Sachdev 1988; Sachdev 1990; Khatun 2001; Fajolu 2008; Jin 2013; Jiang 2016), or at high risk of bias (Shimelis 2008).

Nineteen trials reported methods that assured adequate allocation concealment. Of the remaining trials, thirteen were at unclear risk of bias (Sachdev 1988; Sachdev 1990; Roy 1998; Khatun 2001; Al-Sonboli 2003; Brooks 2005a; Boran 2006; Fajolu 2008; Dalgic 2011; Jin 2013; Patel 2015; Tran 2015; Jiang 2016), and one was at high risk of bias (Shimelis 2008).

### Blinding

Twenty-two trials were double blinded. Eight trials were at unclear risk of bias regarding the use of blinding (Sachdev 1988; Sachdev 1990; Khatun 2001; Fajolu 2008; Dalgic 2011; Jin 2013; Passariello 2015; Jiang 2016), and three trials were at high risk of bias (Boran 2006; Shimelis 2008; Patel 2015).

### Incomplete outcome data

Twenty-one trials included more than 90% of the randomized participants in the analysis. Seven trials included less than 90% of the randomized participants, which we assessed as at high risk of bias (Roy 1997; Bhutta 1999; Roy 2008a; Patro 2010; Karamyyar 2013; Crisinel 2015; Tran 2015), and the five remaining trials were at unclear risk of bias (Sachdev 1988; Sachdev 1990; Roy 1998; Dutta 2000; Fajolu 2008).

### Selective reporting

Only three included trials were at low risk of bias regarding selective reporting (Roy 2008a; Patel 2009; Karamyyar 2013). The risk of bias was unclear for all other included trials, and the most frequent reason for this was the fact that the trial was not registered.

### Other potential sources of bias

No information was available to evaluate other sources of bias. Therefore we judged each of the included trials as at unclear risk of bias regarding other potential sources of bias.

## Effects of interventions

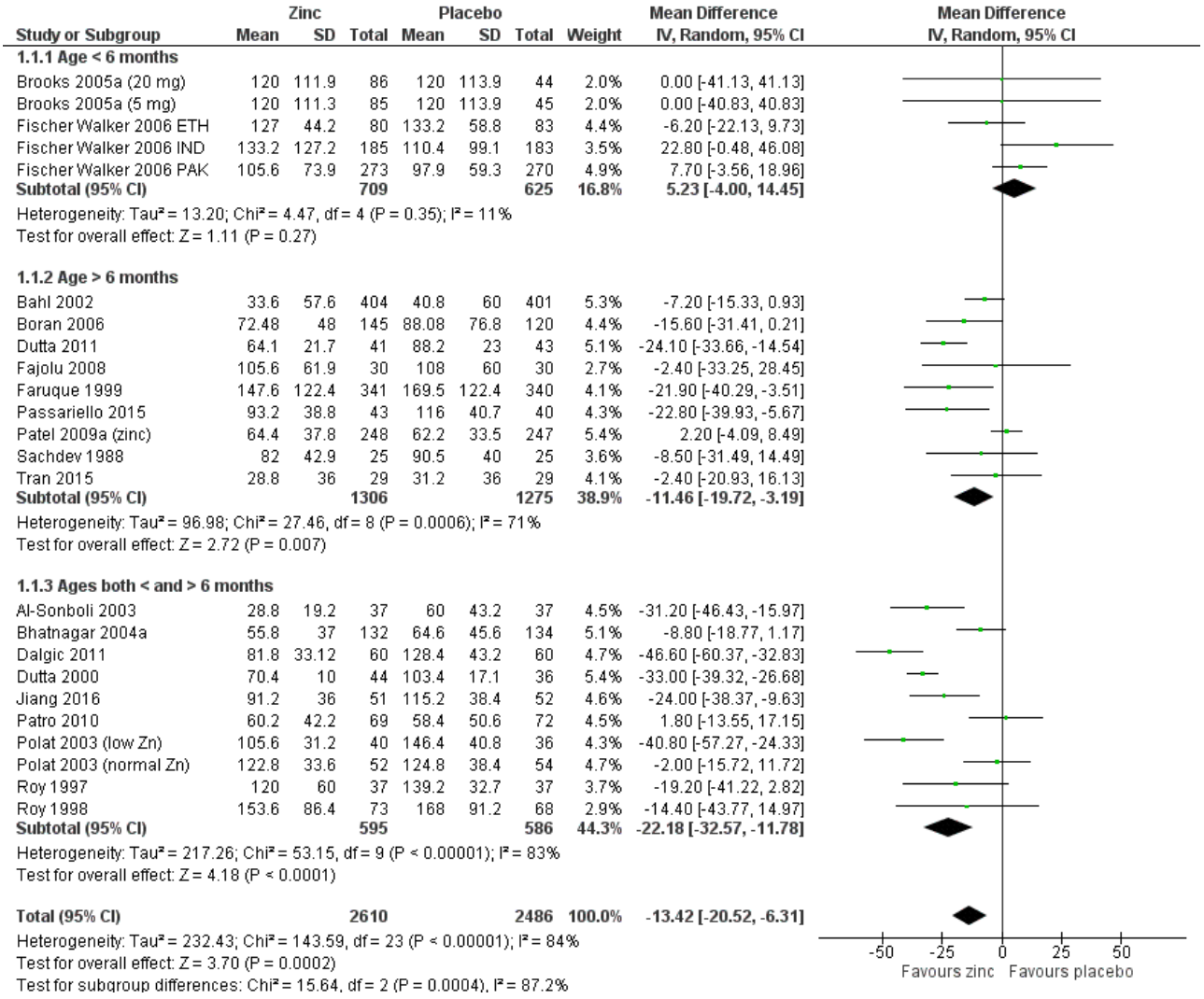
See: **Summary of findings for the main comparison** 'Summary of findings' table 1; **Summary of findings 2** 'Summary of findings' table 2; **Summary of findings 3** 'Summary of findings' table 3

### Comparison 1: Zinc versus placebo for children with acute diarrhoea

#### *Diarrhoea duration*

On average, the mean duration of diarrhoea in children given zinc was around 13 hours shorter than those given placebo (mean difference (MD) −13.42 hours, 95% confidence interval (CI) −20.52 to −6.31; 5096 children, 20 trials, 24 comparisons; Analysis 1.1; Figure 4), but there was substantial statistical heterogeneity between trials ($I^2$ statistic = 84%).

**Figure 4. Zinc versus placebo for acute diarrhoea: diarrhoea duration (h)**




In the primary analysis stratified by age, the benefit was only apparent in trials that recruited children over six months of age (MD −11.46 hours, 95% CI −19.72 to −3.19 hours; 2581 children, 9 trials; Summary of findings for the main comparison; Analysis 1.1; Figure 4), and trials that recruited all age groups (MD −22.18 hours, 95% CI −32.57 to −11.78 hours; 1181 children, 9 trials, 10 comparisons). In trials that only recruited children less than six months of age, no effect was demonstrated (1334 children, 2 trials, 5 comparisons; Summary of findings 2).

This age stratification did not adequately explain the statistical heterogeneity so we conducted a series of further subgroup analyses excluding the trials which only recruited children less than six months of age (Analysis 1.2 to Analysis 1.9). None of these subgroupings adequately explained the heterogeneity, but several observations are worth noting.

- When subgrouped by the nutritional status of participants, the smallest average effect was seen in trials that only recruited well-nourished children, and the largest average effect in trials

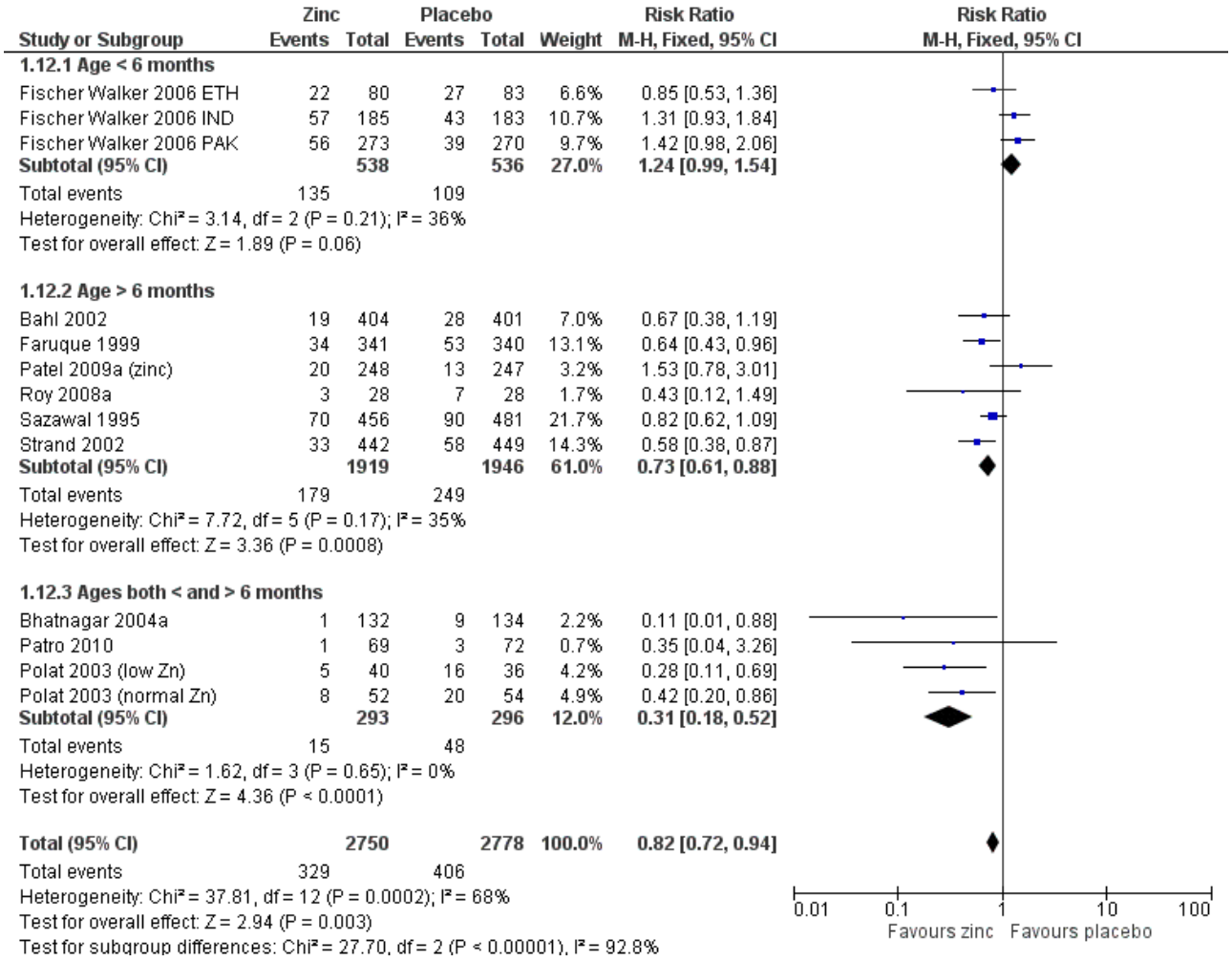
that only recruited children with signs of malnutrition (Analysis 1.2).

- There was only one included trial from the African continent, and this trial failed to show a benefit (Analysis 1.4).
- When subgrouped by the national risk of zinc deficiency, the smallest average effect was in countries at low risk of zinc deficiency (Analysis 1.5).

***Diarrhoea on days 3, 5, and 7***

On average, treatment with zinc resulted in fewer children continuing to have diarrhoea at day three (risk ratio (RR) 0.77, 95% CI 0.69 to 0.86; 2063 children, 8 trials, 9 comparisons, Analysis 1.10), at day five (RR 0.76, 95% CI 0.64 to 0.91; 2307 children, eight trials, Analysis 1.11), and at day seven (RR 0.82, 95% CI 0.72 to 0.94; 5528 children, 10 trials, 13 comparisons; Analysis 1.12; Figure 5; Summary of findings for the main comparison; Summary of findings 2). For all the three outcomes there was significant statistical heterogeneity between trials.

**Figure 5. Zinc versus placebo for acute diarrhoea: diarrhoea on day 7**




For diarrhoea at day seven we conducted a series of subgroup analyses to explore the heterogeneity (Analysis 1.13 to Analysis 1.20), which found similar patterns as seen with duration of diarrhoea.

- No subgrouping completely explained the statistical heterogeneity.
- There was no evidence of benefit in the single trial that recruited only children less than six months of age (1074 children, 1 trial, 3 comparisons; Analysis 1.12). This was also the only trial conducted in the African continent.
- The average effect was largest in trials that only recruited children with signs of undernutrition (Analysis 1.13).

***Stool frequency***

There was no significant benefit of zinc on reducing stool frequency (RR −0.10, 95% CI −0.25 to 0.04; 2643 children, 7 trials, 10 comparisons; Analysis 1.21). Heterogeneity was markedly reduced if results were stratified by age, and while no benefit of zinc was detected in children under six months of age (1334 children, 2 trials, 5 comparisons), zinc had a significant benefit in children older than six months (RR −0.32, 95% CI −0.58 to −0.06; 1235 children, 4 trials)

and in the trial that recruited both age groups (RR −5.90, 95% CI −9.44 to −2.36; 74 children, 1 trial; Analysis 1.21).

### *Stool output*

The included trials measured stool output using different units at different time points, thus we were unable to pool results (Table 3). We expressed results are expressed as arithmetic mean difference (AMD) or geometric mean ratio (GMR) values.

One trial reported on children less than six months of age with no evidence of a difference (Brooks 2005a). Two trials reported on children more than six months of age with inconsistent results (Patel 2009; Dutta 2011). Three trials reported on children aged less than and greater than six months: two of these trials showed a reduction in stool output with zinc (Dutta 2000; Bhatnagar 2004a), while one trial showed no evidence of an effect (Roy 1997).

### *Hospitalization*

Two community trials reported no hospitalizations in the zinc group and only one in the placebo group (Fischer Walker 2006, 1074 participants under six months of age; Penny 1999, 276 children over six months of age).

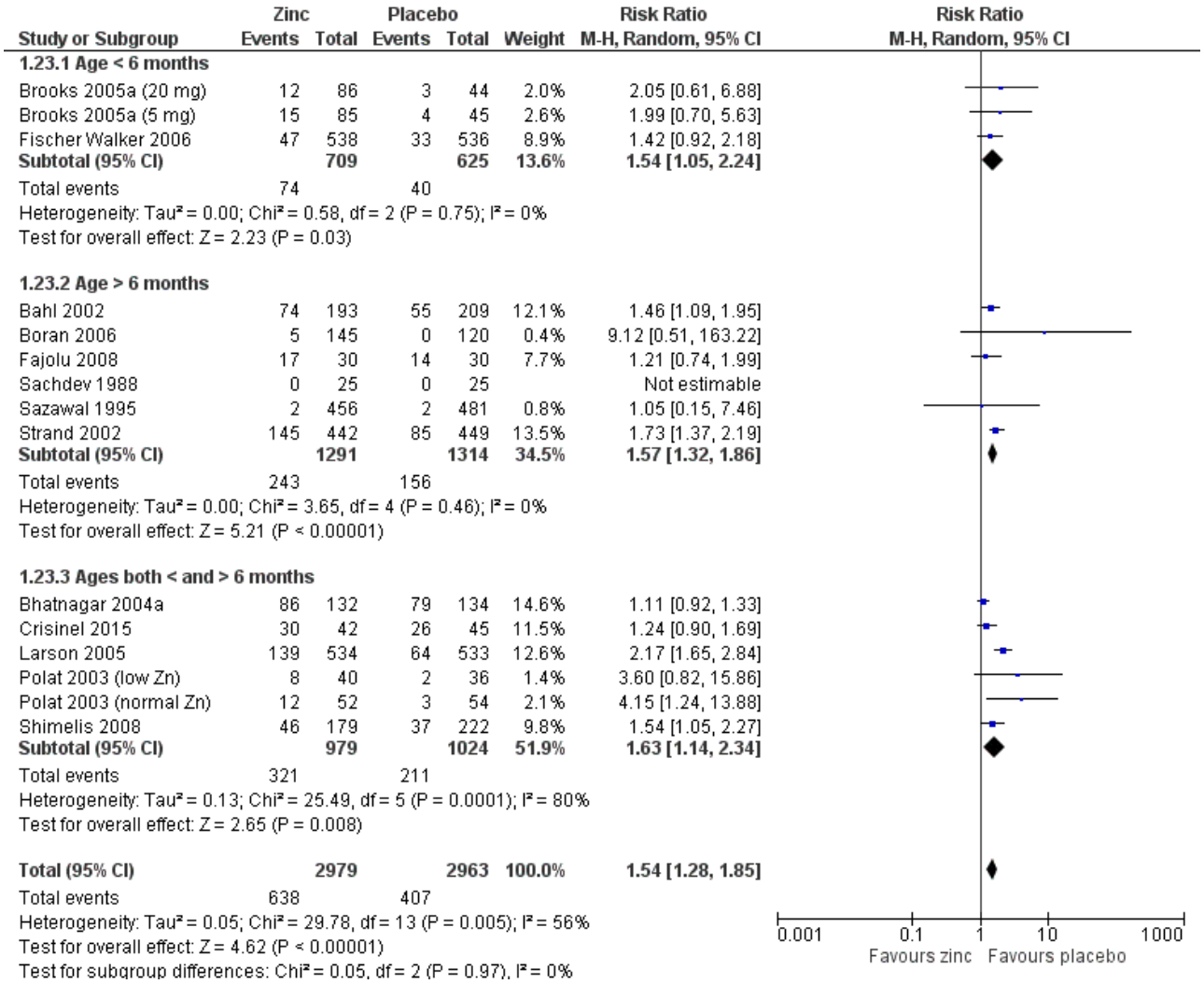
### *Death*

The trials reported a low number of deaths without significant difference between the zinc group and placebo group (Analysis 1.22).

### *Adverse events*

Vomiting was more common in those given zinc across all age groups (RR 1.54, 95% CI 1.28 to 1.85; 5942 children, 15 comparisons, 13 trials; Figure 6). There was moderate heterogeneity among trials (P = 0.005; $I^2$ statistic = 56%), and differences in control event rates (from 0.4% to 13.5%). In one large trial with adequate allocation concealment that was designed to look at safety reports, vomiting was limited to one episode in most children and mainly occurred within 10 minutes of administration (Larson 2005). Two trials found no difference in time to resolution of vomiting between zinc and placebo, although we could not pool the results (mean duration 13.63 ± 10.33 hours versus 16.35 ± 11.34 hours, P = 0.1; Dalgic 2011; median duration 2 days (interquartile range (IQR) 1 to 3) versus 2.5 days (IQR 1 to 5), P > 0.5; Crisinel 2015).

**Figure 6. Zinc versus placebo for acute diarrhoea: adverse events (vomiting)**



One small trial reported a non-statistically significant difference between the two treatment groups for difficulties in treatment administration (19/45 (45%) in the zinc group versus 20/44 (44%) in the placebo group (Crisinel 2015).

Three trials reported on copper levels, with no significant differences between the zinc and placebo groups. Two trials reported the mean change in serum copper on the last day of supplementation (seven and 14 days after recovery): −1.1 ± 5.5 µmol/dL in the zinc group versus −1.5 ± 4.2 µmol/dL in the placebo group in Strand 2002, and −41.2 ± 418.8 µg/dL in the zinc group versus −79.4 ± 429.2 µg/dL in the placebo group in Patel 2009. Mean serum copper after 14 days was 121 mg/L in zinc group versus 127 mg/L in the control in Bhatnagar 2004a.

No other side effects were reported.

***Publication bias***

We constructed funnel plots for trials that reported diarrhoea duration (Figure 7) and diarrhoea at day 7 (Figure 8). The funnel plots are both asymmetric due to the absence of smaller trials at the base and, for diarrhoea at day 7, also at the right of the pooled estimate. Asymmetry in the funnel plot could result from possible selection bias where smaller studies reporting greater treatment benefit for the experimental group were published (publication bias). The gap in the bottom corner of the graph suggests that smaller studies without statistically significant effects remain unpublished. However, asymmetry in the funnel plot may also be due to other reasons, such as poor methodological quality in smaller studies leading to spuriously inflated effects in the treatment effect, true heterogeneity, sampling variation or chance (Higgins 2011).

**Figure 7. Funnel plot of comparison: 1 Zinc versus placebo for children with acute diarrhoea, outcome: 1.1 Diarrhoea duration (hours).**

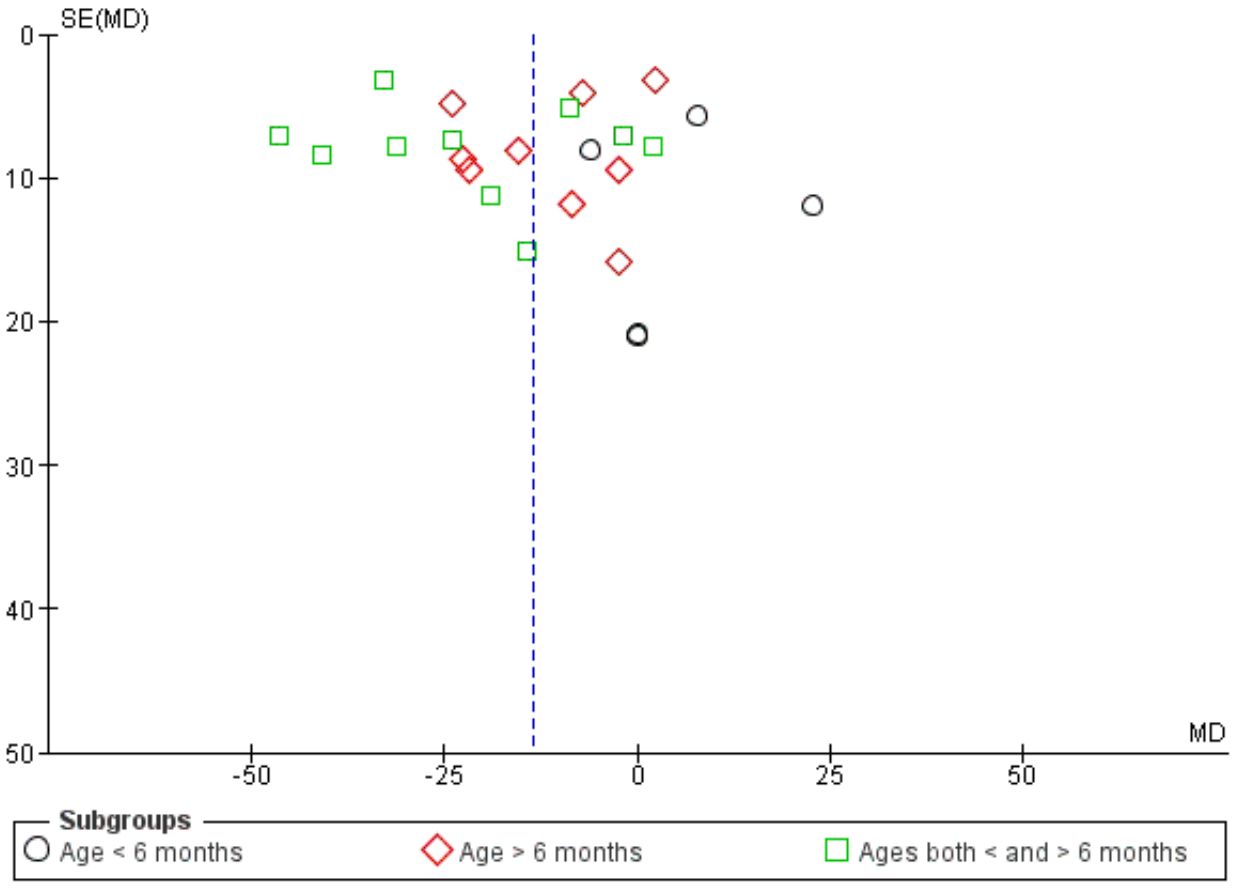
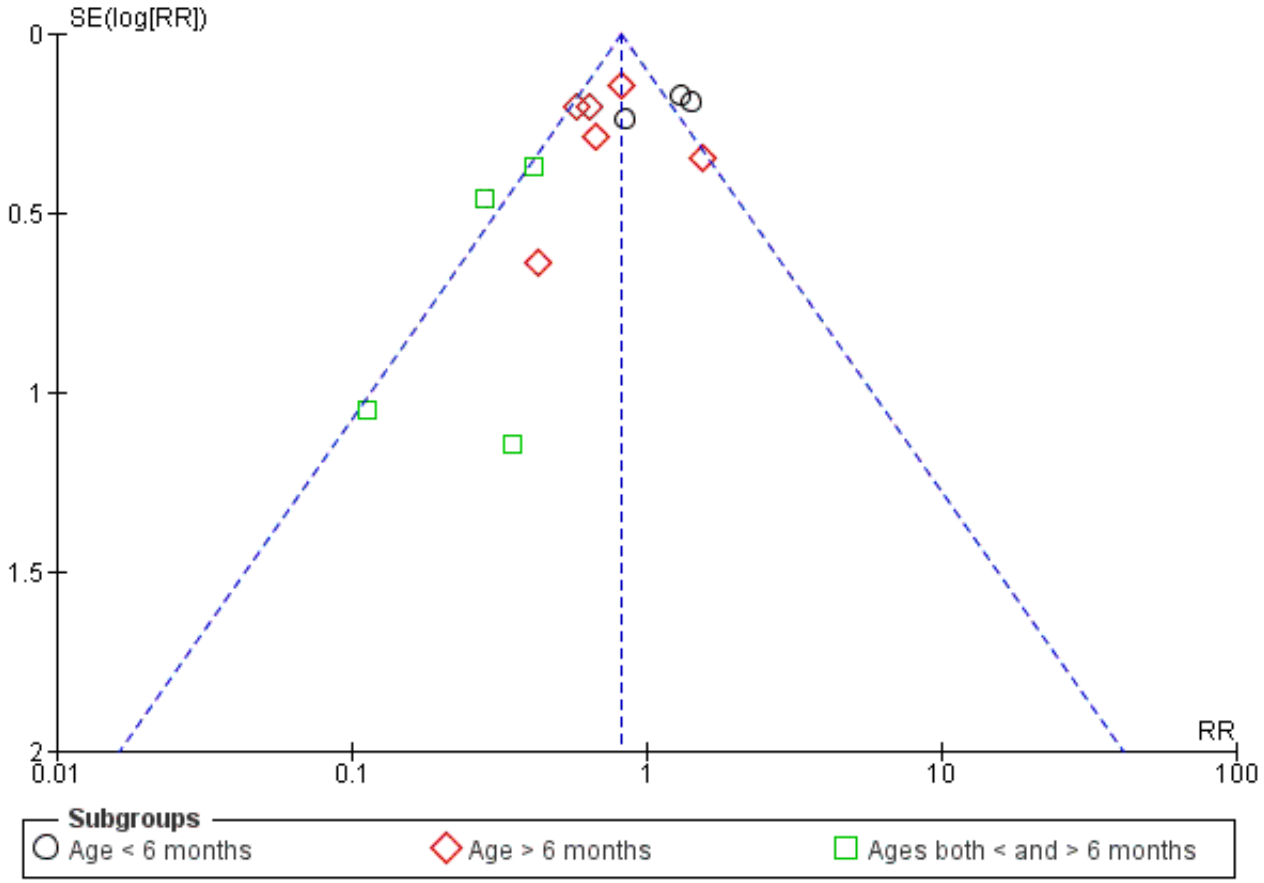


**Figure 8. Funnel plot of comparison: 1 Zinc versus placebo for children with acute diarrhoea, outcome: 1.12 Diarrhoea on day 7.**




***Sensitivity analysis***

The sensitivity analysis against markers of methodological quality did not affect the direction of results. There was some loss of significance with diarrhoea duration, but overall the analysis did not change the point estimate of effects. The ITT analysis for worst-case/best-case scenarios did not alter the statistical significance of the results.

**Comparison 2: Zinc versus placebo for children with persistent diarrhoea**

All trials of persistent diarrhoea enrolled children aged over six months.

***Diarrhoea duration***

On average, zinc supplementation reduced the duration of persistent diarrhoea by around 16 hours (MD −15.84 hours, 95% CI −25.43 to −6.24 hours; 529 children, 5 trials; Analysis 2.1), with no evidence of heterogeneity.

***Diarrhoea on days 3, 5, and 7***

There was no evidence of a benefit with zinc in the one trial that reported on diarrhoea at days three (Analysis 2.2) and five (Analysis 2.3) (Penny 1999), and two trials that reported on diarrhoea at day seven (Analysis 2.4; Penny 1999; Khatun 2001).

***Stool frequency***

One small trial reported on stool frequency, Sachdev 1990, but the result did not reach statistical significance (40 participants, Analysis 2.5).

***Stool output***

Stool output was measured using different units at different time points, thus we could not pool results (Table 4). We expressed the results as the AMD or GMR. Two trials, Bhutta 1999 and Khatun 2001, reported on children greater than six months of age, with five comparisons (Additional tables). Of these, one trial reported a significant reduction in cumulative stool output at day seven in the zinc group (AMD −338 mg/kg bodyweight, 95% CI −413.6 to −262.4 mg/kg bodyweight; P ≤ 0.001) (Khatun 2001).

***Hospitalization***

The only community trial that reported on hospitalization did not observe any hospitalizations in the zinc or placebo group (Penny 1999; 275 participants).

***Death***

One trial reported one death in the zinc group compared to five deaths in the placebo group, out of 95 participants in each group

(Roy 1998). Two trials did not observe deaths in any participants, irrespective of their allocated group (Penny 1999; Khatun 2001).

#### *Adverse events*

Four trials that reported on vomiting (505 children) showed no difference between the zinc and placebo groups (Analysis 2.6): three of the trials reported no incidences of vomiting in either group (Khatun 2001; Roy 1998; Sachdev 1990); one trial that used 3 mg/kg/day zinc for 14 days in moderately malnourished and severely malnourished children reported a significantly lower plasma copper levels in the zinc-treated group by the end of the second week of therapy (56.2 ± 17.8 µg/dL versus 72.7 ± 18.3 µg/dL, P = 0.02; Bhutta 1999, 87 children).

#### *Statistical heterogeneity*

There was heterogeneity between two trials for diarrhoea at day seven. This may be explained by differences in the geographical regions (India and Peru) or to other factors not explored in this Cochrane Review. Reporting of vomiting was heterogeneous between trials, and this may be due to difference in the population or in the definition of event, or to reporting bias.

#### *Sensitivity analysis*

The sensitivity analyses did not affect the direction of results. There was some loss of significance with diarrhoea duration, but no changes in the point estimate of effects. An ITT analysis for worst-case/best-case scenarios did not alter the point estimate or the significance of results.

## DISCUSSION

### Summary of main results

Thirty-three trials, enrolling 10,841 children, met our inclusion criteria. Most included trials were conducted in Asian countries where the risk of zinc deficiency is high.

#### Acute diarrhoea

There is currently not enough evidence from well conducted trials to be able to say whether zinc supplementation during acute diarrhoea reduces the number of deaths or the number of children hospitalized (*very low certainty evidence*).

In children aged greater than six months, zinc supplementation may shorten the duration of diarrhoea by around half a day (*low certainty evidence*), and probably reduces the number of children whose diarrhoea persists until day seven (*moderate certainty evidence*). In children with signs of moderate malnutrition the effect appears greater, reducing the duration of diarrhoea by around a day (*high certainty evidence*).

Conversely, in children less than six months of age, the available evidence suggests zinc supplementation may have no impact on the duration of diarrhoea (*low certainty evidence*), and may increase the proportion of children whose diarrhoea persists until day seven (*low certainty evidence*).

No trials reported serious adverse events, but zinc supplementation during acute diarrhoea causes vomiting in both age groups (*moderate certainty evidence*).

#### Persistent diarrhoea

In children with persistent diarrhoea, zinc supplementation probably shortens the duration of diarrhoea by around 16 hours (*moderate certainty evidence*).

### Overall completeness and applicability of evidence

This Cochrane Review showed that zinc overall reduced the duration of acute diarrhoea. However, most trials were conducted in populations with moderate to high risk of zinc deficiency (Asia, Africa, children over six months of age and with some degree of malnutrition). Transferability of these results to other countries is therefore likely to depend on local risk of zinc deficiency and other population characteristics such as the degree of malnutrition and breastfeeding habits. The few trials conducted in populations at low risk of zinc deficiency, namely well-nourished children in countries and continents where zinc deficiency is uncommon (Europe, Australia), overall showed no benefit of zinc.

Most trials were conducted in hospital where participants are more likely to adhere to the intervention, but some community trials also showed a benefit with zinc, which suggests that zinc could be used both at hospital and at community level.

The observed increase in vomiting was consistent across trials in all age groups with one large trial reporting that vomiting was limited to one episode in most children and mainly occurring within 10 minutes of administration (Larson 2005). Zinc has a metallic after-taste, and development of a more palatable formulation may minimize this adverse effect.

### Quality of the evidence

We assessed the certainty of the evidence using the GRADE methodology and displayed it in three 'Summary of findings' tables (Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3).

In general, the methodological quality of the trials included in this review was good.

The evidence for benefits on diarrhoea duration in children aged greater than six months of age is of low to moderate certainty. This implies that we can have some confidence in the results but further research may alter the estimates of benefit and harm. The main reasons to downgrade were 'quality of trials' and 'inconsistency' in the results. Heterogeneity between trials was often high. This is perhaps not surprising given the variations in populations, settings, and interventions. We were unable to completely explain this heterogeneity through subgroup analysis, and so our confidence that zinc supplementation can be broadly applied was decreased.

Most trials were conducted in hospitals where death rates were low, and were consequently not powered to detect an effect on mortality. Large community trials are needed to explore whether zinc treatment for diarrhoea reduces hospitalization and death.

### Potential biases in the review process

We attempted to limit bias by following the rigorous methods provided by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We conducted an extensive search for studies, including ongoing studies. We only included peer-reviewed trials in this review. Two review authors independently scrutinized

the studies, assessed them for eligibility, extracted data, inserted data into RevMan 5 (Review Manager 5), and double checked the final version of the review. The findings of the funnel plots may suggest publication bias. However, asymmetry in the funnel plots may also be due to other reasons, such as poor methodological quality in smaller studies leading to spuriously inflated effects, true heterogeneity in the treatment effect, sampling variation, or chance (Higgins 2011).

### Agreements and disagreements with other studies or reviews

Our results agree with those of other systematic reviews of zinc for treating children that have diarrhoea (Bhutta 2000b; Lukacik 2008; Patro 2008; Haider 2009; Liberato 2015; Zou 2015), except for the finding of no effect of zinc in children aged less than six months, and in populations at low risk of zinc deficiency. Compared to the other recent reviews (Liberato 2015; Zou 2015; Lazzerini 2016), this Cochrane Review includes several new trials, includes a more extensive subgroup analysis, and reports on diarrhoea at different time points, diarrhoea severity, death, and adverse events.

The results of this Cochrane Review in children over six months of age support the current WHO/UNICEF policy to give zinc to children with diarrhoea (WHO/UNICEF 2004), while currently there are no evidence from randomized controlled trials to provide zinc in children younger than six months of age.

## AUTHORS' CONCLUSIONS

### Implications for practice

In areas where diarrhoea is an important cause of child mortality, and the prevalence of zinc deficiency or mild/moderate malnutrition is high, zinc may be of benefit in children with diarrhoea aged six months or more.

### Implications for research

Causes of heterogeneity in the effect of zinc in children over six months should be further explored, and further research is necessary to justify continued supplementation in children less than six months of age and in children with low risk of zinc deficiency.

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# REFERENCES

## References to studies included in this review

**Al-Sonboli 2003** *{published data only}*

* Al-Sonboli N, Gurgel RQ, Shenkin A, Hart CA, Cuevas LE. Zinc supplementation in Brazilian children with acute diarrhoea. *Annals of Tropical Paediatrics* 2003;**23**(1):3-8.

Cuevas LE, Al Sonboli NN, Gurgel RQ, Shenkins A, Hart CA. Impact of zinc on duration of acute diarrhoea in children. *Journal of Infection* 2000;**40**:A29.

**Bahl 2002** *{published data only}*

Bahl R, Bhandari N, Saksena M, Strand T, Kumar GT, Bhan MK, et al. Efficacy of zinc-fortified oral rehydration solution in 6- to 35-month-old children with acute diarrhea. *Journal of Pediatrics* 2002;**141**(5):677-82.

**Bhatnagar 2004a** *{published data only}*

Bhatnagar S, Bahl R, Sharma PK, Kumar GT, Saxena SK, Bhan MK. Zinc with oral rehydration therapy reduces stool output and duration of diarrhea in hospitalized children: a randomized controlled trial. *Journal of Pediatric Gastroenterology and Nutrition* 2004;**38**(1):34-40.

**Bhutta 1999** *{published data only}*

Bhutta ZA, Nizami SQ, Isani Z. Zinc supplementation in malnourished children with persistent diarrhea in Pakistan. *Pediatrics* 1999;**103**(4):e42.

**Boran 2006** *{published data only}*

Boran P, Tokuc G, Vagas E, Oktem S, Gokduman MK. Impact of zinc supplementation in children with acute diarrhoea in Turkey. *Archives of Disease in Childhood* 2006;**91**(4):296-9.

**Brooks 2005a** *{published data only}*

Brooks WA, Santosham M, Roy SK, Faruque AS, Wahed MA, Nahar K, et al. Efficacy of zinc in young infants with acute watery diarrhea. *American Journal of Clinical Nutrition* 2005;**82**(3):605-10.

**Brooks 2005a (20 mg)** *{published data only}*

Brooks WA, Santosham M, Roy SK, Faruque AS, Wahed MA, Nahar K, et al. Efficacy of zinc in young infants with acute watery diarrhea. *American Journal of Clinical Nutrition* 2005;**82**(3):605-10.

**Brooks 2005a (5 mg)** *{published data only}*

Brooks WA, Santosham M, Roy SK, Faruque AS, Wahed MA, Nahar K, et al. Efficacy of zinc in young infants with acute watery diarrhea. *American Journal of Clinical Nutrition* 2005;**82**(3):605-10.

**Crisinel 2015** *{published data only}*

Crisinel PA, Verga ME, Kouame KS, Pittet A, Rey-Bellet CG, Fountaine O, et al. Demonstration of the effectiveness of zinc in diarrhoea of children in Switzerland. *European Journal of Pediatrics* 2015;**174**(8):1061-7.

**Dalgic 2011** *{published data only}*

Dalgic N, Sancar M, Bayraktar B, Pullu M, Hasim O. Probiotic, zinc and lactose-free formula in children with rotavirus diarrhea: are they effective?. *Pediatrics International* 2011;**53**(5):677-82.

**Dutta 2000** *{published data only}*

Dutta P, Mitra U, Datta A, Niyogi SK, Dutta S, Manna B, et al. Impact of zinc supplementation in malnourished children with acute watery diarrhoea. *Journal of Tropical Pediatrics* 2000;**46**(5):259-63.

**Dutta 2011** *{published data only}*

Dutta P, Mitra U, Dutta S, Naik TN, Rajendran K, Chatterjee MK. Zinc, vitamin A, and micronutrient supplementation in children with diarrhea: a randomized controlled clinical trial of combination therapy versus monotherapy. *Journal of Pediatrics* 2011;**159**(4):633-7.

**Fajolu 2008** *{published and unpublished data}*

Fajolu IB, Emokpae A, Oduwole AO, Silva BO, Abidoye RO, Renner JK. Zinc supplementation in children with acute diarrhoea. *Nigerian Quarterly Journal of Hospital Medicine* 2008;**18**(2):101-3.

**Faruque 1999** *{published data only}*

Faruque AS, Mahalanabis D, Haque SS, Fuchs GJ, Habte D. Double-blind, randomized, controlled trial of zinc or vitamin A supplementation in young children with acute diarrhoea. *Acta Paediatrica* 1999;**88**(2):154-60.

**Fischer Walker 2006** *{published data only}*

Fischer Walker CL, Bhutta ZA, Bhandari N, Teka T, Shahid F, Taneja S, et al. Zinc supplementation for the treatment of diarrhea in infants in Pakistan, India and Ethiopia. *Journal of Pediatric Gastroenterology and Nutrition* 2006;**43**(3):357-63.

**Fischer Walker 2006 ETH** *{published data only}*

Fischer Walker CL, Bhutta ZA, Bhandari N, Teka T, Shahid F, Taneja S, et al. Zinc supplementation for the treatment of diarrhea in infants in Pakistan, India and Ethiopia. *Journal of Pediatric Gastroenterology and Nutrition* 2006;**43**(3):357-63.

**Fischer Walker 2006 IND** *{published data only}*

Fischer Walker CL, Bhutta ZA, Bhandari N, Teka T, Shahid F, Taneja S, et al. Zinc supplementation for the treatment of diarrhea in infants in Pakistan, India and Ethiopia. *Journal of Pediatric Gastroenterology and Nutrition* 2006;**43**(3):357-63.

**Fischer Walker 2006 PAK** *{published data only}*

Fischer Walker CL, Bhutta ZA, Bhandari N, Teka T, Shahid F, Taneja S, et al. Zinc supplementation for the treatment of diarrhea in infants in Pakistan, India and Ethiopia. *Journal of Pediatric Gastroenterology and Nutrition* 2006;**43**(3):357-63.

**Jiang 2016** *{published data only}*

Jiang CX, Xu CD, Yang CQ. Therapeutic effects of zinc supplement as adjunctive therapy in infants and young children

with rotavirus enteritis. *Zhongguo Dang Dai Er Ke Za Zhi [Chinese Journal of Contemporary Pediatrics]* 2016;**18**(9):826-30.

**Jin 2013** *{published data only}*

Jin X-L, Luo X-M. Significance of zinc supplementation in infants with rotavirus enteritis. *World Chinese Journal of Digestology* 2013;**21**(35):4030-3.

**Karamyyar 2013** *{published data only}*

Karamyyar M, Gheibi S, Noroozi M, Kord Valeshabad A. Therapeutic effects of oral zinc supplementation on acute diarrhoea with moderate dehydration: a double-blind randomized clinical trial. *Iranian Journal of Medical Sciences* 2013;**38**(2):93-9.

**Khatun 2001** *{published data only}*

* Khatun UH, Malek MA, Black RE, Sarkar NR, Wahed MA, Fuchs G, et al. A randomized controlled clinical trial of zinc, vitamin A or both in undernourished children with persistent diarrhea in Bangladesh. *Acta Paediatrica* 2001;**90**(4):376-80.

Roy SK, Khatun F, Sarkar NR, Saifuddin NM, Islam OE, Fuchs GJ. A randomized four cell clinical trial of zinc and vitamin A in undernourished children with persistent diarrhoea in Bangladesh. *Journal of Pediatric Gastroenterology and Nutrition* 1998;**26**(5):595.

**Larson 2005** *{published data only}*

Larson CP, Hoque AB, Larson CP, Khan AM, Saha UR. Initiation of zinc treatment for acute childhood diarrhoea and risk for vomiting or regurgitation: a randomized, double-blind, placebo-controlled trial. *Journal of Health, Population, and Nutrition* 2005;**23**(4):311-9.

**Passariello 2015** *{published data only}*

Passariello A, Nocerino R, Terrin G, Cecere G, De Marco G, Micillo M, et al. Acceptability and efficacy of a gel hypotonic oral rehydration solution in children with acute gastroenteritis. *European Journal of Gastroenterology and Hepatology* 2015;**27**(5):523-6.

**Patel 2009** *{published and unpublished data}*

Patel A, Dibley MJ, Mamtani M, Badhoniya N, Kulkarni H. Zinc and copper supplementation in acute diarrhea in children: a double-blind randomized controlled trial. *BMC Medicine* 2009;**7**:22.

**Patel 2009a (zinc)** *{published and unpublished data}*

Patel A, Dibley MJ, Mamtani M, Badhoniya N, Kulkarni H. Zinc and copper supplementation in acute diarrhea in children: a double-blind randomized controlled trial. *BMC Medicine* 2009;**7**:22.

**Patel 2009b (zinc + copper)** *{published and unpublished data}*

Patel A, Dibley MJ, Mamtani M, Badhoniya N, Kulkarni H. Zinc and copper supplementation in acute diarrhea in children: a double-blind randomized controlled trial. *BMC Medicine* 2009;**7**:22.

**Patel 2015** *{published data only}*

Patel HN, Shah RB, Gajjar BM. Evaluation of the role of zinc supplementation in treatment of diarrhoea in paediatric patients: a randomized open-label study. *Drugs & Therapy Perspectives* 2015;**31**(1):34-8.

**Patro 2010** *{published and unpublished data}*

Patro B, Szymański H, Szajewska H. Oral zinc for the treatment of acute gastroenteritis in Polish children: a randomized, double-blind, placebo-controlled trial. *Journal of Pediatrics* 2010;**157**(6):984-8.e.1.

**Penny 1999** *{published data only}*

Penny ME, Peerson JM, Marin RM, Duran A, Lanata CF, Lönnerdal B, et al. Randomized, community-based trial of the effect of zinc supplementation, with and without other micronutrients, on the duration of persistent childhood diarrhea in Lima, Peru. *Journal of Pediatrics* 1999;**135**(2 Pt 1):208-17.

**Polat 2003** *{published data only}*

Polat TB, Uysalol M, Cetinkaya F. Efficacy of zinc supplementation on the severity and duration of diarrhea in malnourished Turkish children. *Pediatrics International* 2003;**45**(5):555-9.

**Polat 2003 (low Zn)** *{published data only}*

Polat TB, Uysalol M, Cetinkaya F. Efficacy of zinc supplementation on the severity and duration of diarrhea in malnourished Turkish children. *Pediatrics International* 2003;**45**(5):555-9.

**Polat 2003 (normal Zn)** *{published data only}*

Polat TB, Uysalol M, Cetinkaya F. Efficacy of zinc supplementation on the severity and duration of diarrhea in malnourished Turkish children. *Pediatrics International* 2003;**45**(5):555-9.

**Roy 1997** *{published data only}*

Roy SK. Effect of zinc supplementation in patients with acute and persistent diarrhoea. *Glimpse* 1991;**13**(3):2.

* Roy SK, Tomkins AM, Akramuzzaman SM, Behrens RH, Haider R, Mahalanabis D, et al. Randomised controlled trial of zinc supplementation in malnourished Bangladeshi children with acute diarrhoea. *Archives of Disease in Childhood* 1997;**77**(3):196-200.

**Roy 1998** *{published data only}*

Roy SK. Effect of zinc supplementation in patients with acute and persistent diarrhoea. *Glimpse* 1991;**13**(3):2.

* Roy SK, Tomkins AM, Mahalanabis D, Akramuzzaman SM, Haider R, Behrens RH, et al. Impact of zinc supplementation on persistent diarrhoea in malnourished Bangladeshi children. *Acta Paediatrica* 1998;**87**(12):1235-9.

**Roy 2008a** *{published and unpublished data}*

Roy SK, Raqib R, Khatun W, Azim T, Chowdhury R, Fuchs GJ, et al. Zinc supplementation in the management of shigellosis

in malnourished children in Bangladesh. *European Journal of Clinical Nutrition* 2008;**62**(7):849-55.

**Sachdev 1988** *{published data only}*

Sachdev HP, Mittal NK, Mittal SK, Yadav HS. A controlled trial on utility of oral zinc supplementation in acute dehydrating diarrhea in infants. *Journal of Pediatric Gastroenterology and Nutrition* 1988;**7**(6):877-81.

**Sachdev 1990** *{published data only}*

Sachdev HP, Mittal NK, Yadav HS. Oral zinc supplementation in persistent diarrhoea in infants. *Annals of Tropical Paediatrics* 1990;**10**(1):63-9.

**Sazawal 1995** *{published data only}*

Darmon N, Briend A, Desjeux JF. Zinc in the treatment of diarrhea. *Journal of Pediatric Gastroenterology and Nutrition* 1997;**25**(3):363-5.

Folwaczny C. Role of zinc in treatment of acute diarrhea. *Zeitschrift für Gastroenterologie* 1996;**34**(4):260-2.

* Sazawal S, Black RE, Bhan MK, Bhandari N, Sinha A, Jalla S. Zinc supplementation in young children with acute diarrhea in India. *New England Journal of Medicine* 1995;**333**(13):839-44.

**Shimelis 2008** *{published data only}*

Shimelis D, Benti D, Challi D. Effect of zinc supplementation in treatment of acute diarrhoea among 2-59 months children treated in Black Lion Hospital, Addis Ababa, Ethiopia. *Ethiopian Journal of Health Development* 2008;**22**(2):187-90.

**Strand 2002** *{published data only}*

Strand TA, Chandyo RK, Bahl R, Sharma PR, Adhikari RK, Bhandari N, et al. Effectiveness and efficacy of zinc for the treatment of acute diarrhea in young children. *Pediatrics* 2002;**109**(5):898-903.

**Tran 2015** *{published data only}*

Tran CD, Hawkes J, Graham RD, Kitchen JL, Symonds EL, Davidson GP, et al. Zinc-fortified oral rehydration solution improved intestinal permeability and small intestinal mucosal recovery. *Clinical Pediatrics* 2015;**54**(7):676-82.

## References to studies excluded from this review

**Abraham 2016** *{published data only}*

Abraham AA, Amritha SR, Selvin CDS. A comparative evaluation on the effect of zinc-probiotic and probiotic therapy in paediatric acute diarrhoea and the impact of counselling of mothers. *International Journal of Pharmacy and Pharmaceutical Sciences* 2016;**8**(7):241-3.

**Adu-Afarwuah 2007** *{published data only}*

Adu-Afarwuah S, Lartey A, Brown KH, Zlotkin S, Briend A, Dewey KG. Randomized comparison of 3 types of micronutrient supplements for home fortification of complementary foods in Ghana: effects on growth and motor development. *American Journal of Clinical Nutrition* 2007;**86**(2):412-20.

**Adu-Afarwuah 2008** *{published data only}*

Adu-Afarwuah S, Lartey A, Brown KH, Zlotkin S, Briend A, Dewey KG. Home fortification of complementary foods with micronutrient supplements is well accepted and has positive effects on infant iron status in Ghana. *American Journal of Clinical Nutrition* 2008;**87**(4):929-38.

**Aggarwal 2007** *{published data only}*

Aggarwal R, Sentz J, Miller MA. Role of zinc administration in prevention of childhood diarrhea and respiratory illnesses: a meta-analysis. *Pediatrics* 2007;**119**(6):1120-30.

**Agustina 2007** *{published data only}*

Agustina R, Lukito W, Firmansyah A, Suhardjo HN, Murniati D, Bindels J. The effect of early nutritional supplementation with a mixture of probiotic, prebiotic, fiber and micronutrients in infants with acute diarrhea in Indonesia. *Asia Pacific Journal of Clinical Nutrition* 2007;**16**(3):435-42.

**Alam 2010** *{published data only}*

Alam DS, Yunus M, El Arifeen S, Chowdury HR, Larson CP, Sack DA, et al. Zinc treatment for 5 or 10 days is equally efficacious in preventing diarrhea in the subsequent 3 months among Bangladeshi children. *Journal of Nutrition* 2010;**141**(2):312-5.

**Alarcon 2004** *{published data only}*

Alarcon K, Kolsteren PW, Prada AM, Chian AM, Velarde RE, Pecho IL, et al. Effects of separate delivery of zinc or zinc and vitamin A on hemoglobin response, growth, and diarrhea in young Peruvian children receiving iron therapy for anemia. *American Journal of Clinical Nutrition* 2004;**80**(5):1276-82.

**Awasthi 2006** *{published data only}*

Awasthi S, INCLEN Childnet Zinc Effectiveness for Diarrhea (IC-ZED) Group. Zinc supplementation in acute diarrhea is acceptable, does not interfere with oral rehydration, and reduces the use of other medications: a randomized trial in five countries. *Journal of Pediatric Gastroenterology and Nutrition* 2006;**42**(3):300-5.

**Baqui 2002** *{published data only}*

* Baqui AH, Black RE, El Arifeen S, Yunus M, Chakraborty J, Ahmed S, et al. Effect of zinc supplementation started during diarrhoea on morbidity and mortality in Bangladeshi children: community randomised trial. *BMJ* 2002;**325**(7372):1059.

Baqui AH, Black RE, El Arifeen S, Yunus M, Zaman K, Begum N, et al. Zinc therapy for diarrhoea increased the use of oral rehydration therapy and reduced the use of antibiotics in Bangladeshi children. *Journal of Health, Population, and Nutrition* 2004;**22**(4):440-2.

**Baqui 2003** *{published data only}*

Baqui AH, Zaman K, Persson LA, El Arifeen S, Yunus M, Begum N, et al. Simultaneous weekly supplementation of iron and zinc is associated with lower morbidity due to diarrhea and acute lower respiratory infection in Bangladeshi infants. *Journal of Nutrition* 2003;**133**(12):4150-7.

**Baqui 2006** *{published data only}*

Baqui AH, Black RE, Fischer Walker CL, Arifeen S, Zaman K, Yunus M, et al. Zinc supplementation and serum zinc during diarrhea. *Indian Journal of Pediatrics* 2006;**73**(6):493-7.

**Baum 2010** *{published data only}*

Baum MK, Lai S, Sales S, Page JB, Campa A. Randomized, controlled clinical trial of zinc supplementation to prevent immunological failure in HIV-infected adults. *Clinical Infectious Diseases* 2010;**50**(12):1653-60.

**Becquey 2016** *{published data only}*

Becquey E, Ouedraogo CT, Hess SY, Rouamba N, Prince L, Ouedraogo JB, et al. Comparison of Preventive and Therapeutic Zinc Supplementation in Young Children in Burkina Faso: A Cluster-Randomized, Community-Based Trial. *Journal of Nutrition* 2016;**146**(10):2058-66.

**Behrens 1990** *{published data only}*

Behrens RH, Tomkins AM, Roy SK. Zinc supplementation during diarrhoea, a fortification against malnutrition?. *Lancet* 1990;**336**(8712):442-3.

**Bhandari 2002** *{published data only}*

Bhandari N, Bahl R, Taneja S, Strand T, Mølbak K, Ulvik RJ, et al. Substantial reduction in severe diarrheal morbidity by daily zinc supplementation in young north Indian children. *Pediatrics* 2002;**109**(6):e86.

**Bhandari 2005** *{published data only}*

Bhandari N, Mazumder S, Taneja S, Dube B, Black RE, Fontaine O, et al. A pilot test of the addition of zinc to the current case management package of diarrhea in a primary health care setting. *Journal of Pediatric Gastroenterology and Nutrition* 2005;**41**(5):685-7.

**Bhandari 2007** *{published data only}*

Bhandari N, Taneja S, Mazumder S, Bahl R, Fontaine O, Bhan MK. Adding zinc to supplemental iron and folic acid does not affect mortality and severe morbidity in young children. *Journal of Nutrition* 2007;**137**(1):112-7.

**Bhandari 2008** *{published data only}*

Bhandari N, Mazumder S, Taneja S, Dube B, Agarwal RC, Mahalanabis D, et al. Effectiveness of zinc supplementation plus oral rehydration salts compared with oral rehydration salts alone as a treatment for acute diarrhea in a primary care setting: a cluster randomized trial. *Pediatrics* 2008;**121**(5):e1279-85.

**Bhatnagar 2004b** *{published data only}*

Bhatnagar S, Natchu UC. Zinc in child health and disease. *Indian Journal of Pediatrics* 2004;**71**(11):991-5.

**Bhutta 2000a** *{published data only}*

Bhutta ZA, Raza F, Nizami SQ, Issani Z. Does zinc supplementation influence appetite in malnourished children with persistent diarrhoea? A randomized controlled trial in Pakistan. *Journal of Pediatric Gastroenterology and Nutrition* 2000;**31**(Suppl 2):23.

**Bilenko 2010** *{published data only}*

Bilenko N, Belmaker I, Vardi H, Fraser D. Efficacy of multiple micronutrient supplementations on child health: study design and baseline characteristics. *Israel Medical Association Journal* 2010;**12**(6):342-7.

**Black 2001** *{published data only}*

Black RE, Sazawal S. Zinc and childhood infectious disease morbidity and mortality. *British Journal of Nutrition* 2001;**85**(Suppl 2):S125-9.

**Bobat 2005** *{published data only}*

Bobat R, Coovadia H, Stephen C, Naidoo KL, McKerrow N, Black RE, et al. Safety and efficacy of zinc supplementation for children with HIV-1 infection in South Africa: a randomised double-blind placebo-controlled trial. *Lancet* 2005;**366**(9500):1862-7.

**Borges 2007** *{published data only}*

Borges Dantas CV, Veiga Black AP, dos Santos Barroso G, Oliveira de Jesus EF, Barbosa Serpa RF, Moreira S, et al. Association among serum concentration of minerals, anthropometric indices and diarrhea in low-income children in the metropolitan region of Rio de Janeiro, Brazil [Associação entre concentrações séricas de minerais, índices antropométricos e ocorrência de diarréia entre crianças de baixa renda da região metropolitana do Rio de Janeiro]. *Revista de Nutricao* 2007;**20**(2):159-69.

**Brooks 2005b** *{published data only}*

Brooks WA, Santosham M, Naheed A, Goswami D, Wahed MA, Diener-West M, et al. Effect of weekly zinc supplements on incidence of pneumonia and diarrhoea in children younger than 2 years in an urban, low-income population in Bangladesh: randomised controlled trial. *Lancet* 2005;**366**(9490):999-1004.

**Brown 2007** *{published data only}*

Brown KH, López de Romaña D, Arsenault JE, Peerson JM, Penny ME. Comparison of the effects of zinc delivered in a fortified food or a liquid supplement on the growth morbidity and plasma zinc concentrations of young Peruvian children. *American Journal of Clinical Nutrition* 2007;**85**(2):538-47.

**Bruzzese 2016** *{published data only}*

Bruzzese E, Fedele MC, Bruzzese D, Viscovo S, Giannattasio A, Mandato C, et al. Randomised clinical trial: a Lactobacillus GG and micronutrient-containing mixture is effective in reducing nosocomial infections in children, vs. placebo. *Alimentary Pharmacology & Therapeutics* 2016;**44**(6):568-75.

**Cárcamo 2006** *{published data only}*

Cárcamo C, Hooton T, Weiss NS, Gilman R, Wener MH, Chavez V, et al. Randomized controlled trial of zinc supplementation for persistent diarrhea in adults with HIV-1 infection. *Journal of Acquired Immune Deficiency Syndromes* 2006;**43**(2):197-201.

**Chandyo 2010** *{published data only}*

Chandyo RK, Shrestha PS, Valentiner-Branth P, Mathisen M, Basnet S, Ulak M, et al. Two weeks of zinc administration to Nepalese children with pneumonia does not reduce the incidence of pneumonia or diarrhea during the next six months. *Journal of Nutrition* 2010;**140**(9):1677-82.

**Chang 2010** *{published data only}*

Chang S, El Arifeen S, Bari S, Wahed MA, Rahman KM, Rahman MT, et al. Supplementing iron and zinc: double blind, randomized evaluation of separate or combined delivery. *European Journal of Clinical Nutrition* 2010;**64**(2):153-60.

**Chen 2010** *{published data only}*

Chen K, Zhang X, Li TY, Chen L, Wei XP, Qu P, et al. Effect of vitamin A, vitamin A plus iron and multiple micronutrient-fortified seasoning powder on infectious morbidity of preschool children. *Nutrition* 2010;**27**(4):428-34.

**Chhagan 2009** *{published data only}*

Chhagan MK, Van den Broeck J, Luabeya KK, Mpontshane N, Tucker KL, Bennish ML. Effect of micronutrient supplementation on diarrhoeal disease among stunted children in rural South Africa. *European Journal of Clinical Nutrition* 2009;**63**(7):850-7.

**Chhagan 2010** *{published data only}*

Chhagan MK, Van den Broeck J, Luabeya KK, Mpontshane N, Tomkins A, Bennish ML. Effect on longitudinal growth and anemia of zinc or multiple micronutrients added to vitamin A: a randomized controlled trial in children aged 6-24 months. *BMC Public Health* 2010;**10**:145.

**Christian 2009** *{published data only}*

Christian P, Stewart CP, LeClerq SC, Wu L, Katz J, West KP Jr, et al. Antenatal and postnatal iron supplementation and childhood mortality in rural Nepal: a prospective follow-up in a randomized, controlled community trial. *American Journal of Epidemiology* 2009;**170**(9):1127-36.

**CIGNIS 2010** *{published data only}*

Chilenje Infant Growth, Nutrition and Infection (CIGNIS) Study Team. Micronutrient fortification to improve growth and health of maternally HIV-unexposed and exposed Zambian infants: a randomised controlled trial. *PLOS ONE* 2010;**5**(6):e11165.

**Colgate 2016** *{published data only}*

Colgate ER, Haque R, Dickson DM, Carmolli MP, Mychaleckyj JC, Nayak U, et al. Delayed dosing of oral rotavirus vaccine demonstrates decreased risk of rotavirus gastroenteritis associated with serum zinc: a randomized controlled trial. *Clinical Infectious Diseases* 2016;**63**(5):634-41.

**Coronel Carbajal 2000** *{published data only}*

Coronel Carbajal C. Micronutrients: an option in the treatment of acute diarrheal diseases [Micronutrientes: una opción en el tratamiento de las enfermedades diarreicas agudas]. *Revista Cubana de Pediatría* 2000;**72**(4):261-6.

**Cross 2009** *{published data only}*

Cross AJ, Heath AL, Ferguson EL, Gray AR, Szymlek-Gay EA. Rates of common communicable illnesses in non-anaemic 12-24 month old South Island, New Zealand children. *New Zealand Medical Journal* 2009;**122**(1290):24-35.

**Dhingra 2009** *{published data only}*

Dhingra U, Hiremath G, Menon VP, Dhingra P, Sarkar A, Sazawal S. Zinc deficiency: descriptive epidemiology and morbidity among preschool children in peri-urban population in Delhi, India. *Journal of Health, Population, and Nutrition* 2009;**27**(5):632-9.

**Doherty 1998** *{published data only}*

Doherty CP, Sarkar MA, Shakur MS, Ling SC, Elton RA, Cutting WA. Zinc and rehabilitation from severe protein-energy malnutrition: higher-dose regimens are associated with increased mortality. *American Journal of Clinical Nutrition* 1998;**68**(3):742-8.

**Ebrahimi 2006** *{published data only}*

Ebrahimi S, Pormahmodi A, Kamkar A. Study of zinc supplementation on growth of schoolchildren in Yasuj, Southwest of Iran. *Pakistan Journal of Nutrition* 2006;**5**(4):341-2.

**Ellis 2007** *{published data only}*

Ellis AA, Winch P, Daou Z, Gilroy KE, Swedberg E. Home management of childhood diarrhoea in southern Mali--implications for the introduction of zinc treatment. *Social Science and Medicine* 2007;**64**(3):701-12.

**Ferraz 2007** *{published data only}*

Ferraz IS, Daneluzzi JC, Vannucchi H, Jordão Jr AA, Ricco RG, Del Ciampo LA, et al. Zinc serum levels and their association with vitamin A deficiency in preschool children [Nível sérico de zinco e sua associação com deficiência de vitamina A em crianças pré-escolares]. *Jornal de Pediatria* 2007;**83**(6):512-7.

**Ferrufino 2007** *{unpublished data only}*

Ferrufino B, Sagrario A. Aceptabilidad de las madres de la suplementación del sulfato de zinc en el manejo de las enfermedades diarreicas en menores de 5 años, municipio de Jinotega. Noviembre del año 2006 a marzo del año 2007 [Acceptability of mothers of zinc sulphate supplementation in children under 5 years in the municipality of Jinotega. November 2006 to March 2007]. [Masters thesis]. Managua: Universidad Nacional Autónoma de Nicaragua, 2007.

**Fischer Walker 2008** *{published data only}*

Fischer Walker CL, Black RE, Baqui AH. Does age affect the response to zinc therapy for diarrhoea in Bangladeshi infants?. *Journal of Health, Population, and Nutrition* 2008;**26**(1):105-9.

**Gardner 2005** *{published data only}*

Gardner JM, Powell CA, Baker-Henningham H, Walker SP, Cole TJ, Grantham-McGregor SM. Zinc supplementation and psychosocial stimulation: effects on the development of undernourished Jamaican children. *American Journal of Clinical Nutrition* 2005;**82**(2):399-405.

**Garenne 2007** *{published data only}*

Garenne M, Becher H, Ye Y, Kouyate B, Muller O. Sex-specific responses to zinc supplementation in Nouna, Burkina Faso. *Journal of Pediatric Gastroenterology and Nutrition* 2007;**44**(5):619-28.

**Gebremedhin 2016** *{published data only}*

Gebremedhin S, Mamo G, Gezahign H, Kung'u J, Adish A. The effectiveness bundling of zinc with Oral Rehydration Salts (ORS) for improving adherence to acute watery diarrhea treatment in

Ethiopia: cluster randomised controlled trial. *BMC Public Health* 2016;**16**:457.

**Gregorio 2007** *{published data only}*

Gregorio GV, Dans LF, Cordero CP, Panelo CA. Zinc supplementation reduced cost and duration of acute diarrhea in children. *Journal of Clinical Epidemiology* 2007;**60**(6):560-6.

**Gupta 2003** *{published data only}*

Gupta DN, Mondal SK, Ghosh S, Rajendran K, Sur D, Manna B. Impact of zinc supplementation on diarrhoeal morbidity in rural children of West Bengal, India. *Acta Paediatrica* 2003;**92**(5):531-6.

**Gupta 2007** *{published data only}*

Gupta DN, Rajendran K, Mondal SK, Ghosh S, Bhattacharya SK. Operational feasibility of implementing community-based zinc supplementation: impact on childhood diarrheal morbidity. *Pediatric Infectious Disease Journal* 2007;**26**(4):306-10.

**Habib 2010** *{published data only}*

Habib MA, Soofi SB, Bhutta ZA. Effect of zinc in tablet and suspension formulations in the treatment of acute diarrhoea among young children in an emergency setting of earthquake affected region of Pakistan. *Journal of the College of Physicians and Surgeons Pakistan* 2010;**20**(12):837-8.

**Habib 2013** *{published data only}*

Habib MA, Soofi S, Sadiq K, Samejo T, Hussain M, Mirani M, et al. A study to evaluate the acceptability, feasibility and impact of packaged interventions ("Diarrhea Pack") for prevention and treatment of childhood diarrhea in rural Pakistan. *BMC Public Health* 2013;**13**:922.

**Heinig 2006** *{published data only}*

Heinig MJ, Brown KH, Lönnerdal B, Dewey KG. Zinc supplementation does not affect growth, morbidity, or motor development of US term breastfed infants at 4-10 mo of age. *American Journal of Clinical Nutrition* 2006;**84**(3):594-601.

**Hess 2015** *{published data only}*

Hess SY, Abbeddou S, Jimenez EY, Somé JW, Vosti SA, Ouédraogo ZP, et al. Small-quantity lipid-based nutrient supplements, regardless of their zinc content, increase growth and reduce the prevalence of stunting and wasting in young Burkinabe children: a cluster-randomized trial. *PLOS ONE* 2015;**10**(3):e0122242.

**Hettiarachchi 2008** *{published data only}*

Hettiarachchi M, Liyanage C, Wickremasinghe R, Hilmers DC, Abrams SA. The efficacy of micronutrient supplementation in reducing the prevalence of anaemia and deficiencies of zinc and iron among adolescents in Sri Lanka. *European Journal of Clinical Nutrition* 2008;**62**(7):856-65.

**Hidayat 1998** *{published data only}*

Hidayat A, Achadi A, Sunoto, Soedarmo SP. The effect of zinc supplementation in children under three years of age with acute diarrhea in Indonesia. *Medical Journal of Indonesia* 1998;**7**(4):237–41.

**Hoque 2006** *{published data only}*

Hoque KM, Binder HJ. Zinc in the treatment of acute diarrhea: current status and assessment. *Gastroenterology* 2006;**130**(7):2201-5.

**Hyder 2007** *{published data only}*

Hyder SM, Haseen F, Khan M, Schaetzel T, Jalal CS, Rahman M, et al. A multiple-micronutrient-fortified beverage affects hemoglobin, iron, and vitamin A status and growth in adolescent girls in rural Bangladesh. *Journal of Nutrition* 2007;**137**(9):2147-53.

**Iannotti 2010** *{published data only}*

Iannotti LL, Zavaleta N, León Z, Huasquiche C, Shankar AH, Caulfield LE. Maternal zinc supplementation reduces diarrheal morbidity in Peruvian infants. *Journal of Pediatrics* 2010;**156**(6):960-4, 964.e1-2.

**Islam 2010** *{published data only}*

Islam MN, Chowdhury MA, Siddika M, Qurishi SB, Bhuiyan MK, Hoque MM, et al. Effect of oral zinc supplementation on the growth of preterm infants. *Indian Pediatrics* 2010;**47**(10):845-9.

**Jimenez 2000** *{published data only}*

Jimenez R, Sagaro E, Lafita Y. How growth infants supplemented with zinc sulfate after an episode of persistent diarrhea. *Journal of Pediatric Gastroenterology and Nutrition* 2000;**31 Suppl 2**:S26.

**Kelly 1999** *{published data only}*

Kelly P, Musonda R, Kafwembe E, Kaetano L, Keane E, Farthing M. Micronutrient supplementation in the AIDS diarrhoea-wasting syndrome in Zambia: a randomized controlled trial. *AIDS* 1999;**13**(4):495-500.

**Kelly 2010** *{published data only}*

Kelly P, Shawa T, Mwanamakondo S, Soko R, Smith G, Barclay GR, et al. Gastric and intestinal barrier impairment in tropical enteropathy and HIV: limited impact of micronutrient supplementation during a randomised controlled trial. *BMC Gastroenterology* 2010;**10**:72.

**Kianmehr 2016** *{published data only}*

Kianmehr M, Saber A, Moshari J, Ahmadi R, Basiri-Moghadam M. The effect of G-ORS along with rice soup in the treatment of acute diarrhea in children: a single-blind randomized controlled trial. *Nursing and Midwifery Studies* 2016;**5**(2):e25852.

**Larson 2010** *{published data only}*

Larson CP, Nasrin D, Saha A, Chowdhury MI, Qadri F. The added benefit of zinc supplementation after zinc treatment of acute childhood diarrhoea: a randomized, double-blind field trial. *Tropical Medicine & International Health* 2010;**15**(6):754-61.

**Lin 2008** *{published data only}*

Lin CA, Manary MJ, Maleta K, Briend A, Ashorn P. An energy-dense complementary food is associated with a modest increase in weight gain when compared with a fortified porridge in Malawian children aged 6-18 months. *Journal of Nutrition* 2008;**138**(3):593-8.

**Lind 2004** *{published data only}*

Lind T, Lönnerdal B, Stenlund H, Gamayanti IL, Ismail D, Seswandhana R, et al. A community-based randomized controlled trial of iron and zinc supplementation in Indonesian infants: effects on growth and development. *American Journal of Clinical Nutrition* 2004;**80**(3):729-36.

**Lind 2008** *{published data only}*

Lind T, Seswandhana R, Persson LA, Lönnerdal B. Iron supplementation of iron-replete Indonesian infants is associated with reduced weight-for-age. *Acta Paediatrica* 2008;**97**(6):770-5.

**Lira 1998** *{published data only}*

Lira PI, Ashworth A, Morris SS. Effect of zinc supplementation on the morbidity, immune function, and growth of low-birth-weight, full-term infants in northeast Brazil. *American Journal of Clinical Nutrition* 1998;**68**(2 Suppl):418S-24S.

**Long 2006** *{published data only}*

Long KZ, Montoya Y, Hertzmark E, Santos JI, Rosado JL. A double-blind, randomized, clinical trial of the effect of vitamin A and zinc supplementation on diarrheal disease and respiratory tract infections in children in Mexico City, Mexico. *American Journal of Clinical Nutrition* 2006;**83**(3):693-700.

**Long 2007** *{published data only}*

Long KZ, Rosado JL, Montoya Y, de Lourdes Solano M, Hertzmark E, DuPont HL, et al. Effect of vitamin A and zinc supplementation on gastrointestinal parasitic infections among Mexican children. *Pediatrics* 2007;**120**(4):e846-55.

**Lopez 2005** *{published data only}*

López de Romaña G, Cusirramos S, López de Romaña D, Gross R. Efficacy of multiple micronutrient supplementation for improving anemia, micronutrient status, growth, and morbidity of Peruvian infants. *Journal of Nutrition* 2005;**135**(3):646S-52S.

**Luabeya 2007** *{published data only}*

Luabeya KK, Mpontshane N, Mackay M, Ward H, Elson I, Chhagan M, et al. Zinc or multiple micronutrient supplementation to reduce diarrhea and respiratory disease in South African children: a randomized controlled trial. *PLOS ONE* 2007;**2**(6):e541.

**Makonnen 2003a** *{published data only}*

Makonnen B, Venter A, Joubert G. A randomized controlled study of the impact of dietary zinc supplementation in the management of children with protein-energy malnutrition in Lesotho. I: Mortality and morbidity. *Journal of Tropical Pediatrics* 2003;**49**(6):340-52.

**Makonnen 2003b** *{published data only}*

Makonnen B, Venter A, Joubert G. A randomized controlled study of the impact of dietary zinc supplementation in the management of children with protein-energy malnutrition in Lesotho. II: Special investigations. *Journal of Tropical Pediatrics* 2003;**49**(6):353-60.

**Manger 2008** *{published data only}*

Manger MS, McKenzie JE, Winichagoon P, Gray A, Chavasit V, Pongcharoen T, et al. A micronutrient-fortified seasoning powder reduces morbidity and improves short-term cognitive function, but has no effect on anthropometric measures in primary school children in northeast Thailand: a randomized controlled trial. *American Journal of Clinical Nutrition* 2008;**87**(6):1715-22.

**Maragkoudaki 2016** *{published data only}*

Maragkoudaki M, Chouliaras G, Moutafi A, Thomas A, Orfanakou A, Papadopoulou A. Efficacy of an ORS enriched with L. reuteri DSM 17938 and zinc in infants with acute gastroenteritis: A double blind, placebo controlled trial. Journal of Pediatric Gastroenterology and Nutrition Conference: 49th Annual Meeting of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition, ESPGHAN. 2016.

**Martinez-Estevez 2016** *{published data only}*

Martinez-Estevez NS, Alvarez-Guevara AN, Rodriguez-Martinez CE. Effects of zinc supplementation in the prevention of respiratory tract infections and diarrheal disease in Colombian children: A 12-month randomised controlled trial. *Allergologia et Immunopathologia* 2016;**44**(4):368-75.

**Mazariegos 2010** *{published data only}*

Mazariegos M, Hambidge KM, Westcott JE, Solomons NW, Raboy V, Das A, et al. Neither a zinc supplement nor phytate-reduced maize nor their combination enhance growth of 6- to 12-month-old Guatemalan infants. *Journal of Nutrition* 2010;**140**(5):1041-8.

**Mazumder 2010** *{published data only}*

Mazumder S, Taneja S, Bhandari N, Dube B, Agarwal RC, Mahalanabis D, et al. Effectiveness of zinc supplementation plus oral rehydration salts for diarrhoea in infants aged less than 6 months in Haryana state, India. *Bulletin of the World Health Organization* 2010;**88**(10):754-60.

**Mda 2010** *{published data only}*

Mda S, van Raaij JM, de Villiers FP, MacIntyre UE, Kok FJ. Short-term micronutrient supplementation reduces the duration of pneumonia and diarrheal episodes in HIV-infected children. *Journal of Nutrition* 2010;**140**(5):969-74.

**Meeks Gardner 1998** *{published data only}*

Meeks Gardner J, Witter MM, Ramdath DD. Zinc supplementation: effects on the growth and morbidity of undernourished Jamaican children. *European Journal of Clinical Nutrition* 1998;**52**(1):34-9.

**Müller 2001** *{published data only}*

Müller O, Becher H, van Zweeden AB, Ye Y, Diallo DA, Konate AT, et al. Effect of zinc supplementation on malaria and other causes of morbidity in west African children: randomised double blind placebo controlled trial. *BMJ* 2001;**322**(7302):1567.

**Naheed 2009** *{published data only}*

Naheed A, Walker Fischer CL, Mondal D, Ahmed S, Arifeen SE, Yunus M, et al. Zinc therapy for diarrhoea improves growth

among Bangladeshi infants 6 to 11 months of age. *Journal of Pediatric Gastroenterology and Nutrition* 2009;**48**(1):89-93.

**Nasrin 2005** *{published data only}*

Nasrin D, Larson CP, Sultana S, Khan TU. Acceptability of and adherence to dispersible zinc tablet in the treatment of acute childhood diarrhoea. *Journal of Health, Population, and Nutrition* 2005;**23**(3):215-21.

**Negi 2014** *{published data only}*

Negi R, Dewan P, Shah D, Das S, Bhatnagar S, Gupta P. Oral zinc supplements are ineffective for treating acute dehydrating diarrhoea in 5-12-year-olds. *Acta Paediarica* 2014;**104**(8):e367-71.

**Nga 2009** *{published data only}*

Nga TT, Winichagoon P, Dijkhuizen MA, Khan NC, Wasantwisut E, Furr H, et al. Multi-micronutrient-fortified biscuits decreased prevalence of anemia and improved micronutrient status and effectiveness of deworming in rural Vietnamese school children. *Journal of Nutrition* 2009;**139**(5):1013-21.

**Osendarp 2002** *{published data only}*

Osendarp SJ, Santosham M, Black RE, Wahed MA, van Raaij JM, Fuchs GJ. Effect of zinc supplementation between 1 and 6 mo of life on growth and morbidity of Bangladeshi infants in urban slums. *American Journal of Clinical Nutrition* 2002;**76**(6):1401-8.

**Ouedraogo 2008** *{published data only}*

Ouedraogo HZ, Dramaix-Wilmet M, Zeba AN, Hennart P, Donnen P. Effect of iron or multiple micronutrient supplements on the prevalence of anaemia among anaemic young children of a malaria-endemic area: a randomized double-blind trial. *Tropical Medicine and International Health* 2008;**13**(10):1257-66.

**Passariello 2010** *{published data only}*

Passariello A, Terrin G, De Marco G, Cecere G, Ruotolo S, Marino A, et al. Efficacy of a new hypotonic oral rehydration solution containing zinc and prebiotics in the treatment of childhood acute diarrhea: a randomized controlled trial. *Journal of Pediatrics* 2011;**158**(2):288-92.e1.

**Patel 2005** *{published data only}*

Patel AB, Dhande LA, Rawat MS. Therapeutic evaluation of zinc and copper supplementation in acute diarrhea in children: double blind randomized trial. *Indian Pediatrics* 2005;**42**(5):433-42.

**Patel 2010a** *{published data only}*

Patel AB, Dibley MJ, Mamtani M, Badhoniya N, Kulkarni H. Influence of zinc supplementation in acute diarrhea differs by the isolated organism. *International Journal of Pediatrics* 2010;**2010**:671587.

**Patel 2010b** *{published data only}*

Patel A, Mamtani M, Dibley MJ, Badhoniya N, Kulkarni H. Therapeutic value of zinc supplementation in acute and persistent diarrhea: a systematic review. *PLOS ONE* 2010;**5**(4):e10386.

**Patel 2012** *{published data only}*

Patel AB, Dibley MJ, Mamtani M, Badhoniya N, Kulkarni H. Therapeutic zinc and copper supplementation in acute diarrhea does not influence short-term morbidity and growth: double-blind randomized controlled trial. *Pediatric Infectious Disease Journal* 2013;**32**(1):91-3.

**Penny 2004a** *{published data only}*

Penny ME, Marin RM, Duran A, Peerson JM, Lanata CF, Lönnerdal B, et al. Randomized controlled trial of the effect of daily supplementation with zinc or multiple micronutrients on the morbidity, growth, and micronutrient status of young Peruvian children. *American Journal of Clinical Nutrition* 2004;**79**(3):457-65.

**Penny 2004b** *{published data only}*

Penny ME, Black RE, Brown KH, Lönnerdal B. Reply to RJ Walden [Letter to the Editor]. *American Journal of Clinical Nutrition* 2004;**80**(4):1084-5.

**Polat 2006** *{published data only}*

Polat B, Tokuc G, Vagas E, Oktem S, Gokduman MK. Impact of zinc supplementation in children with acute diarrhoea in Turkey. *Archives of Disease in Childhood* 2006;**91**(4):296-9.

**Prado 2016** *{published data only}*

Prado EL, Abbeddou S, Jimenez EY, Some JW, Ouedraogo ZP, Vosti SA, et al. Lipid-based nutrient supplements plus malaria and diarrhea treatment increase infant development scores in a cluster-randomized trial in Burkina Faso. *Journal of Nutrition* 146;**4**:814-22.

**Rahman 2001** *{published data only}*

Rahman MM, Vermund SH, Wahed MA, Fuchs GJ, Baqui AH, Alvarez JO. Simultaneous zinc and vitamin A supplementation in Bangladeshi children: randomised double blind controlled trial. *BMJ* 2001;**323**(7308):314-8.

**Rahman 2005** *{published data only}*

Rahman MJ, Sarker P, Roy SK, Ahmad SM, Chisti J, Azim T, et al. Effects of zinc supplementation as adjunct therapy on the systemic immune responses in shigellosis. *American Journal of Clinical Nutrition* 2005;**81**(2):495-502.

**Raqib 2004** *{published data only}*

Raqib R, Roy SK, Rahman MJ, Azim T, Ameer SS, Chisti J, et al. Effect of zinc supplementation on immune and inflammatory responses in pediatric patients with shigellosis. *American Journal of Clinical Nutrition* 2004;**79**(3):444-50.

**Richard 2006** *{published data only}*

Richard SA, Zavaleta N, Caulfield LE, Black RE, Witzig RS, Shankar AH. Zinc and iron supplementation and malaria, diarrhea, and respiratory infections in children in the Peruvian Amazon. *American Journal of Tropical Medicine and Hygiene* 2006;**75**(1):126-32.

**Rollins 2007** *{published data only}*

Rollins NC, van den Broeck J, Kindra G, Pent M, Kasambira T, Bennish ML. The effect of nutritional support on weight

gain of HIV-infected children with prolonged diarrhoea. *Acta Paediatrica* 2007;**96**(1):62-8.

**Rosado 1997** *{published data only}*

Rosado JL, López P, Muñoz E, Martinez H, Allen LH. Zinc supplementation reduced morbidity, but neither zinc nor iron supplementation affected growth or body composition of Mexican preschoolers. *American Journal of Clinical Nutrition* 1997;**65**(1):13-9.

**Rosado 1998** *{published data only}*

Rosado JL. Zinc deficiency and its functional implications [Deficiencia de zinc y sus implicaciones funcionales]. *Salud Pública de México* 1998;**40**(2):181-8.

**Rosado 2009** *{published data only}*

Rosado JL, Caamaño MC, Montoya YA, de Lourdes Solano M, Santos JI, Long KZ. Interaction of zinc or vitamin A supplementation and specific parasite infections on Mexican infants' growth: a randomized clinical trial. *European Journal of Clinical Nutrition* 2009;**63**(10):1176-84.

**Roy 1992** *{published data only}*

Roy SK, Akramuzzaman SM, Haider R, Mahalanabis D, Behrens RH, Wahed MA, et al. Zinc supplementation in diarrhoea: nutritional implication on clinical recovery and intestinal permeability [Abstract]. *Journal of Gastroenterology and Hepatology* 1994;**9**(6):A166.

* Roy SK, Behrens RH, Haider R, Akramuzzaman SM, Mahalanabis D, Wahed MA, et al. Impact of zinc supplementation on intestinal permeability in Bangladeshi children with acute diarrhoea and persistent diarrhoea syndrome. *Journal of Pediatric Gastroenterology and Nutrition* 1992;**15**(3):289-96.

**Roy 1999** *{published data only}*

Roy SK, Tomkins AM, Haider R, Behren RH, Akramuzzaman SM, Mahalanabis D, et al. Impact of zinc supplementation on subsequent growth and morbidity in Bangladeshi children with acute diarrhoea. *European Journal of Clinical Nutrition* 1999;**53**(7):529-34.

**Roy 2007** *{published data only}*

Roy SK, Tomkins AM, Akramuzzaman SM, Chakraborty B, Ara G, Biswas R, et al. Impact of zinc supplementation on subsequent morbidity and growth in Bangladeshi children with persistent diarrhoea. *Journal of Health, Population, and Nutrition* 2007;**25**(1):67-74.

**Roy 2008b** *{published data only}*

Roy SK, Hossain MJ, Khatun W, Chakraborty B, Chowdhury S, Begum A, et al. Zinc supplementation in children with cholera in Bangladesh: randomised controlled trial. *BMJ* 2008;**336**(7638):266-8.

**Ruel 1997** *{published data only}*

Ruel MT, Rivera JA, Santizo MC, Lönnerdal B, Brown KH. Impact of zinc supplementation on morbidity from diarrhea and respiratory infections among rural Guatemalan children. *Pediatrics* 1997;**99**(6):808-13.

**Sabatier 1997** *{published data only}*

Sabatier García FJ, Izquierdo Estévez A, León García RE, Díaz Fernández L. Benefits of zinc in the treatment of infants presenting with diarrhea [Beneficios del cinc en el tratamiento de niños con diarrea]. *Revista Cubana de Pediatría* 1997;**69**(3/4):197-200.

**Sáenz De Pipaón 2007** *{published data only}*

Sáenz De Pipaón M, Sancho Martinez A, Quero Jiménez J. Effects of supplementation with zinc in the first year of life [Efectos de la suplementación con cinc en el primer año de vida]. *Revista Española De Pediatría* 2007;**63**(6):464-82.

**Samuel 1995** *{published data only}*

Samuel MJ. Paediatrics Forum. Acute diarrhoea. *Africa Health* 1995;**17**(5):27, 29-30.

**Sazawal 1996** *{published data only}*

Sazawal S, Black RE, Bhan MK, Jalla S, Bhandari N, Sinha A, et al. Zinc supplementation reduces the incidence of persistent diarrhea and dysentery among low socio-economic children in India. *Journal of Nutrition* 1996;**126**(2):443-50.

**Sazawal 1997a** *{published data only}*

Sazawal S, Black RE, Bhan MK, Jalla S, Sinha A, Bhandari N. Efficacy of zinc supplementation in reducing the incidence and prevalence of acute diarrhea - a community-based, double-blind, controlled trial. *American Journal of Clinical Nutrition* 1997;**66**(2):413-8.

**Sazawal 2004** *{published data only}*

Sazawal S, Marwah D, Sazawal S, Black RE, Deb S, Dhingra U, et al. Efficacy of zinc and iron fortification of milk in prevention of anemia, diarrhea pneumonia, and iron deficiency- a community based double masked randomized trial. *Journal of Pediatric Gastroenterology and Nutrition* 2004;**39 Suppl 1**:417-8.

**Sazawal 2007a** *{published data only}*

Sazawal S, Dhingra U, Dhingra P, Hiremath G, Kumar J, Sarkar A, et al. Effects of fortified milk on morbidity in young children in north India: community based randomised double masked placebo controlled trial. *BMJ* 2007;**334**(7585):140.

**Sazawal 2007b** *{published data only}*

Sazawal S, Dhingra U, Deb S, Bhan MK, Menon VP, Black RE. Effect of zinc added to multi-vitamin supplementation containing low-dose vitamin A on plasma retinol level in children--a double-blind randomized, controlled trial. *Journal of Health, Population, and Nutrition* 2007;**25**(1):62-6.

**Sazawal 2007c** *{published data only}*

Sazawal S, Black RE, Ramsan M, Chwaya HM, Dutta A, Dhingra U, et al. Effect of zinc supplementation on mortality in children aged 1-48 months: a community-based randomised placebo-controlled trial. *Lancet* 2007;**369**(9565):927-34.

**Shamir 2005** *{published data only}*

Shamir R, Makhoul IR, Etzioni A, Shehadeh N. Evaluation of a diet containing probiotics and zinc for the treatment of mild diarrheal illness in children younger than one year of age. *Journal of the American College of Nutrition* 2005;**24**(5):370-5.

**Shankar 1998** *{published data only}*

Shankar AH, Prasad AS. Zinc and immune function: the biological basis of altered resistance to infection. *American Journal of Clinical Nutrition* 1998;**68**(2 Suppl):447S-63S.

**Sharieff 2006** *{published data only}*

Sharieff W, Bhutta Z, Schauer C, Tomlinson G, Zlotkin S. Micronutrients (including zinc) reduce diarrhoea in children: the Pakistan Sprinkles Diarrhoea Study. *Archives of Disease in Childhood* 2006;**91**(7):573-9.

**Sheikh 2010** *{published data only}*

Sheikh A, Shamsuzzaman S, Ahmad SM, Nasrin D, Nahar S, Alam MM, et al. Zinc influences innate immune responses in children with enterotoxigenic Escherichia coli-induced diarrhea. *Journal of Nutrition* 2010;**140**(5):1049-56.

**Sur 2003** *{published data only}*

Sur D, Gupta DN, Mondal SK, Ghosh S, Manna B, Rajendran K, et al. Impact of zinc supplementation on diarrheal morbidity and growth pattern of low birth weight infants in Kolkata, India: a randomized, double-blind, placebo-controlled, community-based study. *Pediatrics* 2003;**112**(6 Pt 1):1327-32.

**Taneja 2009** *{published data only}*

Taneja S, Bhandari N, Rongsen-Chandola T, Mahalanabis D, Fontaine O, Bhan MK. Effect of zinc supplementation on morbidity and growth in hospital-born, low-birth-weight infants. *American Journal of Clinical Nutrition* 2009;**90**(2):385-91.

**Taneja 2010** *{published data only}*

Taneja S, Strand TA, Sommerfelt H, Bahl R, Bhandari N. Zinc supplementation for four months does not affect growth in young north Indian children. *Journal of Nutrition* 2010;**140**(3):630-4.

**Tielsch 2006** *{published data only}*

Tielsch JM, Khatry SK, Stoltzfus RJ, Katz J, LeClerq SC, Adhikari R, et al. Effect of routine prophylactic supplementation with iron and folic acid on preschool child mortality in southern Nepal: community-based, cluster-randomised, placebo-controlled trial. *Lancet* 2006;**367**(9505):144-52.

**Tielsch 2007** *{published data only}*

Tielsch JM, Khatry SK, Stoltzfus RJ, Katz J, LeClerq SC, Adhikari R, et al. Effect of daily zinc supplementation on child mortality in southern Nepal: a community-based, cluster randomised, placebo-controlled trial. *Lancet* 2007;**370**(9594):1230-9.

**Umeta 2000** *{published data only}*

Umeta M, West CE, Haidar J, Deurenberg P, Hautvast JG. Zinc supplementation and stunted infants in Ethiopia: a randomised controlled trial. *Lancet* 2000;**355**(9220):2021-6.

**Untoro 2005** *{published data only}*

Untoro J, Karyadi E, Wibowo L, Erhardt MW, Gross R. Multiple micronutrient supplements improve micronutrient status and anemia but not growth and morbidity of Indonesian infants: a randomized, double-blind, placebo-controlled trial. *Journal of Nutrition* 2005;**135**(3):639S-45S.

**Valery 2005** *{published data only}*

Valery PC, Torzillo PJ, Boyce NC, White AV, Stewart PA, Wheaton GR, et al. Zinc and vitamin A supplementation in Australian Indigenous children with acute diarrhoea: a randomised controlled trial. *Medical Journal of Australia* 2005;**182**(10):530-5.

**Veenemans 2011** *{published data only}*

Veenemans J, Mank T, Ottenhof M, Baidjoe A, Mbugi EV, Demir AY, et al. Protection against diarrhea associated with Giardia intestinalis Is lost with multi-nutrient supplementation: a study in Tanzanian children. *PLoS Neglected Tropical Diseases* 2011;**5**(6):e1158.

**Wadhwa 2011** *{published data only}*

Wadhwa N, Natchu UC, Sommerfelt H, Strand TA, Kapoor V, Saini S, et al. ORS containing zinc does not reduce duration or stool volume of acute diarrhea in hospitalized children. *Journal of Pediatric Gastroenterology and Nutrition* 2011;**53**(2):161-7.

**Walden 2004** *{published data only}*

Walden RJ. Supplementation with zinc and other minerals. *American Journal of Clinical Nutrition* 2004;**80**(4):1084.

**Walker 2007** *{published data only}*

Walker CL, Bhutta ZA, Bhandari N, Teka T, Shahid F, Taneja S, et al. Zinc during and in convalescence from diarrhea has no demonstrable effect on subsequent morbidity and anthropometric status among infants <6 mo of age. *American Journal of Clinical Nutrition* 2007;**85**(3):887-94.

**Wieringa 2010** *{published data only}*

Wieringa FT, Dijkhuizen MA, Muhilal, Van der Meer JW. Maternal micronutrient supplementation with zinc and beta-carotene affects morbidity and immune function of infants during the first 6 months of life. *European Journal of Clinical Nutrition* 2010;**64**(10):1072-9.

**Winch 2006** *{published data only}*

Winch PJ, Gilroy KE, Doumbia S, Patterson AE, Daou Z, Coulibaly S, et al. Prescription and administration of a 14-day regimen of zinc treatment for childhood diarrhea in Mali. *American Journal of Tropical Medicine and Hygiene* 2006;**74**(5):880-3.

**Winch 2008** *{published data only}*

Winch PJ, Gilroy KE, Doumbia S, Patterson AE, Daou Z, Diawara A, et al. Operational issues and trends associated with the pilot introduction of zinc for childhood diarrhoea in Bougouni district, Mali. *Journal of Health, Population, and Nutrition* 2008;**26**(2):151-62.

**Wuehler 2008** *{published data only}*

Wuehler SE, Sempértegui F, Brown KH. Dose-response trial of prophylactic zinc supplements, with or without copper, in young Ecuadorian children at risk of zinc deficiency. *American Journal of Clinical Nutrition* 2008;**87**(3):723-33.

## References to ongoing studies

**NCT01140074** *{unpublished data only}*

NCT01140074. Efficacy of zinc sulfate with probiotics for the treatment of acute diarrhea in children (zinc) [Effectiveness and efficacy of zinc with probiotics for the treatment of acute diarrhea in young children]. https://clinicaltrials.gov/ct2/show/NCT01140074 (first received 7 June 2010).

**NCT01198587** *{unpublished data only}*

NCT01198587. Oral zinc for the treatment of acute diarrhea in US children [A double blind randomized placebo controlled trial of oral zinc for children with acute diarrhea in a developed nation]. https://clinicaltrials.gov/ct2/show/NCT01198587 (first received 2 September 2010).

## Additional references

**Albert 2003**

Albert MJ, Qadri F, Wahed MA, Ahmed T, Rahman AS, Ahmed F, et al. Supplementation with zinc, but not vitamin A, improves seroconversion to vibriocidal antibody in children given an oral cholera vaccine. *Journal of Infectious Diseases* 2003;**187**(6):909-13.

**Berni Canani 2010**

Berni Canani R, Buccigrossi V, Passariello A. Mechanisms of action of zinc in acute diarrhea. *Current Opinion in Gastroenterology* 2011;**27**(1):8-12.

**Beshgetoor 1998**

Beshgetoor D, Hambidge M. Clinical conditions altering copper metabolism in humans. *American Journal of Clinical Nutrition* 1998;**67**(5 Suppl):1017S-21S.

**Bhutta 2000b**

Bhutta ZA, Bird SM, Black RE, Brown KH, Gardner JM, Hidayat A, et al. Therapeutic effects of oral zinc in acute and persistent diarrhea in children in developing countries: pooled analysis of randomized controlled trials. *American Journal of Clinical Nutrition* 2000;**72**(6):1516-22.

**Brown 2003**

Brown KH. Diarrhea and malnutrition. *Journal of Nutrition* 2003;**133**(1):328S-32S.

**Das 2014**

Das JK, Salam RA, Bhutta ZA. Global burden of childhood diarrhea and interventions. *Current Opinion in Infectious Diseases* 2014;**27**(5):451-8.

**Dijkhuizen 2001**

Dijkhuizen MA, Wieringa FT, West CE, Martuti S, Muhilal. Effects of iron and zinc supplementation in Indonesian infants on micronutrient status and growth. *Journal of Nutrition* 2001;**131**(11):2860-5.

**Fischer Walker 2005**

Fischer Walker C, Kordas K, Stoltzfus RJ, Black RE. Interactive effects of iron and zinc on biochemical and functional outcomes in supplementation trials. *American Journal Clinical Nutrition* 2005;**82**(1):5-12.

**Fontaine 2001**

Fontaine O. Effect of zinc supplementation on clinical course of acute diarrhoea. *Journal of Health, Population, and Nutrition* 2001;**19**(4):339-46.

**Garenne 2005**

Garenne M, Becher H, Ye Y, Kouyate B, Müller O. Sex-specific responses to zinc supplementation in Nouna, Burkina Faso. *Journal of Pediatric Gastroenterology and Nutrition* 2007;**44**(5):619-28.

**GRADEpro GDT 2014 [Computer program]**

GRADE Working Group, McMaster University. GRADEpro GDT. Version accessed 1 September 2016. Hamilton (ON): GRADE Working Group, McMaster University, 2014.

**Gunshin 1997**

Gunshin H, Mackenzie B, Berger UV, Gunshin Y, Romero MF, Boron WF, et al. Cloning and characterization of a mammalian proton-coupled metal-ion transporter. *Nature* 1997;**388**(6641):482-8.

**Haider 2009**

Haider BA, Bhutta ZA. The effect of therapeutic zinc supplementation among young children with selected infections:a review of the evidence. *Food and Nutrition Bulletin* 2009;**30**(1 Suppl):S41-59.

**Hess 2009**

Hess SY, Lönnerdal B, Hotz C, Rivera JA, Brown KH. Recent advances in knowledge of zinc nutrition and human health. *Food and Nutrition Bulletin* 2009;**30**(1 Suppl):S5-11.

**Higgins 2011**

Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org. The Cochrane Collaboration.

**Hoque 2005**

Hoque KM, Rajendran VM, Binder HJ. Zinc inhibits cAMP-stimulated Cl secretion via basolateral K-channel blockade in rat ileum. *American Journal of Physiology, Gastrointestinal and Liver Physiology* 2005;**288**(5):G956-63.

**Hoque 2009**

Hoque KM, Sarker R, Guggino SE, Tse CM. A new insight into pathophysiological mechanisms of zinc in diarrhea. *Annals of the New York Academy of Sciences* 2009;**1165**:279–84.

**Iqbal 2001**

Iqbal AS, Shahidullah M, Islam MN, Akhter S, Banu S. Serum zinc and copper levels in the maternal blood and cord blood of neonates. *Indian Journal of Pediatrics* 2001;**68**(6):523-6.

**IZiNCG 2004**

International Zinc Nutrition Consultative Group (IZiNCG), Hotz C, Brown KH, editor(s). Assessment of the risk of zinc

deficiency in population and options for its control. *Food and Nutrition Bulletin* 2004;**25**(1 Suppl 2):S91-202.

**Kordas 2004**

Kordas K, Stoltzfus RJ. New evidence of iron and zinc interplay at the enterocyte and neural tissues. *Journal of Nutrition* 2004;**134**(6):1295-8.

**Krebs 1999**

Krebs NF. Zinc transfer to the breastfed infant. *Journal of Mammary Gland Biology and Neoplasia* 1999;**4**(3):259-68.

**Krebs 2014**

Krebs NF, Miller LV, Hambidge KM. Zinc deficiency in infants and children: a review of its complex and synergistic interactions. *Paediatrics and International Child Health* 2014;**34**(4):279–88.

**Lazzerini 2016**

Lazzerini M. Oral zinc provision in acute diarrhea. *Current Opinion in Clinical Nutrition and Metabolic Care* 2016;**19**(3):239-43.

**Liberato 2015**

Liberato SC, Singh G, Mulholland K. Zinc supplementation in young children: a review of the literature focusing on diarrhoea prevention and treatment. *Clinical Nutrition* 2015;**34**(2):181-8.

**Liu 2015a**

Liu L, Oza S, Hogan D, Perin J, Rudan I, Lawn JE, et al. Global, regional, and national causes of child mortality in 2000-13, with projections to inform post-2015 priorities: an updated systematic analysis. *Lancet* 2015;**385**(9966):430-40.

**Liu 2015b**

Liu L, Black RE, Cousens S, Mathers C, Lawn JE, Hogan DR. Causes of child death: comparison of MCEE and GBD 2013 estimates. *Lancet* 2015;**385**(9986):2461-2.

**Lukacik 2008**

Lukacik M, Thomas RL, Aranda JV. A meta-analysis of the effects of oral zinc in the treatment of acute and persistent diarrhea. *Pediatrics* 2008;**121**(2):326-36.

**MacDonald 2000**

MacDonald RS. The role of zinc in growth and cell proliferation. *Journal of Nutrition* 2000;**130**(5S Suppl):1500S-8S.

**O'Dell 2000**

O'Dell BL. Role of zinc in plasma membrane function. *Journal of Nutrition* 2000;**130**(5S Suppl):1432S-6S.

**Patro 2008**

Patro B, Golicki D, Szajewska H. Meta-analysis: zinc supplementation for acute gastroenteritis in children. *Alimentary Pharmacology & Therapeutics* 2008;**28**(6):713-23.

**Powell 2000**

Powell SR. The antioxidant properties of zinc. *Journal of Nutrition* 2000;**130**(5S Suppl):1447S-54S.

**Prasad 2008**

Prasad AS. Zinc in human health: effect of zinc on immune cells. *Molecular Medicine* 2008;**14**(5-6):353-7.

**Prasad 2014**

Prasad AS. Zinc is an antioxidant and anti-inflammatory agent: its role inhuman health. *Frontiers in Nutrition* 2014;**1**:14. [DOI: 10.3389/fnut.2014.00014]

**Review Manager 5 [Computer program]**

Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

**Sazawal 1997b**

Sazawal S, Jalla S, Mazumder S, Sinha A, Black RE, Bhan MK. Effect of zinc supplementation on cell-mediated immunity and lymphocyte subsets in preschool children. *Indian Pediatrics* 1997;**34**(7):589-97.

**Wagstaff 2004**

Wagstaff A, Bustreo F, Bryce J, Claeson M, WHO-World Bank Child Health and Poverty Working Group. Child health: reaching the poor. *American Journal of Public Health* 2004;**94**(5):726-36.

**Wessells 2012**

Wessells KR, Brown KH. Estimating the global prevalence of zinc deficiency: results based on zinc availability in national food supplies and the prevalence of stunting. *PLOS ONE* 2012;**7**(11):e50568. [DOI: 10.1371/journal.pone.0050568]

**WHO/UNICEF 2004**

World Health Organization Department of Child and Adolescent Health and Development/UNICEF. Clinical management of acute diarrhoea: WHO/UNICEF joint statement [WHO/FCH/CAH/04.7; UNICEF/PD/Diarrhoea/01]. Geneva: World Health Organization, 2004.

**Wieringa 2015**

Wieringa FT, Dijkhuizen MA, Fiorentino M, Laillou A, Berger J. Determination of zinc status in humans: which indicator should we use?. *Nutrients* 2015;**7**(5):3252–63.

**Zlotkin 1988**

Zlotkin SH, Cherian MG. Hepatic metallothionein as a source of zinc and cysteine during the first year of life. *Pediatric Research* 1988;**24**(3):326-9.

**Zlotkin 2003**

Zlotkin S, Arthur P, Schauer C, Antwi KY, Yeung G, Piekarz A. Home-fortification with iron and zinc sprinkles or iron sprinkles alone successfully treats anemia in infants and young children. *Journal of Nutrition* 2003;**133**(4):1075-80.

**Zou 2015**

Zou TT, Mou J, Zhan X. Zinc supplementation in acute diarrhea. *Indian Journal of Pediatrics* 2015;**82**(5):415-20. [DOI: 10.1007/s12098-014-1504-6]

## References to other published versions of this review

**Lazzerini 2005**

Lazzerini M, Ronfani L. Oral zinc for treating diarrhoea in children. *Cochrane Database of Systematic Reviews* 2005, Issue 3. [DOI: 10.1002/14651858.CD005436]

**Lazzerini 2008**

Lazzerini M, Ronfani L. Oral zinc for treating diarrhoea in children. *Cochrane Database of Systematic Reviews* 2008, Issue 3. [DOI: 10.1002/14651858.CD005436.pub2]

**Lazzerini 2012**

Lazzerini M, Ronfani L. Oral zinc for treating diarrhoea in children. *Cochrane Database of Systematic Reviews* 2012, Issue 6. [DOI: 10.1002/14651858.CD005436.pub3]

**Lazzerini 2013**

Lazzerini M, Ronfani L. Oral zinc for treating diarrhoea in children. *Cochrane Database of Systematic Reviews* 2013, Issue 1. [DOI: 10.1002/14651858.CD005436.pub4]

* Indicates the major publication for the study

## CHARACTERISTICS OF STUDIES

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

#### Al-Sonboli 2003

| | |
|---|---|
| Methods | Randomized controlled trial (RCT) |
| Participants | Number of participants (N): 81 participants<br>Inclusion criteria: age 3 to 60 months; diarrhoea < 7 days, or 1 or more loose stool containing blood in the previous 24 hours and at least mild dehydration<br>Exclusion criteria: suspected or confirmed severe systemic infections; antimicrobial or antidiarrhoeal treatment within 72 hours before admission; severe malnutrition (< 60% median for weight for age of the National Center for Health Statistic (NCHC) standards) |
| Interventions | 1. Zinc sulphate: 22.5 mg (3 to 6 months) or 45 mg (7 to 60 months).<br>2. Placebo. |
| Outcomes | 1. Average duration of diarrhoea.<br>2. Stool frequency. |
| Notes | Location: Brazil<br>Setting: hospital |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | The trial used a random numbers table to randomize participants. |
| Allocation concealment (selection bias) | Unclear risk | The trial authors did not provide any details regarding allocation concealment. |
| Blinding (performance bias and detection bias) All outcomes | Low risk | This trial was double blinded. |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | 8.6% of participants were lost to follow-up. |
| Selective reporting (reporting bias) | Unclear risk | There was no protocol available. |

**Al-Sonboli 2003** *(Continued)*

| | | |
|---|---|---|
| Other bias | Unclear risk | There was no further information available. |

**Bahl 2002**

| | |
|---|---|
| Methods | RCT |
| Participants | N: 1219 participants<br>Inclusion criteria: age 6 to 35 months; acute diarrhoea (less than 4 days duration)<br>Exclusion criteria: visible blood in stools; likely to emigrate in the next 4 weeks; required hospitalization; previously enrolled; sibling concurrently enrolled; refusal of consent |
| Interventions | 1. Zinc gluconate 30 mg (≥ 12 months) or 15 mg (< 12 months).<br>2. Placebo. |
| Outcomes | 1. Average duration of diarrhoea.<br>2. Diarrhoea at day 3.<br>3. Diarrhoea at day 5.<br>4. Diarrhoea at day 7.<br>5. Stool frequency.<br>6. Adverse events (vomiting). |
| Notes | Location: India<br>Setting: community |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | This trial used computer-generated randomization lists. |
| Allocation concealment (selection bias) | Low risk | An independent individual who was not involved in participant enrolment labelled the glass bottles that contained the products with the participant's number that corresponded to the randomization list. Randomization codes were secured until the completion of data collection and initial analysis. There was no difference between zinc and the placebo in appearance; a minor metallic aftertaste of zinc was hardly detectable. |
| Blinding (performance bias and detection bias) All outcomes | Low risk | Four-blinded (participant, intervention provider, data collector, data analyst). |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | 2% of participants were lost to follow-up. |
| Selective reporting (reporting bias) | Unclear risk | There was no available protocol. |
| Other bias | Unclear risk | There was no further information available. |

**Bhatnagar 2004a**

| | |
|---|---|
| Methods | RCT |
| Participants | N: 287 participants<br>Inclusion criteria: male; 3 to 36 months; acute diarrhoea (< 72 hours) with mild dehydration<br>Exclusion criteria: severe malnutrition (weight/height < 65% of NCHS median); visible blood in stool; severe systemic illness |
| Interventions | 1. Zinc sulphate: 15 mg (< 12 months) or 30 mg (> 12 months) syrup.<br>2. Placebo.<br>Both groups: multivitamin |
| Outcomes | 1. Average duration of diarrhoea.<br>2. Diarrhoea at day 5.<br>3. Diarrhoea at day 7.<br>4. Stool output.<br>5. Adverse events (vomiting).<br>6. Adverse events (copper levels). |
| Notes | Location: India<br>Setting: hospital |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | The trial authors used a table of random numbers to assign participants to treatment. |
| Allocation concealment (selection bias) | Low risk | Central randomization was performed at a site remote from trial location (World Health Organization (WHO), Geneva). |
| Blinding (performance bias and detection bias)<br>All outcomes | Low risk | The trial was double blinded. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | 7% of participants were lost to follow-up. |
| Selective reporting (reporting bias) | Unclear risk | There was no available protocol. |
| Other bias | Unclear risk | There was no further information available on other risks of bias. |

**Bhutta 1999**

| | |
|---|---|
| Methods | RCT |
| Participants | N: 87 participants |

**Bhutta 1999** *(Continued)*

| | |
|---|---|
| | Inclusion criteria: 6 to 36 months; persistent diarrhoea (> 4 unformed stools/day for at least 14 days); malnutrition (weight-for-age z score < −2.0)<br><br>Exclusion criteria: kwashiorkor; clinical signs of vitamin A or zinc deficiency; needing intravenous fluids or unable to tolerate oral feeds after a 24-hour period of stabilization |
| Interventions | 1. Zinc sulphate: 3 mg/kg/day.<br>2. Placebo.<br><br>Both groups: multivitamins |
| Outcomes | 1. Average duration of diarrhoea.<br>2. Stool output.<br>3. Adverse events (copper levels). |
| Notes | Location: Pakistan<br><br>Setting: hospital |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Random numbers table. |
| Allocation concealment (selection bias) | Low risk | An independent pharmacy performed central randomization; the pharmacy maintained the table block randomization. |
| Blinding (performance bias and detection bias)<br>All outcomes | Low risk | The trial was double blinded. |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | 11% of participants were lost to follow-up. |
| Selective reporting (reporting bias) | Unclear risk | There was no protocol available. |
| Other bias | Unclear risk | There was no further information available. |

**Boran 2006**

| | |
|---|---|
| Methods | RCT |
| Participants | N: 280 participants<br><br>Inclusion criteria: acute diarrhoea of <14 days presenting at the paediatric emergency and outpatient clinic<br><br>Exclusion criteria: refusal of consent, malnutrition, medical condition requiring hospitalization, received anti-diarrhoea medication or antibiotics |
| Interventions | 1. 3 RDA zinc sulphate in a syrup once daily (15 mg zinc for 6 to 12 months children and 30 mg for 12 to 60 months) for 14 days + ORS. |

**Boran 2006** *(Continued)*

| | |
|---|---|
| | 2. ORS. |
| Outcomes | 1. Duration of diarrhoea.<br>2. Adverse events (vomiting). |
| Notes | We requested additional information from the trial author, but did not receive any reply |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | The trial used block randomization with 8 numbers in each block. |
| Allocation concealment (selection bias) | Unclear risk | The trial did not mention these details. |
| Blinding (performance bias and detection bias) All outcomes | High risk | There was no blinding. |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | Fifteen participants (5.36%) were lost to follow-up |
| Selective reporting (reporting bias) | Unclear risk | The trial authors did not include the RCT protocol registration number. |
| Other bias | Unclear risk | There was no further information available on other sources of bias. |

**Brooks 2005a**

| | |
|---|---|
| Methods | RCT |
| Participants | N: 275 participants<br>Inclusion criteria: male, 1 to 6 months; onset < 72 hours; some dehydration or > 100 mL of watery stool within a 4-hour observation period<br>Exclusion criteria: clinical signs of zinc deficiency; kwashiorkor, weight/age < 60% NCHS; grossly bloody stool comorbidity; cholera |
| Interventions | 1. Zinc acetate: 20 mg.<br>2. Zinc acetate: 5 mg.<br>3. Placebo. |
| Outcomes | 1. Death.<br>2. Average duration of diarrhoea.<br>3. Stool output.<br>4. Stool frequency.<br>5. Adverse events (vomiting). |
| Notes | Location: Bangladesh<br>Setting: hospital |

**Brooks 2005a** *(Continued)*

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | The trial used a random numbers table to randomize participants to treatment. |
| Allocation concealment (selection bias) | Unclear risk | The trial used bottles labelled with randomization numbers; but did not provide any other details. |
| Blinding (performance bias and detection bias) All outcomes | Low risk | The trial was double blinded. |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | 5% of participants were lost to follow-up. |
| Selective reporting (reporting bias) | Unclear risk | There was no protocol available. |
| Other bias | Unclear risk | There was no information available on other sources of bias. |

**Brooks 2005a (20 mg)**

| | |
|---|---|
| Methods | See Brooks 2005a |
| Participants | N: 91 participants (5% lost to follow-up) |
| Interventions | 1. Zinc acetate: 20 mg.<br>2. Placebo. |
| Outcomes | See Brooks 2005a |
| Notes | See Brooks 2005a |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | See Brooks 2005a for all descriptions. |
| Allocation concealment (selection bias) | Unclear risk | See Brooks 2005a for all descriptions. |
| Blinding (performance bias and detection bias) All outcomes | Low risk | See Brooks 2005a for all descriptions. |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | 5% of participants were lost to follow-up. |

**Brooks 2005a (20 mg)** *(Continued)*

| | | |
|---|---|---|
| Selective reporting (reporting bias) | Unclear risk | See Brooks 2005a for all descriptions. |
| Other bias | Unclear risk | See Brooks 2005a for all descriptions. |

**Brooks 2005a (5 mg)**

| | |
|---|---|
| Methods | See Brooks 2005a |
| Participants | N: 91 participants (7% lost to follow-up) |
| Interventions | 1. Zinc acetate: 5 mg.<br>2. Placebo. |
| Outcomes | See Brooks 2005a |
| Notes | See Brooks 2005a |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | See Brooks 2005a for all descriptions. |
| Allocation concealment (selection bias) | Unclear risk | See Brooks 2005a for all descriptions. |
| Blinding (performance bias and detection bias)<br>All outcomes | Low risk | See Brooks 2005a for all descriptions. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | 7% of participants were lost to follow-up. |
| Selective reporting (reporting bias) | Unclear risk | See Brooks 2005a for all descriptions. |
| Other bias | Unclear risk | See Brooks 2005a for all descriptions. |

**Crisinel 2015**

| | |
|---|---|
| Methods | RCT |
| Participants | N = 148 participants<br><br>Inclusion criteria: children 2 months to 5 years of age, acute diarrhoea (3 or more stools a day for < 72 hours) at emergency department<br><br>Exclusion criteria: severe malnutrition (−3 standard deviations (SDs)), ongoing zinc treatment, overwhelming chronic medical condition, non-French speaking parents, hypersensitivity to component of zinc or placebo, phenylketonuria |

**Crisinel 2015** *(Continued)*

| | |
|---|---|
| Interventions | 1. Zinc tablets of 10 mg (children < 6 months) or 20 mg (children ≥ 6 months) once a day for 10 days plus ORS.<br>2. Placebo plus ORS. |
| Outcomes | 1. Diarrhoea at day 3 and day 5.<br>2. Adverse events (vomiting, difficulties in treatment administration). |
| Notes | Results recorded as medians with IQR because data was not normally distributed. |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | WHO performed block randomization. |
| Allocation concealment (selection bias) | Low risk | An institutional pharmacy assigned a study number to each package of zinc or placebo. |
| Blinding (performance bias and detection bias)<br>All outcomes | Low risk | The same packaging and dosage were used for the intervention and control groups. |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | Over 40% of participants were lost to follow-up. |
| Selective reporting (reporting bias) | Unclear risk | This RCT was not registered. |
| Other bias | Unclear risk | No information. |

**Dalgic 2011**

| | |
|---|---|
| Methods | RCT |
| Participants | N: 120 participants<br>Inclusion criteria: 1 to 28 months and, on admission, stool positive for rotavirus antigen.<br>Exclusion criteria: severe malnutrition (weight for height < −3SD as for WHO standards): duration of diarrhoea > 96 hours; severe dehydration; exclusively breast-feeding; toxic clinical appearance; immunosuppression; any known allergies to any drugs or foods. |
| Interventions | 1. Zinc 20 mg/day.<br>2. Placebo. |
| Outcomes | 1. Average duration of diarrhoea.<br>2. Hospitalization. |
| Notes | Location: Turkey<br>Setting: hospital |

***Risk of bias***

**Dalgic 2011** *(Continued)*

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Computer generated. |
| Allocation concealment (selection bias) | Unclear risk | Allocation concealment was not specified. |
| Blinding (performance bias and detection bias) All outcomes | Unclear risk | The trial authors stated the trial was "single blind", but did not provide further details. |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | All children completed the study. |
| Selective reporting (reporting bias) | Unclear risk | There was no protocol available. |
| Other bias | Unclear risk | There was no further information available. |

**Dutta 2000**

| | |
|---|---|
| Methods | RCT |
| Participants | N: 80 participants<br>Inclusion criteria: male, 3 to 24 months; malnourished (< 80% Harvard Standard weight for age); clinical signs of dehydration<br>Exclusion criteria: antibiotics; systemic infections; chronic diseases; need for intensive care; exclusively breastfed |
| Interventions | 1. Zinc sulphate: 40 mg/day.<br>2. Placebo. |
| Outcomes | 1. Average duration of diarrhoea.<br>2. Diarrhoea at day 5.<br>3. Stool output. |
| Notes | Location: India<br>Setting: hospital |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | The trial used random numbers to assign participants to treatment. |
| Allocation concealment (selection bias) | Low risk | The trial kept code numbers in a sealed envelope; zinc and placebo bottles were identical. |
| Blinding (performance bias and detection bias) | Low risk | The trial was double blinded. |

**Dutta 2000** *(Continued)*

| | | |
|---|---|---|
| All outcomes | | |
| Incomplete outcome data (attrition bias) All outcomes | Unclear risk | The trial did not specify the number of participants lost to follow-up. |
| Selective reporting (reporting bias) | Unclear risk | There was no protocol available. |
| Other bias | Unclear risk | There was no further information available on other sources of bias. |

**Dutta 2011**

| | |
|---|---|
| Methods | RCT |
| Participants | N: 84 participants<br>Inclusion criteria: age 6 to 24 months, history of acute watery diarrhoea, moderate dehydration<br>Exclusion criteria: severe malnutrition (weight on height < −3SD WHO reference); systemic illness; chronic underlying disease (for example, tuberculosis, liver diseases) or needing intensive care; exclusively breastfed; antibiotics before enrolment or vitamin A within the previous 6 months |
| Interventions | 1. Zinc 20 mg/day.<br>2. Placebo. |
| Outcomes | 1. Average duration of diarrhoea.<br>2. Diarrhoea at day 5.<br>3. Stool output. |
| Notes | Location: India<br>Setting: hospital |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | The trial used random numbers to assign participants to treatment. |
| Allocation concealment (selection bias) | Low risk | The trial kept code numbers in a sealed envelope; zinc and placebo bottles were identical. |
| Blinding (performance bias and detection bias) All outcomes | Low risk | The trial was double blinded. |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | The number of participants lost to follow-up was < 10%. |
| Selective reporting (reporting bias) | Unclear risk | There was no protocol available. |
| Other bias | Unclear risk | There was no further information available on sources of bias. |

**Fajolu 2008**

| | |
|---|---|
| Methods | RCT |
| Participants | N: 60 participants<br>Inclusion criteria: age 6 to 24 months; acute diarrhoea (less than 14 days duration)<br>Exclusion criteria: refusal of consent; protein energy malnutrition; use of stool hardeners, antimotility drugs ant antibiotics; other medical condition requiring hospitalization |
| Interventions | 1. Zinc sulphate 20 mg (>12 months) or 10 mg (< 12 months).<br>2. Placebo. |
| Outcomes | 1. Average duration of diarrhoea.<br>2. Stool frequency. |
| Notes | Location: Nigeria<br>Setting: hospital (follow-up in the community) |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | The trial authors did not provide these details. |
| Allocation concealment (selection bias) | Unclear risk | The trial authors did not provide these details. |
| Blinding (performance bias and detection bias)<br>All outcomes | Unclear risk | The trial authors did not provide these details. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | The trial authors did not specify the number of participants lost to follow-up. |
| Selective reporting (reporting bias) | Unclear risk | There was no protocol available. |
| Other bias | Unclear risk | There was no further information available on other sources of bias. |

**Faruque 1999**

| | |
|---|---|
| Methods | RCT |
| Participants | N: 684 participants<br>Inclusion criteria: children 6 to 24 months with acute diarrhoea, some dehydration and no severe dehydration; underweight or stunted children were not excluded<br>Exclusion criteria: marasmus; kwashiorkor; systemic illnesses |
| Interventions | 1. Zinc acetate: 14.2 mg (first 417 children) or 40 mg (other 273 children randomized). |

**Faruque 1999** *(Continued)*

| | |
|---|---|
| | 2. Placebo.<br><br>Both groups: vitamin A |
| Outcomes | 1. Average duration of diarrhoea.<br>2. Diarrhoea at day 7. |
| Notes | Location: Bangladesh<br><br>Setting: hospital |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | The trial used random numbers to assign participants to treatment. |
| Allocation concealment (selection bias) | Low risk | The trial used bottles serially numbered according to the randomization schedule to correspond to the serial number of the participant; a pharmaceutical company prepared the supplements and provided them in dark-coloured bottles. |
| Blinding (performance bias and detection bias)<br>All outcomes | Low risk | The trial was double blinded. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | 4% of participants were lost to follow-up. |
| Selective reporting (reporting bias) | Unclear risk | There was no protocol available. |
| Other bias | Unclear risk | There was no information available on other sources of bias. |

**Fischer Walker 2006**

| | |
|---|---|
| Methods | RCT |
| Participants | N: 1110 participants<br><br>Inclusion criteria: infants 1 to 5 months of age with acute diarrhoea (< 72 hours)<br><br>Exclusion criteria: severe malnutrition (< −3 z score weight for age); signs of pneumonia if < 2 months (cough and difficult or fast breathing with a respiratory rate of > 60 breaths/minute); signs severe pneumonia if 2 to 5 months of age (cough or difficult fast breathing and chest indrawing, nasal flaring, or grunting); required hospitalization (overnight stay at a healthcare facility) for any reason; known major congenital malformation; any other serious pre-existing medical condition; lived out of or planned to move out of study area within following 3 months; previously enrolled in the study |
| Interventions | 1. Zinc sulphate: 10 mg.<br>2. Placebo. |
| Outcomes | 1. Death.<br>2. Average duration of diarrhoea.<br>3. Diarrhoea at day 7. |

**Fischer Walker 2006** *(Continued)*

| | |
|---|---|
| | 4. Stool frequency.<br>5. Hospitalization.<br>6. Adverse events (vomiting). |
| Notes | Location: Ethiopia, India, and Pakistan<br>Setting: community |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | The trial used random numbers to assign participants to treatment. |
| Allocation concealment (selection bias) | Low risk | The trial assigned the randomization scheme in Geneva and kept it secure until completion of data collection and initial analysis; upon enrolment, infants were assigned chronological study identifiers corresponding to a prelabelled blister pack of either zinc or placebo tablets. |
| Blinding (performance bias and detection bias)<br>All outcomes | Low risk | The trial was double blinded. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | 3% of participants were lost to follow-up. |
| Selective reporting (reporting bias) | Unclear risk | There was no protocol available. |
| Other bias | Unclear risk | There was no further information available on other sources of bias. |

**Fischer Walker 2006 ETH**

| | |
|---|---|
| Methods | See Fischer Walker 2006 |
| Participants | N: 177 participants (8% lost at follow-up) |
| Interventions | See Fischer Walker 2006 |
| Outcomes | See Fischer Walker 2006 |
| Notes | Location: Ethiopia |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | See Fischer Walker 2006. |
| Allocation concealment (selection bias) | Low risk | See Fischer Walker 2006. |

**Fischer Walker 2006 ETH** *(Continued)*

| | | |
|---|---|---|
| Blinding (performance bias and detection bias) All outcomes | Low risk | See Fischer Walker 2006. |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | 8% of participants were lost to follow-up. |
| Selective reporting (reporting bias) | Unclear risk | See Fischer Walker 2006. |
| Other bias | Unclear risk | See Fischer Walker 2006. |

**Fischer Walker 2006 IND**

| | |
|---|---|
| Methods | See Fischer Walker 2006 |
| Participants | N: 373 participants (1% lost to follow-up) |
| Interventions | See Fischer Walker 2006 |
| Outcomes | See Fischer Walker 2006 |
| Notes | Location: India |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | See Fischer Walker 2006. |
| Allocation concealment (selection bias) | Low risk | See Fischer Walker 2006. |
| Blinding (performance bias and detection bias) All outcomes | Low risk | See Fischer Walker 2006. |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | 1% participants were lost to follow-up. |
| Selective reporting (reporting bias) | Unclear risk | See Fischer Walker 2006. |
| Other bias | Unclear risk | See Fischer Walker 2006. |

**Fischer Walker 2006 PAK**

| | |
|---|---|
| Methods | See Fischer Walker 2006 |

**Fischer Walker 2006 PAK** *(Continued)*

| | |
|---|---|
| Participants | N: 560 participants (3% lost to follow-up) |
| Interventions | See Fischer Walker 2006 |
| Outcomes | See Fischer Walker 2006 |
| Notes | Location: Pakistan |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | See Fischer Walker 2006. |
| Allocation concealment (selection bias) | Low risk | See Fischer Walker 2006. |
| Blinding (performance bias and detection bias)<br>All outcomes | Low risk | See Fischer Walker 2006. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | 3% of participants were lost to follow-up. |
| Selective reporting (reporting bias) | Unclear risk | See Fischer Walker 2006. |
| Other bias | Unclear risk | See Fischer Walker 2006. |

**Jiang 2016**

| | |
|---|---|
| Methods | RCT |
| Participants | N: 103 participants<br>Inclusion criteria: children diagnosed with acute diarrhoea,duration within 48 hours, age 3 months to 3 years, rotavirus enteritis (colloidal gold method should be used to detect RV antigen expression) and informed consent<br>Exclusion criteria: mucous and bloody stool, stool routine shows white blood cells > 5 /high power field or red blood cells > 5 /high power field, total white blood cells > $12 \times 10^9$/L, C reactive protein > 10 mg/L, children with some underlying diseases such as congenital heart disease, hepatopathy and epilepsy |
| Interventions | 1. Zinc gluconate granules (10mg) in children 3 to 6 months, and 20 mg in children over 6 months.<br>2. Microecologic products with some extra treatments for myocardial nutrients, protect liver, relieve cough, reduce phlegm, and improve microcirculation (vitamin C) for children with abnormal laboratory indexes. |
| Outcomes | 1. Duration of diarrhoea.<br>2. Diarrhoea at day 3. |
| Notes | None |

**Jiang 2016** *(Continued)*

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | The trial authors did not mention how allocation sequence was generated. |
| Allocation concealment (selection bias) | Unclear risk | The trial authors did not mention how allocation concealment was conducted. |
| Blinding (performance bias and detection bias) All outcomes | Unclear risk | The trial authors did not mention how blinding was achieved for participants, intervention providers, and assessors. |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | There was no loss to follow-up of participants. |
| Selective reporting (reporting bias) | Unclear risk | There was no number of protocol registration. |
| Other bias | Unclear risk | The trial was not registered. |

**Jin 2013**

| | |
|---|---|
| Methods | RCT |
| Participants | N: 103 participants<br>Inclusion criteria: 4 to 40 months of age; infants with acute rotavirus diarrhoea; parental consent<br>Exclusion criteria: not reported |
| Interventions | 1. Zinc gluconate (20 mg of zinc/day).<br>2. Montmorillonite. |
| Outcomes | 1. Diarrhoea at day 3.<br>2. Average number of hospitalization (days). |
| Notes | We requested additional information from the trial author, but received no reply |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | There was no mention of how random sequence was generated. |
| Allocation concealment (selection bias) | Unclear risk | There was no mention of how allocation concealment was performed. |
| Blinding (performance bias and detection bias) All outcomes | Unclear risk | It was unclear whether or not blinding was done. |

**Jin 2013** *(Continued)*

| | | |
|---|---|---|
| Incomplete outcome data (attrition bias) All outcomes | Low risk | There was no loss of participants to follow-up. |
| Selective reporting (reporting bias) | Unclear risk | There was no RCT protocol registration number. |
| Other bias | Unclear risk | There was no information available on other sources of bias. |

**Karamyyar 2013**

| | |
|---|---|
| Methods | RCT |
| Participants | N: 379 participants<br>Inclusion criteria: children aged 9 months to 5 years, admission to hospital with acute watery diarrhoea and moderate dehydration<br>Exclusion criteria: chronic diseases (cystic fibrosis, inflammatory bowel disease, malabsorption), severe malnutrition (weight curve under 3% for age), dysentery and bloody diarrhoea with red blood cells (RBCs) or white blood cells (WBCs) in stool, recent consumption of antibiotics, severe dehydration, persistent vomiting, consumption of zinc supplements (in the last month), drug intolerance, refusal to consent |
| Interventions | 1. Zinc supplementation (syrup 1ml/kg/day with 1 mg zinc sulphate divided into two doses) + ORS.<br>2. ORS. |
| Outcomes | 1. Stool frequency. |
| Notes | We requested additional information from the trial author, but received no reply |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | The trial used computer-generated allocation sequence. |
| Allocation concealment (selection bias) | Low risk | A randomization list (simple randomly allocation of two group) was given to the pharmacist prior to enrolment. Randomization codes were secured until the completion of data collection and neither the physician, participants (or their parents), nor nurse were unaware of the drug or placebo. |
| Blinding (performance bias and detection bias) All outcomes | Low risk | The glass bottles that contained the products (zinc Sulfate or placebo) were labelled with participants' code (with keeping the names of participants) by pharmacists who was not involved in the treatments. A placebo with similar taste, colour, and smell and with a similar option (1 mL/kg/day) was given to the control group. |
| Incomplete outcome data (attrition bias) All outcomes | High risk | 15.5% of participants were lost to follow-up (> 10%). |
| Selective reporting (reporting bias) | Low risk | The outcomes were reported according to the protocol. The RCT was registered (IRCT201201241580N2). |

**Karamyyar 2013** *(Continued)*

| | | |
|---|---|---|
| Other bias | Unclear risk | There was no information available on other sources of bias. |

**Khatun 2001**

| | |
|---|---|
| Methods | RCT |
| Participants | N: 100 participants<br>Inclusion criteria: 6 to 36 months; moderately malnourished (61% to 75% of the median NCHS median weight for age); persistent diarrhoea<br>Exclusion criteria: systemic infection; clinical signs of vitamin A deficiency; received vitamin A supplementation within 3 months; received prior antibiotics therapy; bloody mucoid diarrhoea; kwashiorkor; no longer received breast milk |
| Interventions | 1. Zinc acetate: 20 mg.<br>2. Placebo.<br>Both groups: multivitamins |
| Outcomes | 1. Death.<br>2. Average duration of diarrhoea.<br>3. Diarrhoea at day 7.<br>4. Stool output.<br>5. Adverse events (vomiting). |
| Notes | Location: Bangladesh<br>Setting: hospital |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | The trial authors did not provide these details. |
| Allocation concealment (selection bias) | Unclear risk | The trial authors did not provide these details. |
| Blinding (performance bias and detection bias)<br>All outcomes | Unclear risk | The trial authors did not provide these details. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | 4% of participants were lost to follow-up. |
| Selective reporting (reporting bias) | Unclear risk | There was no protocol available. |
| Other bias | Unclear risk | There was no further information available on other sources of bias. |

**Larson 2005**

| | |
|---|---|
| Methods | RCT |
| Participants | N: 1067 participants<br>Inclusion criteria: children aged 3 to 59 months; acute diarrhoea; having taken ORS as instructed; no vomiting in the past 2 hours for the short-stay ward or 30 minutes in the outpatient clinic, and no longer dehydrated<br>Exclusion criteria: returning to the hospital with diarrhoea; receiving zinc |
| Interventions | 1. Zinc sulphate: 20 mg.<br>2. Placebo. |
| Outcomes | 1. Adverse events (vomiting). |
| Notes | Location: Bangladesh<br>Setting: hospital |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | The trial used random numbers to assign participants to treatment. |
| Allocation concealment (selection bias) | Low risk | The trial used opaque envelopes, numbered, in which the assigned zinc tablet, placebo tablet, or a similar-sized button was placed; and kept the randomization schedule in a locked cabinet. |
| Blinding (performance bias and detection bias) All outcomes | Low risk | The trial was double blinded. |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | No participants were lost to follow-up. |
| Selective reporting (reporting bias) | Unclear risk | There was no protocol available. |
| Other bias | Unclear risk | There was no information available on other sources of bias. |

**Passariello 2015**

| | |
|---|---|
| Methods | RCT |
| Participants | N: 83 participants<br>Inclusion criteria: children aged between 5 to 36 months, diarrhoea lasting less than 24 hours with mild-moderate dehydration<br>Exclusion criteria: malnutrition ( weight/height ratio) < $5^{th}$ percentile), severe dehydration, concomitant severe or chronic systemic illness, immunodeficiency, cystic fibrosis, food allergy, chronic gastrointestinal disease, endocrine disease, use of pre/pro/symbiotic antibiotics, any anti-diarrhoea medication in the previous 3 weeks |

**Passariello 2015** *(Continued)*

| | |
|---|---|
| Interventions | 1. Hypotonic super ORS containing zinc in a gel formulation.<br>2. Standard hypotonic ORS. |
| Outcomes | 1. Duration of diarrhoea.<br>2. Diarrhoea on day 3.<br>3. Adverse events (vomiting). |
| Notes | We requested additional information from the trial authors, but received no reply |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | The trial used computer-generated randomization to assign participants to treatment. |
| Allocation concealment (selection bias) | Low risk | The hospital pharmacy produced identical white aluminium fold sachets contained in a blank blinded code-labelled paper box for intervention and controls. |
| Blinding (performance bias and detection bias)<br>All outcomes | Unclear risk | We requested additional information from the trial authors, but received no reply. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | There was no loss of participants to follow-up. |
| Selective reporting (reporting bias) | Unclear risk | The RCT was registered retrospectively (ACTRN12614000028606). |
| Other bias | Unclear risk | There was no further information available on other sources of bias. |

**Patel 2009**

| | |
|---|---|
| Methods | RCT |
| Participants | N: 808 participants<br>Inclusion criteria: age 6 to 59 months; acute diarrhoea (duration up to 72 hours); ability to accept oral fluids or feeds<br>Exclusion criteria: severe dehydration and unable to drink, chronic or severe complicating illness, known positive HIV status, kwashiorkor, residing outside a radius of 30 km around the hospital, participating in another study or already enrolled in this study |
| Interventions | 1. Zinc sulcates 2 mg/kg/day.<br>2. Zinc sulphate 2 mg/kg/day + copper 0.2 mg/kg/day.<br>3. Placebo. |
| Outcomes | 1. Death.<br>2. Average duration of diarrhoea.<br>3. Diarrhoea at day 3.<br>4. Diarrhoea at day 5. |

**Patel 2009** *(Continued)*

| | |
|---|---|
| | 5. Diarrhoea at day 7. |
| Notes | Location: India<br>Setting: hospital (follow-up in the community) |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Single-site, blocked randomization procedure with blocks of sizes 3, 6, and 9 in equal proportions. |
| Allocation concealment (selection bias) | Low risk | Randomization list generated off site by an investigator not directly involved in the data collection. The code list of the placebo and the treatment groups was secured and held only by the pharmacist at the Universal Medicaments Pvt. Ltd, Nagpur, until initial data analysis was completed. |
| Blinding (performance bias and detection bias)<br>All outcomes | Low risk | Double blind: bottle packs sequentially labelled according to the treatment allocation list and assigned to participants by the research physician. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | 7% lost at follow-up. |
| Selective reporting (reporting bias) | Low risk | The protocol was available. The trial was registered in the *meta*Register of Controlled Trials (ISRCTN85071383). |
| Other bias | Unclear risk | There was no information available on other sources of bias. |

**Patel 2009a (zinc)**

| | |
|---|---|
| Methods | RCT |
| Participants | N: 808 participants<br>Inclusion criteria: age 6 to 59 months; acute diarrhoea (duration up to 72 hours); ability to accept oral fluids or feeds<br>Exclusion criteria: severe dehydration and unable to drink,chronic or severe complicating illness, known positive HIV status, kwashiorkor, residing outside a radius of 30 km around the hospital, participating in another study or already enrolled in this study |
| Interventions | 1. Zinc sulphate 2 mg/kg/die.<br>2. Zinc sulphate 2 mg/kg/die + copper 0.2 mg/kg/die.<br>3. Placebo. |
| Outcomes | 1. Death.<br>2. Average duration of diarrhoea.<br>3. Diarrhoea at day 3.<br>4. Diarrhoea at day 5.<br>5. Diarrhoea at day 7. |
| Notes | Location: India |

**Patel 2009a (zinc)** *(Continued)*

| | |
|---|---|
| | Setting: hospital (follow-up in the community) |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | See Patel 2009. |
| Allocation concealment (selection bias) | Low risk | See Patel 2009. |
| Blinding (performance bias and detection bias) All outcomes | Low risk | See Patel 2009. |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | See Patel 2009. |
| Selective reporting (reporting bias) | Low risk | See Patel 2009. |
| Other bias | Unclear risk | See Patel 2009. |

**Patel 2009b (zinc + copper)**

| | |
|---|---|
| Methods | See Patel 2009a (zinc) |
| Participants | See Patel 2009a (zinc) |
| Interventions | See Patel 2009a (zinc) |
| Outcomes | See Patel 2009a (zinc) |
| Notes | See Patel 2009a (zinc) |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | See Patel 2009. |
| Allocation concealment (selection bias) | Low risk | See Patel 2009. |
| Blinding (performance bias and detection bias) All outcomes | Low risk | See Patel 2009. |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | See Patel 2009. |

**Patel 2009b (zinc + copper)** *(Continued)*

| | | |
|---|---|---|
| Selective reporting (reporting bias) | Low risk | See Patel 2009. |
| Other bias | Unclear risk | See Patel 2009. |

**Patel 2015**

| | |
|---|---|
| Methods | RCT |
| Participants | N: 100 participants<br>Inclusion criteria: children < 12 years (but all enrolled had ≤ 5 years), presentation to hospital with diarrhoea<br>Exclusion criteria: serious illness, intensive care admission, use of ventilators, impossibility of communication |
| Interventions | 1. Oral zinc sulphate (10 mg for < 6 months a day or 20 mg for ≥ 6 months) per 14 days + standard of care (ORS, intravenous fluid, antibiotics).<br>2. Standard of care (ORS, intravenous fluid, antibiotics). |
| Outcomes | 1. Diarrhoea at day 3 and 5. |
| Notes | We requested additional information from the trial authors, but received no reply |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Random sequence generation was computer generated. |
| Allocation concealment (selection bias) | Unclear risk | The trial authors did not clearly describe allocation concealment. |
| Blinding (performance bias and detection bias)<br>All outcomes | High risk | This was an open label trial. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | 4% of participants were lost to follow-up. |
| Selective reporting (reporting bias) | Unclear risk | There was no RCT registration number. |
| Other bias | Unclear risk | There was no information on other sources of bias. |

**Patro 2010**

| | |
|---|---|
| Methods | RCT |
| Participants | N: 160 participants |

**Patro 2010** *(Continued)*

| | |
|---|---|
| | Inclusion criteria: age 3 to 48 months diagnosed with acute diarrhoea lasting less than 5 days, with at least some degree of dehydration<br><br>Exclusion criteria: diarrhoea lasting <1 day or >5 days, recent history of diarrhoea (last 2 weeks before enrolment day), chronic gastrointestinal disease with diarrhoea manifestation, (for example, food allergy, coeliac disease), weight-to-height ratio < 5$^{th}$ percentile, severe dehydration, coexistence of serious systemic disease(s), coadministration of antibiotics, exclusive or > 50% breastfeeding, immunodeficiency, immunosuppressive therapy. |
| Interventions | 1. Zinc sulphate (20 mg in children > 6 months or 10 mg in children < 6 months).<br>2. Placebo. |
| Outcomes | 1. Average duration of diarrhoea.<br>2. Diarrhoea at day 7. |
| Notes | Location: Poland<br><br>Setting: hospital (90% of children) and outpatient (10%) |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | An investigator at the Medical University of Warsaw computer-generated 2 different randomization lists for each centre. |
| Allocation concealment (selection bias) | Low risk | The glass bottles containing the products were labelled with the participant's number corresponding to the randomization list by an independent individual who was not involved in participant enrolment. Randomization codes were secured until the completion of data collection and initial analysis. The placebo was identically supplied and formulated. There was no difference between zinc and the placebo in appearance; a minor metallic aftertaste of zinc was hardly detectable. |
| Blinding (performance bias and detection bias)<br>All outcomes | Low risk | Investigators, participants, outcome assessors, and data analysts were blinded. |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | 11.8% of participants were lost to follow-up. |
| Selective reporting (reporting bias) | Unclear risk | There was no protocol available. |
| Other bias | Unclear risk | Note: the source of funding was Nutricia. |

**Penny 1999**

| | |
|---|---|
| Methods | RCT |
| Participants | Number: 413<br><br>Inclusion criteria: 6 to 36 months, persistent diarrhoea |

**Penny 1999** *(Continued)*

| | |
|---|---|
| | Exclusion criteria: vitamins or minerals within 6 weeks; major congenital malformation affecting growth; severe dehydration; requiring hospitalization |
| Interventions | 1. Zinc gluconate: 20 mg.<br>2. Placebo. |
| Outcomes | 1. Death.<br>2. Hospitalization.<br>3. Diarrhoea at day 3.<br>4. Diarrhoea at day 5.<br>5. Diarrhoea at day 7.<br>6. Adverse events (vomiting). |
| Notes | Location: Peru<br>Setting: community |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | The trial used computer-generated random numbers to assign participants to treatment. |
| Allocation concealment (selection bias) | Low risk | Randomization numbers were linked to letter codes, each indicating 1 treatment group; codes were kept secret; independent laboratories provided supplements. |
| Blinding (performance bias and detection bias) All outcomes | Low risk | The trial was double blinded. |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | No participants were lost to follow-up. |
| Selective reporting (reporting bias) | Unclear risk | No protocol was available. |
| Other bias | Unclear risk | No information was available on other sources of bias. |

**Polat 2003**

| | |
|---|---|
| Methods | RCT |
| Participants | N: 200 participants<br>Inclusion criteria: 2 to 29 months; malnourished children (weight for age scale, score < 76% according to NCHS standards); acute non-bacterial diarrhoea<br>Exclusion criteria: concomitant illness or oedema |
| Interventions | 1. Zinc sulphate: 20 mg.<br>2. Placebo. |
| Outcomes | 1. Average duration of diarrhoea. |

**Polat 2003** *(Continued)*

| | |
|---|---|
| | 2. Diarrhoea at day 3.<br>3. Diarrhoea at day 7.<br>4. Adverse events (vomiting). |
| Notes | Location: Turkey<br>Setting: hospital |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | The trial used random numbers to assign participants to treatment. |
| Allocation concealment (selection bias) | Low risk | Bottles were labelled with randomization numbers. |
| Blinding (performance bias and detection bias)<br>All outcomes | Low risk | The trial was double blinded. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | 9% of participants were lost to follow-up. |
| Selective reporting (reporting bias) | Unclear risk | No protocol was available. |
| Other bias | Unclear risk | No information was available on other sources of bias. |

**Polat 2003 (low Zn)**

| | |
|---|---|
| Methods | See Polat 2003 |
| Participants | N: 76 participants<br>Children with low zinc serum levels |
| Interventions | See Polat 2003 |
| Outcomes | See Polat 2003 |
| Notes | See Polat 2003 |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | See Polat 2003. |
| Allocation concealment (selection bias) | Low risk | See Polat 2003. |

**Polat 2003 (low Zn)** *(Continued)*

| | | |
|---|---|---|
| Blinding (performance bias and detection bias) All outcomes | Low risk | See Polat 2003. |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | See Polat 2003. |
| Selective reporting (reporting bias) | Unclear risk | See Polat 2003. |
| Other bias | Unclear risk | See Polat 2003. |

**Polat 2003 (normal Zn)**

| | |
|---|---|
| Methods | See Polat 2003 |
| Participants | N: 106 participants<br>Children with normal zinc serum levels |
| Interventions | See Polat 2003 |
| Outcomes | See Polat 2003 |
| Notes | See Polat 2003 |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | See Polat 2003. |
| Allocation concealment (selection bias) | Low risk | See Polat 2003. |
| Blinding (performance bias and detection bias) All outcomes | Low risk | See Polat 2003. |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | See Polat 2003. |
| Selective reporting (reporting bias) | Unclear risk | See Polat 2003. |
| Other bias | Unclear risk | See Polat 2003. |

**Roy 1997**

| | |
|---|---|
| Methods | RCT |

**Roy 1997** *(Continued)*

| | |
|---|---|
| Participants | N: 111 participants<br>Inclusion criteria: 2 to 24 months; weight below the 76$^{th}$ centile of weight-for-age according to the NCHS standard 18 (by Gomez classification, protein energy malnutrition grades II and III included)<br>Exclusion criteria: systemic infection or oedema |
| Interventions | 1. Zinc acetate: 20 mg.<br>2. Placebo.<br>Both groups: multivitamin |
| Outcomes | 1. Average duration of diarrhoea.<br>2. Stool output. |
| Notes | Location: Bangladesh<br>Setting: hospital |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | The trial used a table of random numbers to assign participants to treatment. |
| Allocation concealment (selection bias) | Low risk | Bottles were labelled with randomization numbers. |
| Blinding (performance bias and detection bias)<br>All outcomes | Low risk | The trial was double blinded. |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | 32.4% of participants were lost to follow-up. |
| Selective reporting (reporting bias) | Unclear risk | No protocol was available |
| Other bias | Unclear risk | No information was available on other sources of bias. |

**Roy 1998**

| | |
|---|---|
| Methods | RCT |
| Participants | N: 190 participants<br>Inclusion criteria: 3 to 24 months; persistent diarrhoea; underweight (low weight-for-age) using a cut-off of 70% weight/age of the 50th centile of the NCHS standard; wasted (low weight/height) using a cut-off of 80%; short (low height/age) using a cut-off of less than 95% of the height/age standard<br>Exclusion criteria: none stated |
| Interventions | 1. Zinc acetate: 20 mg.<br>2. Placebo. |

**Roy 1998** *(Continued)*

| | |
|---|---|
| | Both groups: multivitamin |
| Outcomes | 1. Death.<br>2. Average duration of diarrhoea.<br>3. Adverse events. |
| Notes | Location: Bangladesh<br>Setting: hospital |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | The trial used random numbers to assign participants to treatment. |
| Allocation concealment (selection bias) | Unclear risk | The trial did not provide any details on allocation concealment. |
| Blinding (performance bias and detection bias)<br>All outcomes | Low risk | The trial was double blinded. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | It was unclear whether or not any participants were lost to follow-up; 11% discontinued the intervention. |
| Selective reporting (reporting bias) | Unclear risk | No protocol was available. |
| Other bias | Unclear risk | No information was available on other sources of bias. |

**Roy 2008a**

| | |
|---|---|
| Methods | RCT |
| Participants | N: 56 participants<br>Inclusion criteria: aged 12 to 59 months; moderately malnourished (weight/age 61% to 75% of NCHS median); history suggestive of dysentery (for example, bloody-mucoid diarrhoea or febrile diarrhoea less than 5 days' duration); with culture-proven shigellosis<br>Exclusion criteria: severe malnutrition; receiving zinc supplementation; measles in the last 6 months; living beyond 2 hours of travel time; complications such as haemolytic uraemic syndrome or other systemic illness, including pneumonia, meningitis, and septicaemia |
| Interventions | 1. Zinc acetate: 10 mg.<br>2. Placebo.<br>Both groups: multivitamins |
| Outcomes | 1. Death.<br>2. Average duration of diarrhoea.<br>3. Diarrhoea at day 7. |

**Roy 2008a** *(Continued)*

| | |
|---|---|
| Notes | Location: Bangladesh<br>Setting: hospital |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | The trial used a table of random numbers to assign participants to treatment. |
| Allocation concealment (selection bias) | Low risk | Bottles were identical and labelled with sequential numbers that had earlier been allocated to either intervention or control according to the randomization. |
| Blinding (performance bias and detection bias)<br>All outcomes | Low risk | The trial was double blinded. |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | 11% of participants were lost to follow-up. |
| Selective reporting (reporting bias) | Low risk | The trial was registered at ClinicalTrials.gov (NCT00321126). |
| Other bias | Unclear risk | No information was available on other sources of bias. |

**Sachdev 1988**

| | |
|---|---|
| Methods | RCT |
| Participants | N: 50 participants<br>Inclusion criteria: children 6 to 18 months; dehydration secondary to acute diarrhoea of < 4 days' duration<br>Exclusion criteria: antibiotics; severe malnutrition (grades III and IV); concomitant features (meningitis, pneumonia, liver disease, otitis media, fever > 39°C) |
| Interventions | 1. Zinc sulphate: 20 mg.<br>2. Placebo. |
| Outcomes | 1. Average duration of diarrhoea.<br>2. Stool frequency.<br>3. Adverse events (vomiting). |
| Notes | Location: India<br>Setting: hospital |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|

**Sachdev 1988** *(Continued)*

| | | |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | The trial authors did not provide any details. |
| Allocation concealment (selection bias) | Unclear risk | The trial authors did not provide any details. |
| Blinding (performance bias and detection bias)<br>All outcomes | Unclear risk | The trial authors did not provide any details. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | The trial authors did not provide any details. |
| Selective reporting (reporting bias) | Unclear risk | No protocol was available. |
| Other bias | Unclear risk | No information was available. |

**Sachdev 1990**

| | |
|---|---|
| Methods | RCT |
| Participants | N: 40 participants<br>Inclusion criteria: 6 to 18 months; persistent diarrhoea<br>Exclusion criteria: another diarrhoeal episode 1 month prior; critically ill; obvious parenteral infections; severe malnutrition (grade III and IV) |
| Interventions | 1. Zinc sulphate: 20 mg.<br>2. Placebo. |
| Outcomes | 1. Average duration of diarrhoea.<br>2. Stool frequency.<br>3. Adverse events (vomiting). |
| Notes | Location: India<br>Setting: hospital |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | The trial authors did not provide any details. |
| Allocation concealment (selection bias) | Unclear risk | The trial authors did not provide any details. |
| Blinding (performance bias and detection bias)<br>All outcomes | Unclear risk | The trial authors did not provide any details. |

**Sachdev 1990** *(Continued)*

| | | |
|---|---|---|
| Incomplete outcome data (attrition bias) All outcomes | Unclear risk | The trial authors did not provide any details. |
| Selective reporting (reporting bias) | Unclear risk | No protocol was available. |
| Other bias | Unclear risk | No information was available on other sources of bias. |

**Sazawal 1995**

| | |
|---|---|
| Methods | RCT |
| Participants | N: 947 participants<br>Inclusion criteria: 6 to 35 months; diarrhoea for 7 days; permanent resident in study area; stunted defined (length for age less than −2 SD)<br>Exclusion criteria: second visit; malnutrition requiring hospitalization; not provide consent |
| Interventions | 1. Zinc gluconate: 20 mg.<br>2. Placebo.<br>Both groups: multivitamin |
| Outcomes | 1. Diarrhoea at day 7.<br>2. Stool frequency.<br>3. Adverse events (vomiting). |
| Notes | Location: India<br>Setting: hospital |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | The trial used random numbers to assign participants to treatment. |
| Allocation concealment (selection bias) | Low risk | Children were allocated to sequential numbers indicating zinc or placebo; the WHO kept the code, which was not available to the trial investigators. |
| Blinding (performance bias and detection bias) All outcomes | Low risk | The trial was double blinded. |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | 2% of participants were lost to follow-up. |
| Selective reporting (reporting bias) | Unclear risk | No protocol was available. |
| Other bias | Unclear risk | No information was available. |

### Shimelis 2008

| | |
|---|---|
| Methods | RCT |
| Participants | N: 414 participants<br>Inclusion criteria: children 2 to 59 months, presented at the hospital with acute watery diarrhoea for less than 7 days<br>Exclusion criteria:children living far or unsafe areas for follow-up, children requiring antimicrobial for other conditions, immunocompromised (severely malnourished or with known primary immune deficiency) excluding cases of measles or those with HIV positive status, special fluid requirements (that is, renal disease, health hepatic failure), chronic or persistent diarrhoea and dysentery requiring hospitalization or admitted for in-patient care, on zinc supplementation, no consent |
| Interventions | 1. Zinc (2 tablets each containing 10 mg zinc) and ORS.<br>2. ORS. |
| Outcomes | 1. Diarrhoea at day 5.<br>2. Adverse events: vomiting. |
| Notes | We requested additional information from the trial author, but received no reply |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | High risk | The trial used randomly selected days to assign participants to treatment. |
| Allocation concealment (selection bias) | High risk | There was no randomization concealment since participants were randomized depending on the day they reported to the health facility. |
| Blinding (performance bias and detection bias)<br>All outcomes | High risk | This was an open label trial. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | 3% of participants were lost to follow-up. |
| Selective reporting (reporting bias) | Unclear risk | There was no RCT registration number. We requested additional information from the trial authors but received no reply. |
| Other bias | Unclear risk | There was no information available on other sources of bias. |

### Strand 2002

| | |
|---|---|
| Methods | RCT |
| Participants | N: 899 participants<br>Inclusion criteria: 6 to 35 months; diarrhoea < 96 hours<br>Exclusion criteria: massive dose of vitamin A; requiring hospitalization; family intended to leave Bhaktapur within 2 months |

**Strand 2002** *(Continued)*

| | |
|---|---|
| Interventions | 1. Zinc gluconate: 15 mg for infants; 30 mg for older children.<br>2. Placebo. |
| Outcomes | 1. Diarrhoea at day 3.<br>2. Diarrhoea at day 7.<br>3. Adverse events (vomiting).<br>4. Adverse events (copper levels). |
| Notes | Location: Nepal<br>Setting: community |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | The trial used random numbers to assign participants to treatment. |
| Allocation concealment (selection bias) | Low risk | Packing with serial number; the list was kept in Copenhagen; capsules were identical in appearance; the syrup was identical in appearance and taste. |
| Blinding (performance bias and detection bias)<br>All outcomes | Low risk | The trial was double blinded. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | 1% of participants were lost to follow-up. |
| Selective reporting (reporting bias) | Unclear risk | No protocol was available. |
| Other bias | Unclear risk | No information was available. |

**Tran 2015**

| | |
|---|---|
| Methods | RCT |
| Participants | N: 76 participants<br>Inclusion criteria: children 6 months to 12 years,clinically diagnosed with diarrhoea and tolerate oral feed<br>Exclusion criteria: other gastrointestinal symptoms, history of gastrointestinal surgery with organic disease (excluding previous gastrostomy, pyloric stenosis), phenylketonuric or diabetic, taking gastric acid-neutralizing antacids, drugs to suppress gastric acid secretion or anti-diarrhoeal drugs, probiotics or zinc supplement, immunocompromised, proven sucrose intolerance, or previously participated in the study |
| Interventions | 1. ORS (Gastrolyte-R sachets) with zinc sulphate fortification (3 mg elemental zinc in total) to be mixed with 200 mL water for 4 days up to a maximum of 4 sachets in 24 hours).<br>2. ORS (Gastrolyte-R sachets). |
| Outcomes | 1. Duration of diarrhoea. |

**Tran 2015** *(Continued)*

| | |
|---|---|
| Notes | We requested additional information from the trial author, but received no reply |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Computer generated random sequence. |
| Allocation concealment (selection bias) | Unclear risk | Not clearly described. |
| Blinding (performance bias and detection bias)<br>All outcomes | Low risk | All bottles packaged by the manufacturing pharmacy. |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | Lost to follow-up in both study arms = 23.7% (> 10%). |
| Selective reporting (reporting bias) | Unclear risk | No RCT registration number. We did not receive a response from the trial authors. |
| Other bias | Unclear risk | No information available. |

Abbreviations: N: number of participants; NCHS: National Center for Health Statistics; ORS: oral rehydration solution; RCT: randomized controlled trial; WHO: World Health Organization.

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

| Study | Reason for exclusion |
|---|---|
| Abraham 2016 | This study did not concern the intervention of interest to this review |
| Adu-Afarwuah 2007 | This study did not concern the intervention of interest (3 types of micronutrients for food fortification) |
| Adu-Afarwuah 2008 | This study did not concern the intervention of interest (zinc fortification) |
| Aggarwal 2007 | Randomized controlled trial (RCT) on zinc supplementation for prevention of diarrhoea episodes, not for diarrhoea treatment |
| Agustina 2007 | This study did not concern the intervention of interest (probiotic, prebiotic, fibre, and micronutrient mixture) |
| Alam 2010 | Prevention study |
| Alarcon 2004 | A RCT on zinc supplementation for prevention of diarrhoea episodes, not for diarrhoea treatment |
| Awasthi 2006 | This study did not concern the intervention of interest (zinc in oral rehydration solution (ORS)) |
| Baqui 2002 | A community RCT without a placebo group |
| Baqui 2003 | A RCT on zinc supplementation for prevention of diarrhoea episodes, not for diarrhoea treatment |

| Study | Reason for exclusion |
|---|---|
| Baqui 2006 | This study did not concern any outcome of interest (serum zinc) to this review |
| Baum 2010 | This study did not concern the population of interest (adults, HIV-positive) |
| Becquey 2016 | This study did not concern the intervention of interest to this review |
| Behrens 1990 | This study did not concern any outcome of interest (nutritional status) |
| Bhandari 2002 | A RCT on zinc supplementation for prevention of diarrhoea episodes, not for diarrhoea treatment |
| Bhandari 2005 | This was not a RCT |
| Bhandari 2007 | A RCT on zinc supplementation for prevention of diarrhoea episodes, not for diarrhoea treatment |
| Bhandari 2008 | A RCT without a placebo group |
| Bhatnagar 2004b | This was not a RCT |
| Bhutta 2000a | This study did not concern any outcome of interest (appetite) |
| Bilenko 2010 | This study did not concern the intervention of interest (multiple micronutrients in sprinkles) |
| Black 2001 | Not a RCT |
| Bobat 2005 | This study did not concern the population of interest (only children with HIV enrolled) |
| Borges 2007 | This was not a RCT |
| Brooks 2005b | A RCT on zinc supplementation for prevention of diarrhoea episodes, not for diarrhoea treatment |
| Brown 2007 | This study did not concern the Intervention of interest (food fortification) |
| Bruzzese 2016 | This study did not concern the intervention of interest to this review |
| Chandyo 2010 | A RCT on zinc supplementation for prevention of diarrhoea episodes, not for diarrhoea treatment |
| Chang 2010 | A RCT on zinc supplementation for prevention of diarrhoea episodes, not for diarrhoea treatment |
| Chen 2010 | This study did not concern the intervention of interest (food fortification with multiple micronutrients) |
| Chhagan 2009 | A RCT on zinc supplementation for prevention of diarrhoea episodes, not for diarrhoea treatment |
| Chhagan 2010 | A RCT on zinc supplementation for prevention of diarrhoea episodes, not for diarrhoea treatment |
| Christian 2009 | A RCT on zinc supplementation for prevention of diarrhoea episodes, not for diarrhoea treatment, on a different population (pregnant women) |
| CIGNIS 2010 | This study did not concern the intervention of interest (food fortification with multiple micronutrients) |
| Colgate 2016 | This study did not concern the intervention of interest to this review |
| Coronel Carbajal 2000 | This was not a placebo-controlled RCT |

| Study | Reason for exclusion |
|---|---|
| Cross 2009 | Not a RCT |
| Cárcamo 2006 | This study did not concern the population of interest (adults with HIV) |
| Dhingra 2009 | Not a RCT |
| Doherty 1998 | This was not a placebo-controlled RCT, and the criterion for inclusion of children was malnutrition, not diarrhoea |
| Ebrahimi 2006 | Thist study did not concern any outcome of interest (growth) to this review |
| Ellis 2007 | Not a RCT |
| Ferraz 2007 | Not a RCT |
| Ferrufino 2007 | Not a RCT |
| Fischer Walker 2008 | Secondary analysis of a previously excluded study (Baqui 2002) |
| Gardner 2005 | Not a RCT |
| Garenne 2007 | A RCT on zinc supplementation for prevention of diarrhoea episodes, not for diarrhoea treatment |
| Gebremedhin 2016 | This study did not concern the outcomes of interest to this review |
| Gregorio 2007 | This study did not concern the intervention of interest (zinc-fortified ORS) |
| Gupta 2003 | A RCT on zinc supplementation for prevention of diarrhoea episodes, not for diarrhoea treatment |
| Gupta 2007 | A RCT on zinc supplementation for prevention of diarrhoea episodes, not for diarrhoea treatment |
| Habib 2010 | A longitudinal cohort study |
| Habib 2013 | A RCT on zinc supplementation for prevention of diarrhoea episodes, not for diarrhoea treatment |
| Heinig 2006 | This study did not concern any outcome of interest (growth, morbidity, and motor development) |
| Hess 2015 | A RCT on zinc supplementation for prevention of diarrhoea episodes, not for diarrhoea treatment |
| Hettiarachchi 2008 | This study did not concern the population of interest (children 12 to 16 years), nor the outcomes |
| Hidayat 1998 | A community RCT, but we could not compare the results with other studies because of methodological problems (enrolling the same children more than once) and types of outcomes (episodes of diarrhoea and not children with diarrhoea) |
| Hoque 2006 | Not a RCT (review) |
| Hyder 2007 | This study did not concern the population of interest (adolescent girl), the intervention (multiple micronutrients), nor the outcomes |
| Iannotti 2010 | This study did not concern the population of interest (pregnant women) |
| Islam 2010 | This study did not concern the population of interest (preterm infants), nor any outcome of interest (growth) |

| Study | Reason for exclusion |
|---|---|
| Jimenez 2000 | This study did not concern any outcome of interest (growth) |
| Kelly 1999 | The intervention and the population (micronutrient supplementation in AIDS diarrhoea-wasting syndrome) considered in this RCT were not relevant to this review |
| Kelly 2010 | This study did not concern any outcome of interest (intestinal function) to this review |
| Kianmehr 2016 | This study did not concern any interventions of interest to this review |
| Larson 2010 | A RCT on zinc supplementation for prevention of diarrhoea episodes, not for diarrhoea treatment |
| Lin 2008 | This study was not placebo controlled, and did not report outcomes of interest (weight) |
| Lind 2004 | A RCT on zinc supplementation for prevention of diarrhoea episodes, not for diarrhoea treatment |
| Lind 2008 | A secondary analysis of a previously excluded study (Lind 2004) |
| Lira 1998 | This study did not concern the population of interest (low birthweight infants) |
| Long 2006 | A RCT on zinc supplementation for prevention of diarrhoea episodes, not for diarrhoea treatment |
| Long 2007 | A RCT on zinc supplementation for prevention of diarrhoea episodes, not for diarrhoea treatment, with different outcomes (specific intestinal infections) |
| Lopez 2005 | This study did not concern the intervention of interest (multiple micronutrient), nor the outcomes (anaemia, micronutrient status, growth, and morbidity) of interest to this review |
| Luabeya 2007 | A RCT on zinc supplementation for prevention of diarrhoea episodes, not for diarrhoea treatment |
| Makonnen 2003a | This study did not concern any outcome of interest to this review |
| Makonnen 2003b | This study did not concern any outcome of interest to this review |
| Manger 2008 | No placebo control, different intervention (multiple micronutrients), prevention study |
| Maragkoudaki 2016 | This study did not concern any intervention of interest to this review |
| Martinez-Estevez 2016 | This was a prevention study |
| Mazariegos 2010 | This study did not concern any outcome of interest (linear growth) to this review |
| Mazumder 2010 | This was a secondary analysis of a previously excluded study (Bhandari 2008) |
| Mda 2010 | This study did not concern a population of interest (only children with HIV), and used a different intervention (multiple micronutrient) |
| Meeks Gardner 1998 | A RCT on zinc supplementation for prevention of diarrhoea episodes, not for diarrhoea treatment |
| Müller 2001 | A RCT on zinc supplementation for prevention of diarrhoea episodes, not for diarrhoea treatment |
| Naheed 2009 | A secondary analysis of a previously excluded study (Baqui 2002) |
| Nasrin 2005 | Not a RCT |
| Negi 2014 | The study participants were above 5 years (age range 5 to 12 years) |

| Study | Reason for exclusion |
|---|---|
| Nga 2009 | A RCT on zinc supplementation for prevention of diarrhoea episodes, not for diarrhoea treatment |
| Osendarp 2002 | A RCT on zinc supplementation for prevention of diarrhoea episodes, not for diarrhoea treatment |
| Ouedraogo 2008 | A RCT on zinc supplementation for prevention of diarrhoea episodes, not for diarrhoea treatment |
| Passariello 2010 | This study did not concern the intervention of interest (zinc in ORS) to this review |
| Patel 2005 | This study did not concern the intervention of interest (zinc and copper in ORS) |
| Patel 2010a | Secondary analysis of an included study (Patel 2009), with no outcome of interest (by isolated microorganism) |
| Patel 2010b | Not a RCT (review) |
| Patel 2012 | A RCT on zinc supplementation for prevention of diarrhoea episodes, not for diarrhoea treatment |
| Penny 2004a | A RCT on zinc supplementation for prevention of diarrhoea episodes, not for diarrhoea treatment |
| Penny 2004b | Not a RCT |
| Polat 2006 | Not a placebo-controlled RCT |
| Prado 2016 | This study used a different intervention that was not of interest to this review |
| Rahman 2001 | A RCT on zinc supplementation for prevention of diarrhoea episodes, not for diarrhoea treatment |
| Rahman 2005 | This study did not concern any outcome of interest to this review |
| Raqib 2004 | This study did not concern any outcome of interest (immune and inflammatory responses) to this review |
| Richard 2006 | A RCT on zinc supplementation for prevention of diarrhoea episodes, not for diarrhoea treatment |
| Rollins 2007 | This study did not concern the population of interest (only HIV-infected children), and different outcomes (growth, immunity) |
| Rosado 1997 | A RCT on zinc supplementation for prevention of diarrhoea episodes, not for diarrhoea treatment |
| Rosado 1998 | Not a RCT |
| Rosado 2009 | A RCT on zinc supplementation for prevention of diarrhoea episodes, not for diarrhoea treatment, with different outcomes (specific intestinal infections) |
| Roy 1992 | This study did not concern any outcome of interest (intestinal permeability) to this review |
| Roy 1999 | A RCT on zinc supplementation for prevention of diarrhoea episodes, not for diarrhoea treatment |
| Roy 2007 | A RCT on zinc supplementation for prevention of diarrhoea episodes, not for diarrhoea treatment |
| Roy 2008b | This study did not concern the population of interest (children aged between 3 and 14 years) |
| Ruel 1997 | A RCT on zinc supplementation for prevention of diarrhoea episodes, not for diarrhoea treatment |
| Sabatier 1997 | Not a placebo-controlled RCT |

| Study | Reason for exclusion |
|---|---|
| Samuel 1995 | Not a RCT |
| Sazawal 1996 | A RCT on zinc supplementation for prevention of diarrhoea episodes, not for diarrhoea treatment |
| Sazawal 1997a | A RCT on zinc supplementation for prevention of diarrhoea episodes, not for diarrhoea treatment |
| Sazawal 2004 | A RCT on zinc supplementation for prevention of diarrhoea episodes, not for diarrhoea treatment |
| Sazawal 2007a | This study did not concern the intervention of interest to this review(milk fortification) |
| Sazawal 2007b | This study did not concern any outcome of interest to this review (plasma retinol) |
| Sazawal 2007c | A RCT on zinc supplementation for prevention of diarrhoea episodes, not for diarrhoea treatment |
| Shamir 2005 | Different intervention (zinc and probiotics) |
| Shankar 1998 | Not a RCT (review) |
| Sharieff 2006 | A RCT on zinc supplementation for prevention of diarrhoea episodes, not for diarrhoea treatment |
| Sheikh 2010 | Not a RCT |
| Sur 2003 | A RCT on zinc supplementation for prevention of diarrhoea episodes, not for diarrhoea treatment |
| Sáenz De Pipaón 2007 | Not a RCT (review) |
| Taneja 2009 | A RCT on zinc supplementation for prevention of diarrhoea episodes, not for diarrhoea treatment, in a different population (low birthweight infants) |
| Taneja 2010 | A RCT on zinc supplementation for prevention of diarrhoea episodes, not for diarrhoea treatment, with different outcomes (growth) |
| Tielsch 2006 | A RCT on zinc supplementation for prevention of diarrhoea episodes, not for diarrhoea treatment |
| Tielsch 2007 | A RCT on zinc supplementation for prevention of diarrhoea episodes, not for diarrhoea treatment |
| Umeta 2000 | A RCT on zinc supplementation for prevention of diarrhoea episodes, not for diarrhoea treatment |
| Untoro 2005 | This study did not concern the intervention of interest (multiple micronutrient), nor any outcome of interest to this review (anaemia, micronutrient status, growth, and morbidity) |
| Valery 2005 | This study did not concern the population of interest (all children aged under 11 years) |
| Veenemans 2011 | This was a prevention study |
| Wadhwa 2011 | This was a study on zinc-enriched ORS |
| Walden 2004 | Not a RCT |
| Walker 2007 | A RCT on zinc supplementation for prevention of diarrhoea episodes, not for diarrhoea treatment |
| Wieringa 2010 | This study did not concern the population of interest to this review (pregnant women) |
| Winch 2006 | Not a RCT |

| Study | Reason for exclusion |
|---|---|
| Winch 2008 | Not a RCT |
| Wuehler 2008 | A RCT on zinc supplementation for prevention of diarrhoea episodes, not for diarrhoea treatment |

Abbreviations: AIDS: acquired immune deficiency syndrome; HIV: human immunodeficiency virus; ORS: oral rehydration solution; RCT: randomized controlled trial.

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

**NCT01140074**

| | |
|---|---|
| Trial name or title | Efficacy of zinc sulfate with probiotics for the treatment of acute diarrhoea in children |
| Methods | RCT |
| Participants | Inclusion criteria: age 1 to 36 months; a<br>cute diarrhoea defined as 3 or more watery stools per day; informed consent (parents)<br>Exclusion criteria: severe dehydration (> 10%); coexisting severe infection (for example, sepsis, pneumonia, meningitis); immune deficiency; chronic digestive tract disease (for example, coeliac disease, food allergy); on antibiotic therapy |
| Interventions | 1. Zinc sulphate 10 to 20 mg per day orally plus probiotics.<br>2. Zinc sulphate 10 to 20 mg per day orally.<br>3. Placebo. |
| Outcomes | 1. Period of diarrhoea in hours (time frame: 15 days) (designated as safety issue: no).<br>2. Number of stools in consequent days (time frame: 15 days).<br>3. Hospitalization.<br>4. Tolerability.<br>5. Adherence to the therapy. |
| Starting date | July 2010 (not yet recruiting in December 2010) |
| Contact information | Contact: Leszek Szenborn, Prof szenborn@zak.am.wroc.pl (principal investigator)<br>Contact: Ernest P. Kuchar, MD kuchar@zak.am.wroc.pl |
| Notes | Location: Poland<br>Registration number: NCT01140074<br>Source of funding: unclear<br>Sponsor: University Hospital No 1 Wroclaw |

**NCT01198587**

| | |
|---|---|
| Trial name or title | A double blind randomized placebo controlled trial of oral zinc for children with acute diarrhoea in a developed nation |
| Methods | RCT |

**NCT01198587** *(Continued)*

| | |
|---|---|
| Participants | Inclusion criteria<br>• Healthy children with non-bloody diarrhoea illness defined as loose or watery stools.<br>• Symptoms must be present for greater than 24 hours but less than 72 hours.<br>• Comorbid conditions including: asthma, gastroesophageal reflux (unless followed by a gastroenterologist), mild speech, language, motor delays, benign heart murmurs, isolated atrial septal defect (ASD) or ventricular septal defect VSD, epilepsy (unless developmentally delayed), children born prematurely between 33 to 37 weeks without long term sequelae, repaired tetralogy of Fallot (no cardiac issues for > 6 months), diabetes may be enrolled in the study.<br>Exclusion criteria<br>• Children with symptoms less than 24 hours.<br>• Children with symptoms greater than 24 hours.<br>• Failure to thrive.<br>• G or J tube.<br>• Major surgery within last 3 months.<br>• Minor surgery (e.g. tonsillectomy, ear tubes, skin lesion removal) within last 1 month.<br>• Followed by gastrointestinal service for any reason (Crohn, ulcerative colitis, constipation.<br>• Developmental delay, patient > 1 year behind milestones.<br>• Current brain tumour.<br>• Currently being treated for cancer or in remission < 6 months.<br>• Intussuception.<br>• Antibiotics in the last 14 days or currently taking antibiotics for any reason.<br>• Autism.<br>• Children born premature < 33 weeks.<br>• Cystic fibrosis.<br>• Major congenital heart disease (any disease where child's baseline oxygen saturations < 93%).<br>• Short gut.<br>• Liver disease.<br>• History of bowel resection.<br>Age minimum: 6 months<br>Age maximum: 6 years<br>Gender: both |
| Interventions | 1. Zinc sulfate:<br>a. for children aged 6 months to 1 year, 12.5 mg orally daily for 14 days mixed in 60 mL of fluid;<br>b. for children aged 1 year and above 25mg orally daily for 14 days mixed in 60 mL of fluid.<br>2. Placebo. |
| Outcomes | 1. Duration of diarrhoea in acute diarrhoeal illnesses in a developed nation while taking zinc or placebo (time frame: 14 days) |
| Starting date | September 2010 |
| Contact information | Michelle L Niescierenko, MD<br>michelle.niescierenko@childrens.harvard.edu<br>Children's Hospital Boston |
| Notes | Location: USA<br>Registration number: NCT01198587<br>Source of funding: unclear |

NCT01198587 *(Continued)*

Sponsor: Children's Hospital Boston

Abbreviations: MD: medical doctor; RCT: randomized controlled trial.

## DATA AND ANALYSES

### Comparison 1. Zinc versus placebo for children with acute diarrhoea

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Diarrhoea duration (hours) | 24 | 5096 | Mean Difference (IV, Random, 95% CI) | -13.42 [-20.52, -6.31] |
| 1.1 Age < 6 months | 5 | 1334 | Mean Difference (IV, Random, 95% CI) | 5.23 [-2.00, 14.45] |
| 1.2 Age > 6 months | 9 | 2581 | Mean Difference (IV, Random, 95% CI) | -11.46 [-19.72, -3.19] |
| 1.3 Ages both < and > 6 months | 10 | 1181 | Mean Difference (IV, Random, 95% CI) | -22.18 [-32.57, -11.78] |
| 2 Diarrhoea duration (hours): subgrouped by nutritional status | 17 | 3518 | Mean Difference (IV, Random, 95% CI) | -17.54 [-25.49, -9.58] |
| 2.1 Nutritional status: only well-nourished | 2 | 406 | Mean Difference (IV, Random, 95% CI) | -6.79 [-23.84, 10.26] |
| 2.2 Nutritional status: well-nourished plus moderately malnourished | 10 | 2693 | Mean Difference (IV, Random, 95% CI) | -15.46 [-25.55, -5.36] |
| 2.3 Nutritional status: malnourished | 5 | 419 | Mean Difference (IV, Random, 95% CI) | -26.39 [-36.54, -16.23] |
| 3 Diarrhoea duration (hours): subgrouped by sex | 18 | 3621 | Mean Difference (IV, Random, 95% CI) | -17.33 [-25.03, -9.62] |
| 3.1 Sex: male | 3 | 430 | Mean Difference (IV, Random, 95% CI) | -22.35 [-36.40, -8.31] |
| 3.2 Sex: male and female | 15 | 3191 | Mean Difference (IV, Random, 95% CI) | -16.13 [-24.71, -7.55] |
| 4 Diarrhoea duration (hours); subgrouped by continent | 18 | 3621 | Mean Difference (IV, Random, 95% CI) | -17.33 [-25.03, -9.62] |
| 4.1 Continent: Africa | 1 | 60 | Mean Difference (IV, Random, 95% CI) | -2.40 [-33.25, 28.45] |
| 4.2 Continent: Asia | 13 | 3205 | Mean Difference (IV, Random, 95% CI) | -19.01 [-28.19, -9.82] |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 4.3 Continent: South America | 1 | 74 | Mean Difference (IV, Random, 95% CI) | -31.20 [-46.43, -15.97] |
| 4.4 Continent: Europe | 2 | 224 | Mean Difference (IV, Random, 95% CI) | -10.19 [-34.29, 13.91] |
| 4.5 Continent: Australia | 1 | 58 | Mean Difference (IV, Random, 95% CI) | -2.40 [-20.93, 16.13] |
| 5 Diarrhoea duration (hours): subgrouped by national risk of zinc deficiency | 16 | 3253 | Mean Difference (IV, Random, 95% CI) | -16.99 [-25.49, -8.50] |
| 5.1 Region: countries ranked as high risk of zinc deficiency | 8 | 2535 | Mean Difference (IV, Random, 95% CI) | -14.97 [-26.21, -3.72] |
| 5.2 Region: countries ranked as medium risk of zinc deficiency | 5 | 436 | Mean Difference (IV, Random, 95% CI) | -25.92 [-44.80, -7.04] |
| 5.3 Region: countries ranked as low risk of zinc deficiency | 3 | 282 | Mean Difference (IV, Random, 95% CI) | -7.63 [-22.74, 7.48] |
| 6 Diarrhoea duration (hours): subgrouped by zinc dose | 13 | 2018 | Mean Difference (IV, Random, 95% CI) | -20.24 [-28.84, -11.63] |
| 6.1 Zinc dose:≤ 20 mg | 9 | 976 | Mean Difference (IV, Random, 95% CI) | -18.45 [-30.19, -6.71] |
| 6.2 Zinc dose: > 20 mg | 4 | 1042 | Mean Difference (IV, Random, 95% CI) | -23.33 [-38.30, -8.35] |
| 7 Diarrhoea duration (hours): subgrouped by zinc type | 16 | 3454 | Mean Difference (IV, Random, 95% CI) | -16.50 [-25.11, -7.89] |
| 7.1 Zinc type: zinc acetate | 3 | 875 | Mean Difference (IV, Random, 95% CI) | -30.55 [-49.29, -11.82] |
| 7.2 Zinc type: gluconate | 2 | 908 | Mean Difference (IV, Random, 95% CI) | -14.51 [-30.84, 1.81] |
| 7.3 Zinc type: zinc sulphate | 11 | 1671 | Mean Difference (IV, Random, 95% CI) | -13.21 [-24.16, -2.27] |
| 8 Diarrhoea duration (hours): subgrouped by study setting | 18 | 3621 | Mean Difference (IV, Random, 95% CI) | -17.33 [-25.03, -9.62] |
| 8.1 Study setting: hospital | 15 | 2468 | Mean Difference (IV, Random, 95% CI) | -17.86 [-27.01, -8.70] |
| 8.2 Study setting:community | 3 | 1153 | Mean Difference (IV, Random, 95% CI) | -12.65 [-21.76, -3.54] |
| 9 Diarrhoea duration (hours): subgrouped by concomitant treatment | 18 | 3777 | Mean Difference (IV, Random, 95% CI) | -15.68 [-23.53, -7.82] |

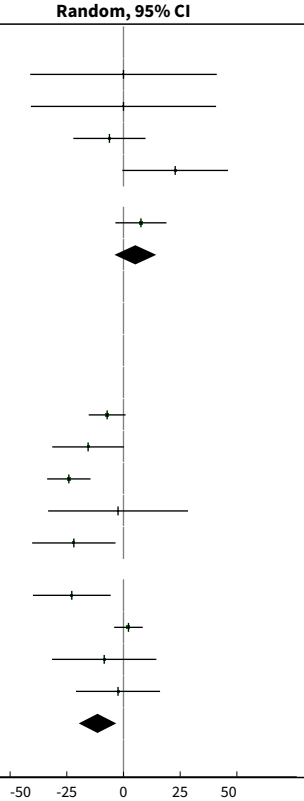
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 9.1 Concomitant treatment: zinc alone | 17 | 3394 | Mean Difference (IV, Random, 95% CI) | -16.95 [-24.85, -9.05] |
| 9.2 Concomitant treatment: zinc plus copper | 1 | 383 | Mean Difference (IV, Random, 95% CI) | 2.20 [-5.08, 9.48] |
| 10 Diarrhoea on day 3 | 9 | 2063 | Risk Ratio (M-H, Fixed, 95% CI) | 0.77 [0.69, 0.86] |
| 10.1 Age > 6 months | 4 | 1599 | Risk Ratio (M-H, Fixed, 95% CI) | 0.83 [0.72, 0.94] |
| 10.2 Ages both < and > 6 months | 5 | 464 | Risk Ratio (M-H, Fixed, 95% CI) | 0.66 [0.56, 0.79] |
| 11 Diarrhoea on day 5 | 8 | 2307 | Risk Ratio (M-H, Fixed, 95% CI) | 0.76 [0.64, 0.91] |
| 11.1 Age > 6 months | 3 | 1384 | Risk Ratio (M-H, Fixed, 95% CI) | 0.72 [0.52, 1.01] |
| 11.2 Ages both < and > 6 months | 5 | 923 | Risk Ratio (M-H, Fixed, 95% CI) | 0.78 [0.64, 0.96] |
| 12 Diarrhoea on day 7 | 13 | 5528 | Risk Ratio (M-H, Fixed, 95% CI) | 0.82 [0.72, 0.94] |
| 12.1 Age < 6 months | 3 | 1074 | Risk Ratio (M-H, Fixed, 95% CI) | 1.24 [0.99, 1.54] |
| 12.2 Age > 6 months | 6 | 3865 | Risk Ratio (M-H, Fixed, 95% CI) | 0.73 [0.61, 0.88] |
| 12.3 Ages both < and > 6 months | 4 | 589 | Risk Ratio (M-H, Fixed, 95% CI) | 0.31 [0.18, 0.52] |
| 13 Diarrhoea on day 7: subgrouped by nutritional status | 10 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 13.1 Nutritional status: only well-nourished | 1 | 141 | Risk Ratio (M-H, Fixed, 95% CI) | 0.35 [0.04, 3.26] |
| 13.2 Nutritional status: well-nourished plus moderately malnourished | 6 | 4075 | Risk Ratio (M-H, Fixed, 95% CI) | 0.72 [0.60, 0.86] |
| 13.3 Nutritional status: malnourished | 3 | 238 | Risk Ratio (M-H, Fixed, 95% CI) | 0.37 [0.22, 0.61] |
| 14 Diarrhoea on day 7: subgrouped by sex | 10 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 14.1 Sex: male | 1 | 266 | Risk Ratio (M-H, Fixed, 95% CI) | 0.11 [0.01, 0.88] |
| 14.2 Sex: male and female | 9 | 4188 | Risk Ratio (M-H, Fixed, 95% CI) | 0.68 [0.58, 0.81] |
| 15 Diarrhoea on day 7: subgrouped by continent | 10 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 15.1 Region: Asia | 9 | 4313 | Risk Ratio (M-H, Fixed, 95% CI) | 0.67 [0.56, 0.79] |
| 15.2 Region: Europe | 1 | 141 | Risk Ratio (M-H, Fixed, 95% CI) | 0.35 [0.04, 3.26] |
| 16 Diarrhoea on day 7: subgrouped by national risk of zinc deficiency | 10 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |

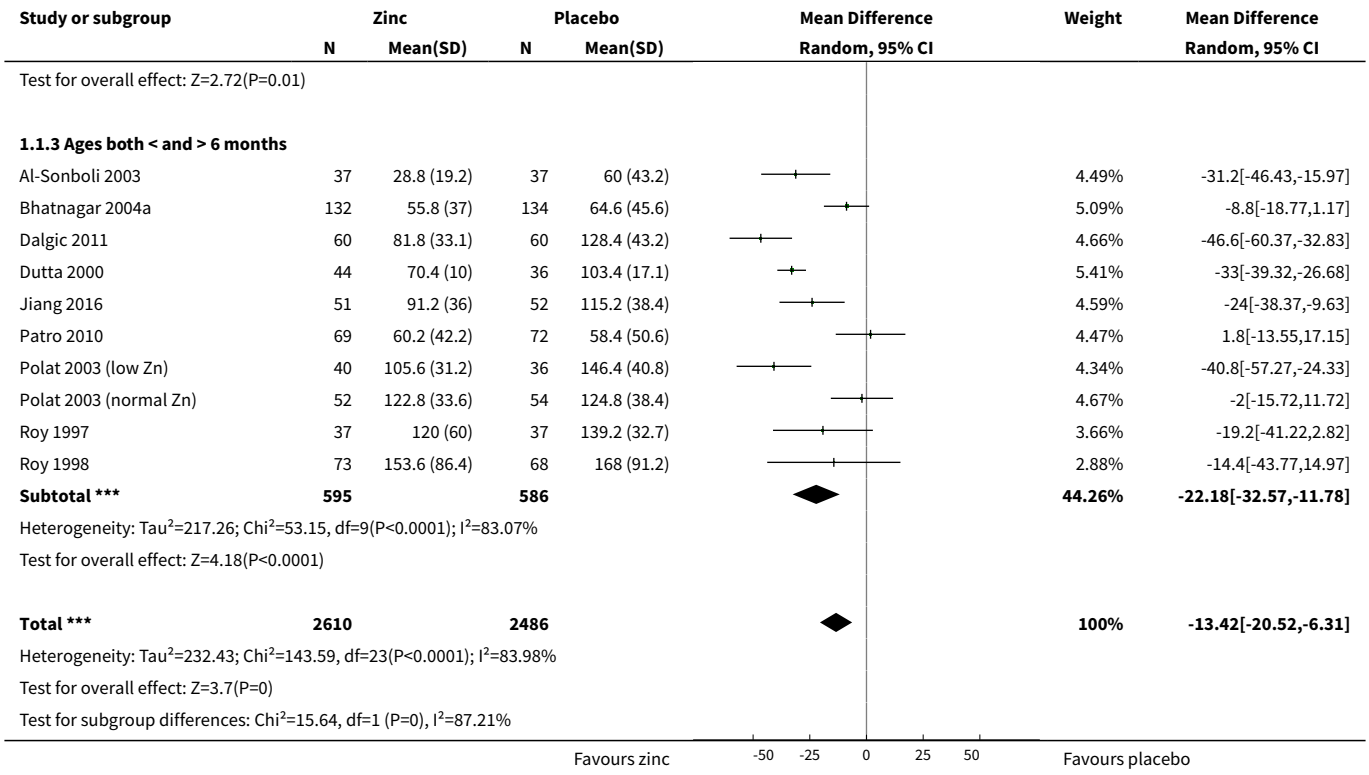
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 16.1 Region: countries ranked as high risk of zinc deficiency | 6 | 3240 | Risk Ratio (M-H, Fixed, 95% CI) | 0.75 [0.62, 0.92] |
| 16.2 Region: countries ranked as medium risk of zinc deficiency | 3 | 1073 | Risk Ratio (M-H, Fixed, 95% CI) | 0.49 [0.35, 0.68] |
| 16.3 Region: countries ranked as low risk of zinc deficiency | 1 | 141 | Risk Ratio (M-H, Fixed, 95% CI) | 0.35 [0.04, 3.26] |
| 17 Diarrhoea on day 7: subgrouped by zinc dose | 9 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 17.1 Zinc dose: 20 mg | 8 | 3154 | Risk Ratio (M-H, Fixed, 95% CI) | 0.62 [0.51, 0.74] |
| 17.2 Zinc dose: >20mg | 1 | 805 | Risk Ratio (M-H, Fixed, 95% CI) | 0.67 [0.38, 1.19] |
| 18 Diarrhoea on day 7: subgrouped by zinc type | 10 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 18.1 Zinc type: zinc acetate | 3 | 1628 | Risk Ratio (M-H, Fixed, 95% CI) | 0.60 [0.45, 0.79] |
| 18.2 Zinc type:gluconate | 1 | 805 | Risk Ratio (M-H, Fixed, 95% CI) | 0.67 [0.38, 1.19] |
| 18.3 Zinc type: zinc sulphate | 6 | 2021 | Risk Ratio (M-H, Fixed, 95% CI) | 0.72 [0.57, 0.90] |
| 19 Diarrhoea on day 7: subgrouped by study setting | 10 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 19.1 Study setting: hospital | 8 | 2758 | Risk Ratio (M-H, Fixed, 95% CI) | 0.69 [0.56, 0.84] |
| 19.2 Study setting: community | 2 | 1696 | Risk Ratio (M-H, Fixed, 95% CI) | 0.61 [0.44, 0.85] |
| 20 Diarrhoea on day 7: subgrouped by concomitant treatment | 11 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 20.1 Concomitant treatment: zinc alone | 10 | 4330 | Risk Ratio (M-H, Fixed, 95% CI) | 0.65 [0.55, 0.78] |
| 20.2 Concomitant treatment: zinc plus copper | 1 | 383 | Risk Ratio (M-H, Fixed, 95% CI) | 1.03 [0.43, 2.45] |
| 21 Stool frequency (stools /day) | 10 | 2643 | Mean Difference (IV, Fixed, 95% CI) | -0.10 [-0.25, 0.04] |
| 21.1 Age < 6 months | 5 | 1334 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [-0.17, 0.17] |
| 21.2 Age > 6 months | 4 | 1235 | Mean Difference (IV, Fixed, 95% CI) | -0.32 [-0.58, -0.06] |
| 21.3 Ages both < and > 6 months | 1 | 74 | Mean Difference (IV, Fixed, 95% CI) | -5.9 [-9.44, -2.36] |
| 22 Death | 8 | 2609 | Risk Ratio (M-H, Fixed, 95% CI) | 0.31 [0.09, 1.07] |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 22.1 Age < 6 months | 2 | 1334 | Risk Ratio (M-H, Fixed, 95% CI) | 1.00 [0.06, 15.89] |
| 22.2 Age > 6 months | 5 | 1134 | Risk Ratio (M-H, Fixed, 95% CI) | 0.29 [0.04, 2.20] |
| 22.3 Ages both < and > 6 months | 1 | 141 | Risk Ratio (M-H, Fixed, 95% CI) | 0.19 [0.02, 1.55] |
| 23 Adverse events (vomiting) | 15 | 5942 | Risk Ratio (M-H, Random, 95% CI) | 1.54 [1.28, 1.85] |
| 23.1 Age < 6 months | 3 | 1334 | Risk Ratio (M-H, Random, 95% CI) | 1.54 [1.05, 2.24] |
| 23.2 Age > 6 months | 6 | 2605 | Risk Ratio (M-H, Random, 95% CI) | 1.57 [1.32, 1.86] |
| 23.3 Ages both < and > 6 months | 6 | 2003 | Risk Ratio (M-H, Random, 95% CI) | 1.63 [1.14, 2.34] |
| 24 Difficulties in treatment administration | 1 | 87 | Odds Ratio (M-H, Fixed, 95% CI) | 1.03 [0.44, 2.41] |

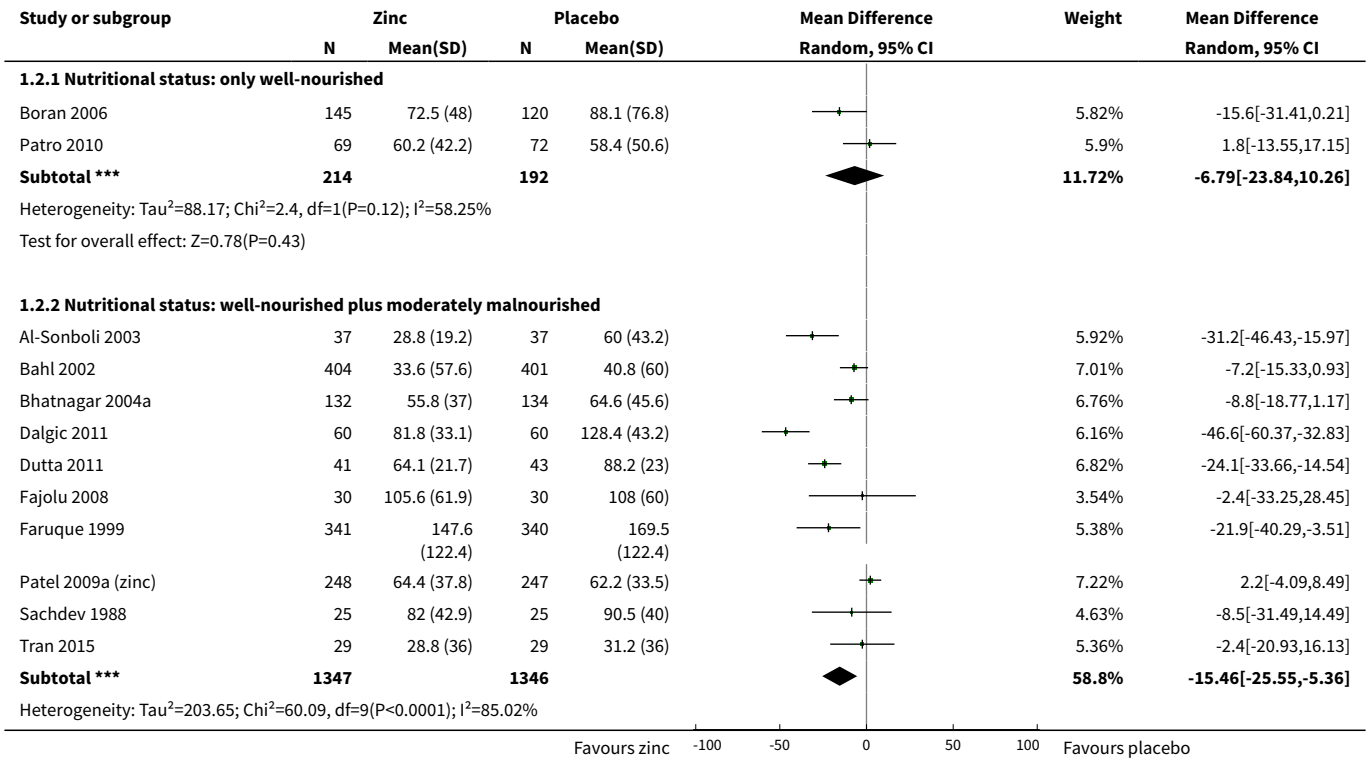
**Analysis 1.1. Comparison 1 Zinc versus placebo for children with acute diarrhoea, Outcome 1 Diarrhoea duration (hours).**

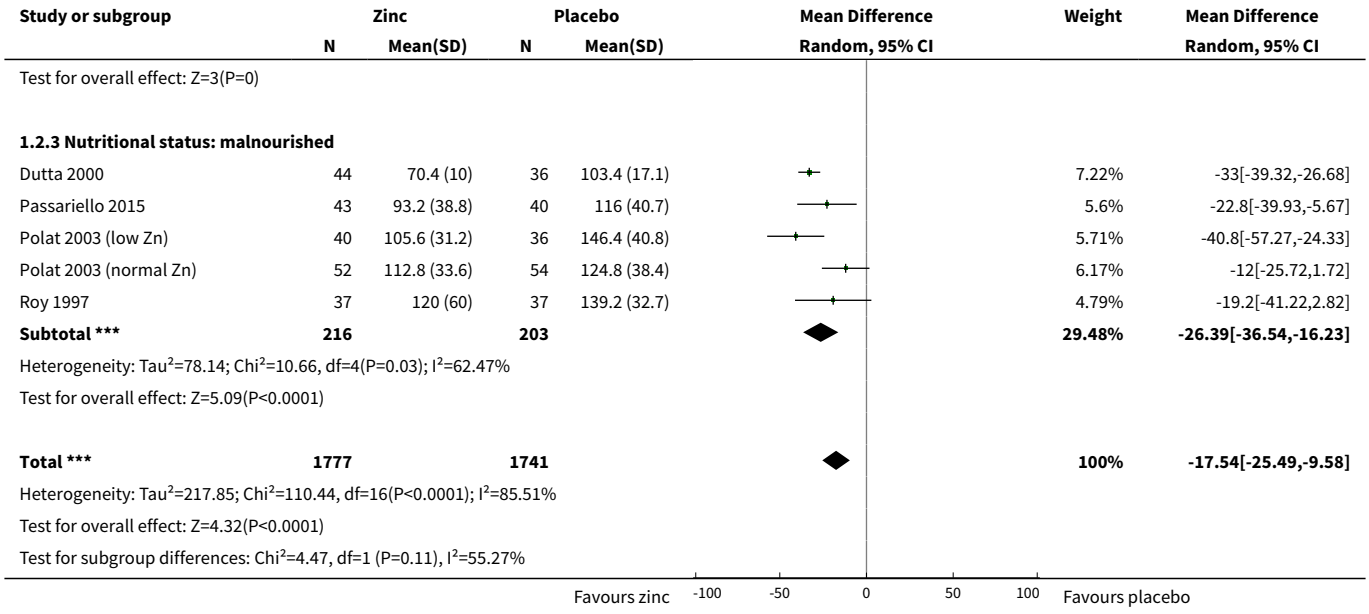
| Study or subgroup | Zinc N | Zinc Mean(SD) | Placebo N | Placebo Mean(SD) | Mean Difference Random, 95% CI | Weight | Mean Difference Random, 95% CI |
|---|---|---|---|---|---|---|---|
| **1.1.1 Age < 6 months** | | | | | | | |
| Brooks 2005a (20 mg) | 86 | 120 (111.9) | 44 | 120 (113.9) | | 1.95% | 0[-41.13,41.13] |
| Brooks 2005a (5 mg) | 85 | 120 (111.3) | 45 | 120 (113.9) | | 1.97% | 0[-40.83,40.83] |
| Fischer Walker 2006 ETH | 80 | 127 (44.2) | 83 | 133.2 (58.8) | | 4.4% | -6.2[-22.13,9.73] |
| Fischer Walker 2006 IND | 185 | 133.2 (127.2) | 183 | 110.4 (99.1) | | 3.52% | 22.8[-0.48,46.08] |
| Fischer Walker 2006 PAK | 273 | 105.6 (73.9) | 270 | 97.9 (59.3) | | 4.95% | 7.7[-3.56,18.96] |
| **Subtotal ***** | **709** | | **625** | | | **16.79%** | **5.23[-4,14.45]** |
| Heterogeneity: $Tau^2$=13.2; $Chi^2$=4.47, df=4(P=0.35); $I^2$=10.6% | | | | | | | |
| Test for overall effect: Z=1.11(P=0.27) | | | | | | | |
| **1.1.2 Age > 6 months** | | | | | | | |
| Bahl 2002 | 404 | 33.6 (57.6) | 401 | 40.8 (60) | | 5.26% | -7.2[-15.33,0.93] |
| Boran 2006 | 145 | 72.5 (48) | 120 | 88.1 (76.8) | | 4.42% | -15.6[-31.41,0.21] |
| Dutta 2011 | 41 | 64.1 (21.7) | 43 | 88.2 (23) | | 5.13% | -24.1[-33.66,-14.54] |
| Fajolu 2008 | 30 | 105.6 (61.9) | 30 | 108 (60) | | 2.74% | -2.4[-33.25,28.45] |
| Faruque 1999 | 341 | 147.6 (122.4) | 340 | 169.5 (122.4) | | 4.1% | -21.9[-40.29,-3.51] |
| Passariello 2015 | 43 | 93.2 (38.8) | 40 | 116 (40.7) | | 4.25% | -22.8[-39.93,-5.67] |
| Patel 2009a (zinc) | 248 | 64.4 (37.8) | 247 | 62.2 (33.5) | | 5.41% | 2.2[-4.09,8.49] |
| Sachdev 1988 | 25 | 82 (42.9) | 25 | 90.5 (40) | | 3.55% | -8.5[-31.49,14.49] |
| Tran 2015 | 29 | 28.8 (36) | 29 | 31.2 (36) | | 4.08% | -2.4[-20.93,16.13] |
| **Subtotal ***** | **1306** | | **1275** | | | **38.95%** | **-11.46[-19.72,-3.19]** |
| Heterogeneity: $Tau^2$=96.98; $Chi^2$=27.46, df=8(P=0); $I^2$=70.86% | | | | | | | |






## Analysis 1.2. Comparison 1 Zinc versus placebo for children with acute diarrhoea, Outcome 2 Diarrhoea duration (hours): subgrouped by nutritional status.

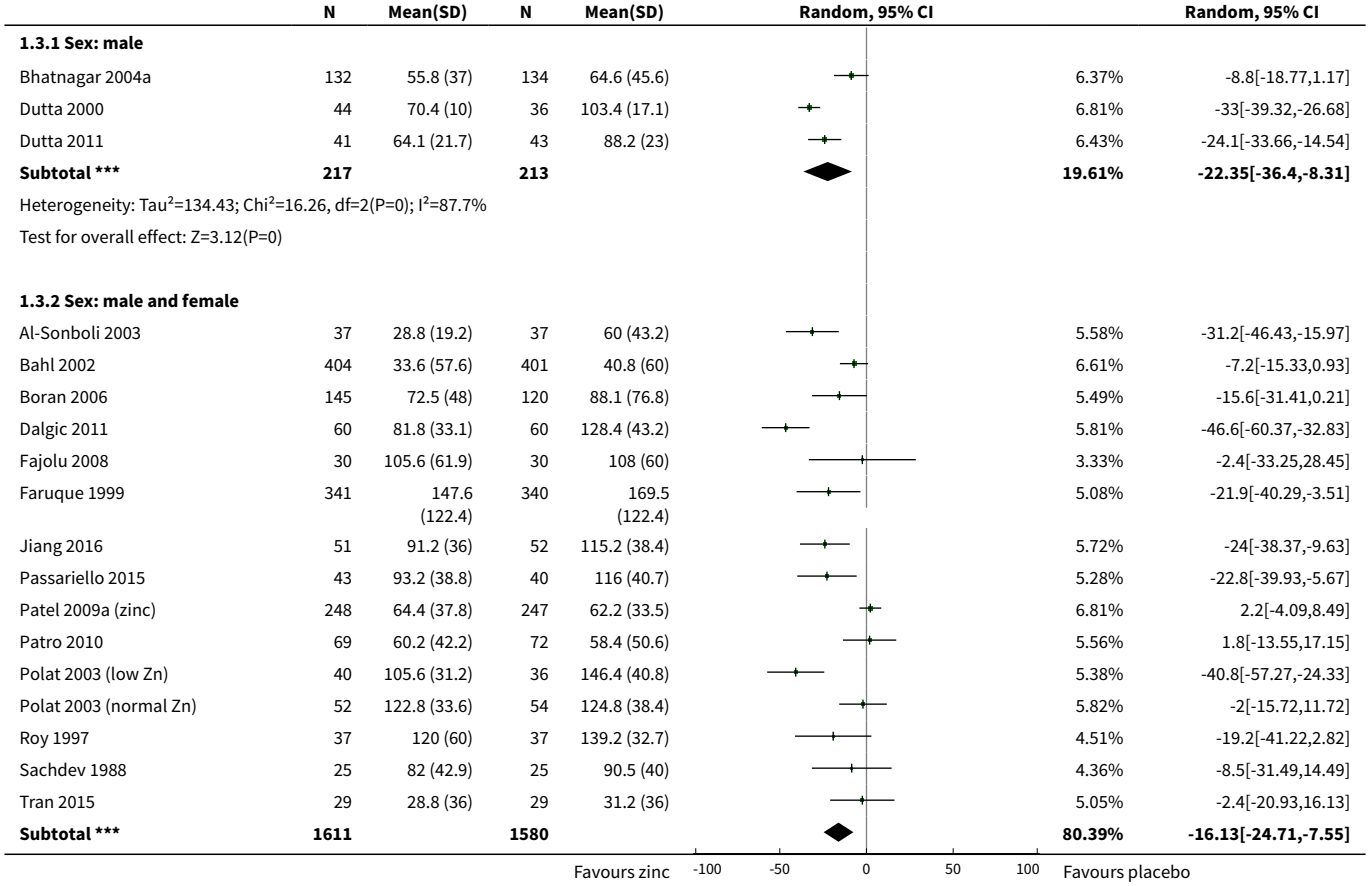




| Study or subgroup | Zinc N | Zinc Mean(SD) | Placebo N | Placebo Mean(SD) | Mean Difference Random, 95% CI | Weight | Mean Difference Random, 95% CI |
|---|---|---|---|---|---|---|---|
| Test for overall effect: Z=3(P=0) | | | | | | | |
| **1.2.3 Nutritional status: malnourished** | | | | | | | |
| Dutta 2000 | 44 | 70.4 (10) | 36 | 103.4 (17.1) | | 7.22% | -33[-39.32,-26.68] |
| Passariello 2015 | 43 | 93.2 (38.8) | 40 | 116 (40.7) | | 5.6% | -22.8[-39.93,-5.67] |
| Polat 2003 (low Zn) | 40 | 105.6 (31.2) | 36 | 146.4 (40.8) | | 5.71% | -40.8[-57.27,-24.33] |
| Polat 2003 (normal Zn) | 52 | 112.8 (33.6) | 54 | 124.8 (38.4) | | 6.17% | -12[-25.72,1.72] |
| Roy 1997 | 37 | 120 (60) | 37 | 139.2 (32.7) | | 4.79% | -19.2[-41.22,2.82] |
| **Subtotal ***** | **216** | | **203** | | | **29.48%** | **-26.39[-36.54,-16.23]** |
| Heterogeneity: $Tau^2$=78.14; $Chi^2$=10.66, df=4(P=0.03); $I^2$=62.47% | | | | | | | |
| Test for overall effect: Z=5.09(P<0.0001) | | | | | | | |
| **Total ***** | **1777** | | **1741** | | | **100%** | **-17.54[-25.49,-9.58]** |
| Heterogeneity: $Tau^2$=217.85; $Chi^2$=110.44, df=16(P<0.0001); $I^2$=85.51% | | | | | | | |
| Test for overall effect: Z=4.32(P<0.0001) | | | | | | | |
| Test for subgroup differences: $Chi^2$=4.47, df=1 (P=0.11), $I^2$=55.27% | | | | | | | |



## Analysis 1.3. Comparison 1 Zinc versus placebo for children with acute diarrhoea, Outcome 3 Diarrhoea duration (hours): subgrouped by sex.



| Study or subgroup | Zinc N | Zinc Mean(SD) | Placebo N | Placebo Mean(SD) | Mean Difference Random, 95% CI | Weight | Mean Difference Random, 95% CI |
|---|---|---|---|---|---|---|---|
| **1.3.1 Sex: male** | | | | | | | |
| Bhatnagar 2004a | 132 | 55.8 (37) | 134 | 64.6 (45.6) | | 6.37% | -8.8[-18.77,1.17] |
| Dutta 2000 | 44 | 70.4 (10) | 36 | 103.4 (17.1) | | 6.81% | -33[-39.32,-26.68] |
| Dutta 2011 | 41 | 64.1 (21.7) | 43 | 88.2 (23) | | 6.43% | -24.1[-33.66,-14.54] |
| **Subtotal ***** | **217** | | **213** | | | **19.61%** | **-22.35[-36.4,-8.31]** |
| Heterogeneity: $Tau^2$=134.43; $Chi^2$=16.26, df=2(P=0); $I^2$=87.7% | | | | | | | |
| Test for overall effect: Z=3.12(P=0) | | | | | | | |
| **1.3.2 Sex: male and female** | | | | | | | |
| Al-Sonboli 2003 | 37 | 28.8 (19.2) | 37 | 60 (43.2) | | 5.58% | -31.2[-46.43,-15.97] |
| Bahl 2002 | 404 | 33.6 (57.6) | 401 | 40.8 (60) | | 6.61% | -7.2[-15.33,0.93] |
| Boran 2006 | 145 | 72.5 (48) | 120 | 88.1 (76.8) | | 5.49% | -15.6[-31.41,0.21] |
| Dalgic 2011 | 60 | 81.8 (33.1) | 60 | 128.4 (43.2) | | 5.81% | -46.6[-60.37,-32.83] |
| Fajolu 2008 | 30 | 105.6 (61.9) | 30 | 108 (60) | | 3.33% | -2.4[-33.25,28.45] |
| Faruque 1999 | 341 | 147.6 (122.4) | 340 | 169.5 (122.4) | | 5.08% | -21.9[-40.29,-3.51] |
| Jiang 2016 | 51 | 91.2 (36) | 52 | 115.2 (38.4) | | 5.72% | -24[-38.37,-9.63] |
| Passariello 2015 | 43 | 93.2 (38.8) | 40 | 116 (40.7) | | 5.28% | -22.8[-39.93,-5.67] |
| Patel 2009a (zinc) | 248 | 64.4 (37.8) | 247 | 62.2 (33.5) | | 6.81% | 2.2[-4.09,8.49] |
| Patro 2010 | 69 | 60.2 (42.2) | 72 | 58.4 (50.6) | | 5.56% | 1.8[-13.55,17.15] |
| Polat 2003 (low Zn) | 40 | 105.6 (31.2) | 36 | 146.4 (40.8) | | 5.38% | -40.8[-57.27,-24.33] |
| Polat 2003 (normal Zn) | 52 | 122.8 (33.6) | 54 | 124.8 (38.4) | | 5.82% | -2[-15.72,11.72] |
| Roy 1997 | 37 | 120 (60) | 37 | 139.2 (32.7) | | 4.51% | -19.2[-41.22,2.82] |
| Sachdev 1988 | 25 | 82 (42.9) | 25 | 90.5 (40) | | 4.36% | -8.5[-31.49,14.49] |
| Tran 2015 | 29 | 28.8 (36) | 29 | 31.2 (36) | | 5.05% | -2.4[-20.93,16.13] |
| **Subtotal ***** | **1611** | | **1580** | | | **80.39%** | **-16.13[-24.71,-7.55]** |

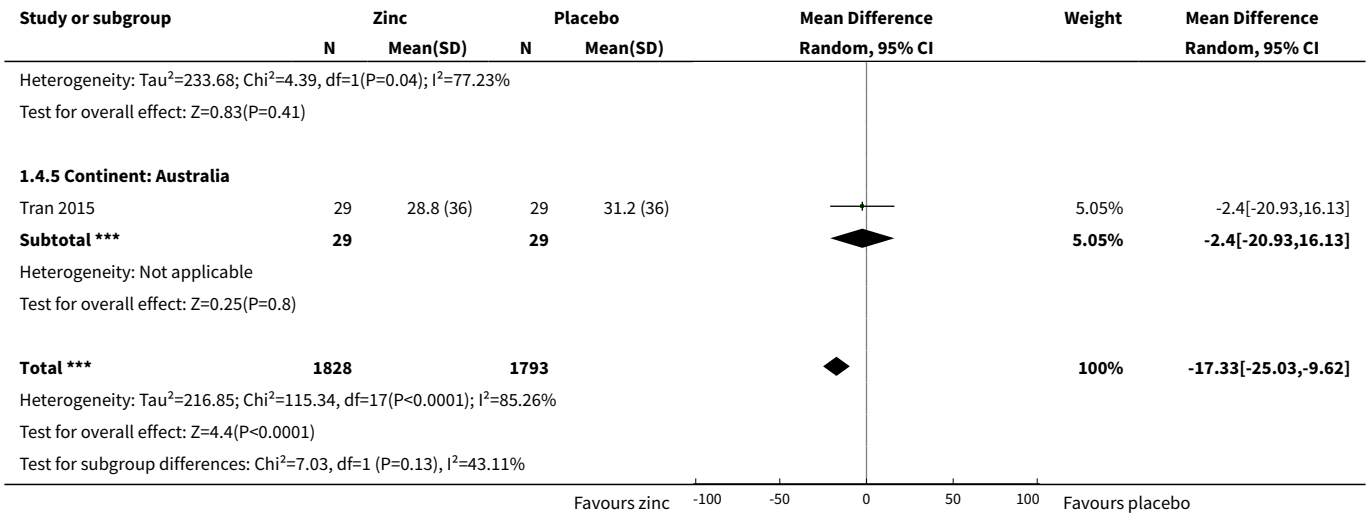
| Study or subgroup | Zinc N | Zinc Mean(SD) | Placebo N | Placebo Mean(SD) | Mean Difference Random, 95% CI | Weight | Mean Difference Random, 95% CI |
|---|---|---|---|---|---|---|---|
| Heterogeneity: Tau²=215.43; Chi²=75.39, df=14(P<0.0001); I²=81.43% | | | | | | | |
| Test for overall effect: Z=3.69(P=0) | | | | | | | |
| **Total ***** | **1828** | | **1793** | | | **100%** | **-17.33[-25.03,-9.62]** |
| Heterogeneity: Tau²=216.85; Chi²=115.34, df=17(P<0.0001); I²=85.26% | | | | | | | |
| Test for overall effect: Z=4.4(P<0.0001) | | | | | | | |
| Test for subgroup differences: Chi²=0.55, df=1 (P=0.46), I²=0% | | | | | | | |

Favours zinc -100 -50 0 50 100 Favours placebo

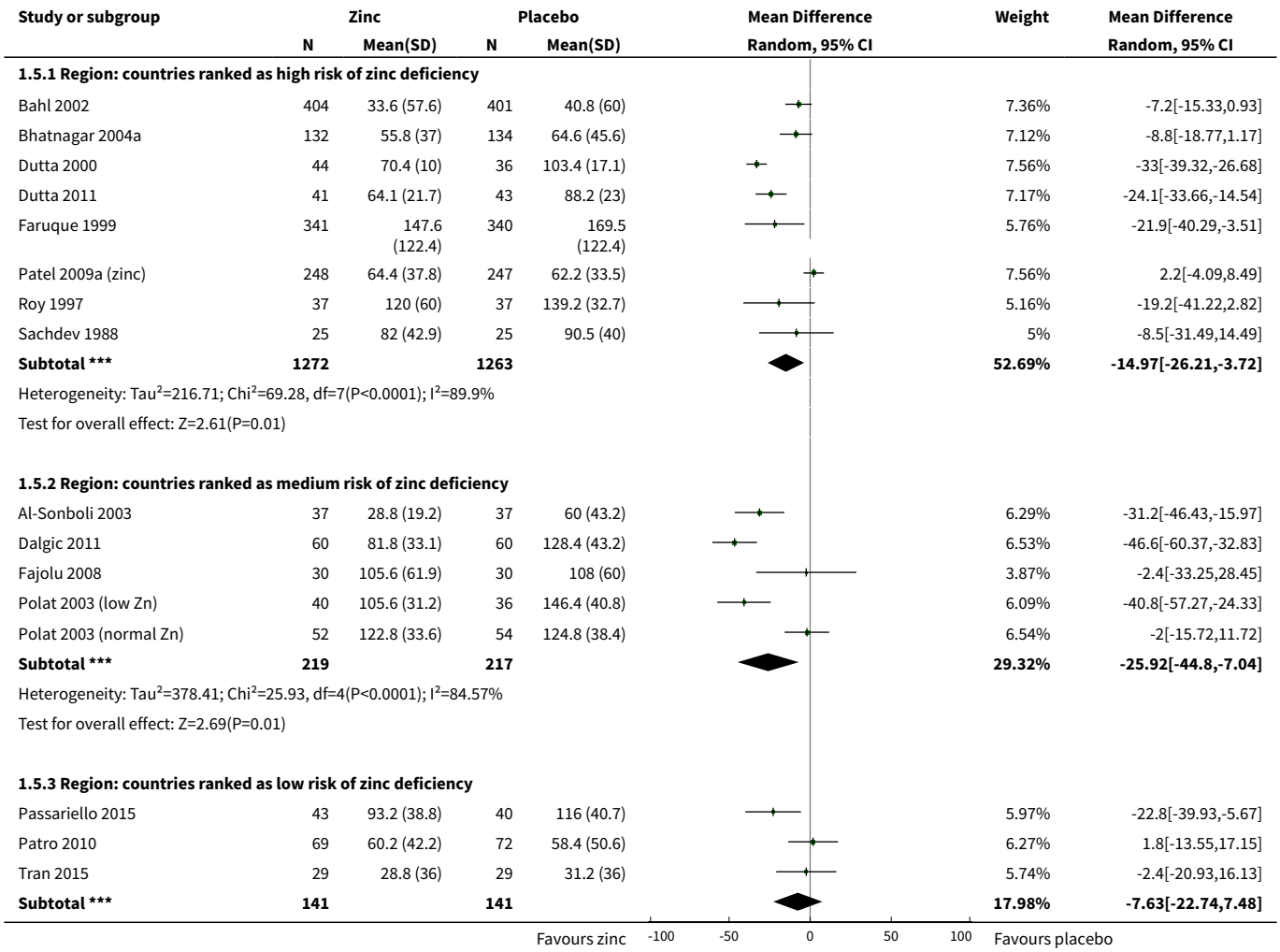
## Analysis 1.4. Comparison 1 Zinc versus placebo for children with acute diarrhoea, Outcome 4 Diarrhoea duration (hours); subgrouped by continent.

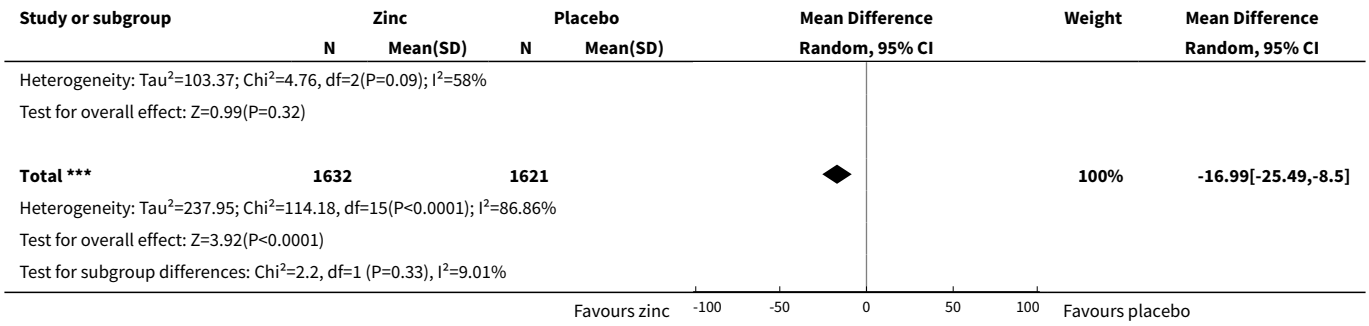
| Study or subgroup | Zinc N | Zinc Mean(SD) | Placebo N | Placebo Mean(SD) | Mean Difference Random, 95% CI | Weight | Mean Difference Random, 95% CI |
|---|---|---|---|---|---|---|---|
| **1.4.1 Continent: Africa** | | | | | | | |
| Fajolu 2008 | 30 | 105.6 (61.9) | 30 | 108 (60) | | 3.33% | -2.4[-33.25,28.45] |
| **Subtotal ***** | **30** | | **30** | | | **3.33%** | **-2.4[-33.25,28.45]** |
| Heterogeneity: Not applicable | | | | | | | |
| Test for overall effect: Z=0.15(P=0.88) | | | | | | | |
| **1.4.2 Continent: Asia** | | | | | | | |
| Bahl 2002 | 404 | 33.6 (57.6) | 401 | 40.8 (60) | | 6.61% | -7.2[-15.33,0.93] |
| Bhatnagar 2004a | 132 | 55.8 (37) | 134 | 64.6 (45.6) | | 6.37% | -8.8[-18.77,1.17] |
| Boran 2006 | 145 | 72.5 (48) | 120 | 88.1 (76.8) | | 5.49% | -15.6[-31.41,0.21] |
| Dalgic 2011 | 60 | 81.8 (33.1) | 60 | 128.4 (43.2) | | 5.81% | -46.6[-60.37,-32.83] |
| Dutta 2000 | 44 | 70.4 (10) | 36 | 103.4 (17.1) | | 6.81% | -33[-39.32,-26.68] |
| Dutta 2011 | 41 | 64.1 (21.7) | 43 | 88.2 (23) | | 6.43% | -24.1[-33.66,-14.54] |
| Faruque 1999 | 341 | 147.6 (122.4) | 340 | 169.5 (122.4) | | 5.08% | -21.9[-40.29,-3.51] |
| Jiang 2016 | 51 | 91.2 (36) | 52 | 115.2 (38.4) | | 5.72% | -24[-38.37,-9.63] |
| Patel 2009a (zinc) | 248 | 64.4 (37.8) | 247 | 62.2 (33.5) | | 6.81% | 2.2[-4.09,8.49] |
| Polat 2003 (low Zn) | 40 | 105.6 (31.2) | 36 | 146.4 (40.8) | | 5.38% | -40.8[-57.27,-24.33] |
| Polat 2003 (normal Zn) | 52 | 122.8 (33.6) | 54 | 124.8 (38.4) | | 5.82% | -2[-15.72,11.72] |
| Roy 1997 | 37 | 120 (60) | 37 | 139.2 (32.7) | | 4.51% | -19.2[-41.22,2.82] |
| Sachdev 1988 | 25 | 82 (42.9) | 25 | 90.5 (40) | | 4.36% | -8.5[-31.49,14.49] |
| **Subtotal ***** | **1620** | | **1585** | | | **75.2%** | **-19.01[-28.19,-9.82]** |
| Heterogeneity: Tau²=234.75; Chi²=102.78, df=12(P<0.0001); I²=88.32% | | | | | | | |
| Test for overall effect: Z=4.05(P<0.0001) | | | | | | | |
| **1.4.3 Continent: South America** | | | | | | | |
| Al-Sonboli 2003 | 37 | 28.8 (19.2) | 37 | 60 (43.2) | | 5.58% | -31.2[-46.43,-15.97] |
| **Subtotal ***** | **37** | | **37** | | | **5.58%** | **-31.2[-46.43,-15.97]** |
| Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100% | | | | | | | |
| Test for overall effect: Z=4.01(P<0.0001) | | | | | | | |
| **1.4.4 Continent: Europe** | | | | | | | |
| Passariello 2015 | 43 | 93.2 (38.8) | 40 | 116 (40.7) | | 5.28% | -22.8[-39.93,-5.67] |
| Patro 2010 | 69 | 60.2 (42.2) | 72 | 58.4 (50.6) | | 5.56% | 1.8[-13.55,17.15] |
| **Subtotal ***** | **112** | | **112** | | | **10.84%** | **-10.19[-34.29,13.91]** |

Favours zinc -100 -50 0 50 100 Favours placebo

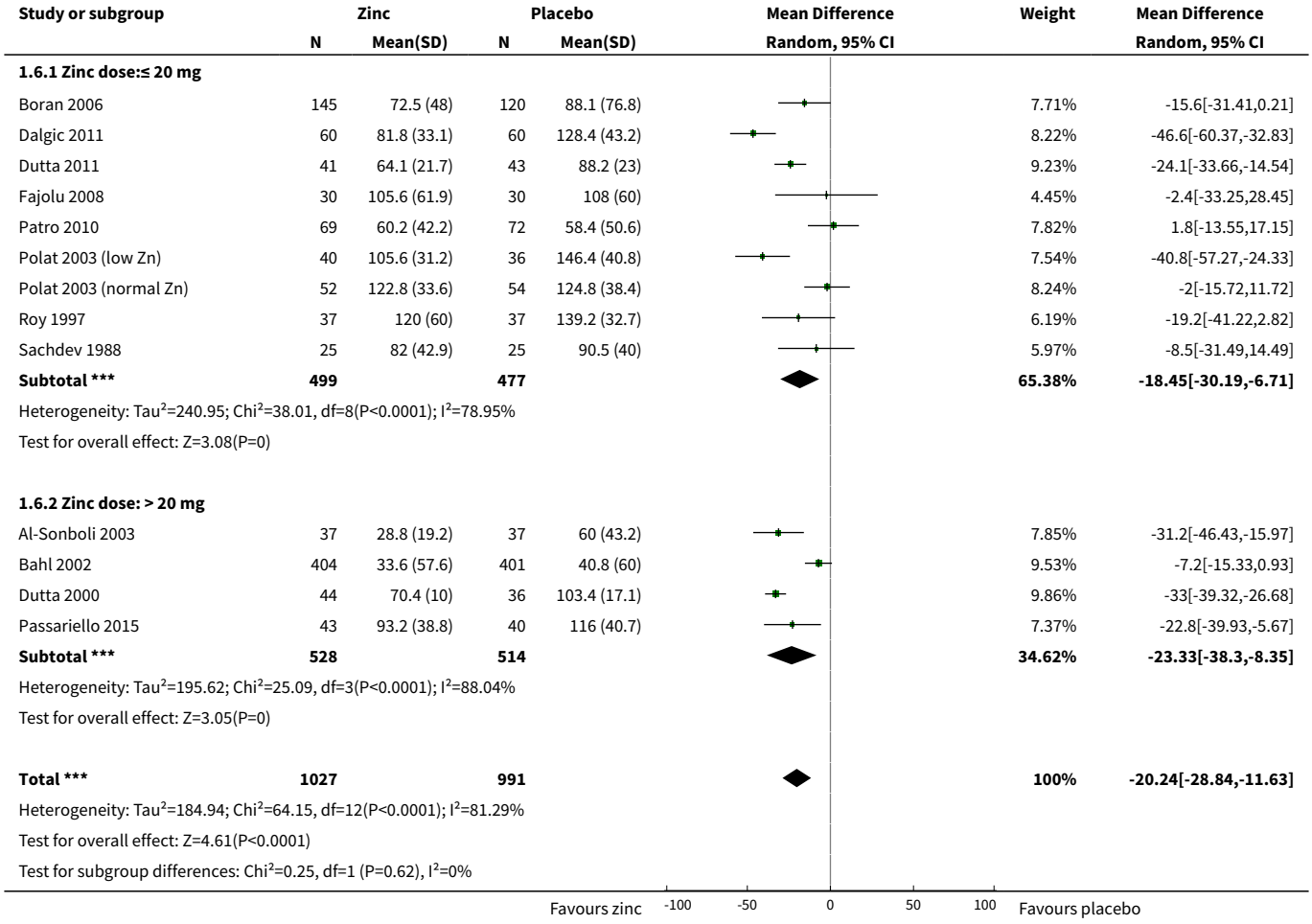



## Analysis 1.5. Comparison 1 Zinc versus placebo for children with acute diarrhoea, Outcome 5 Diarrhoea duration (hours): subgrouped by national risk of zinc deficiency.



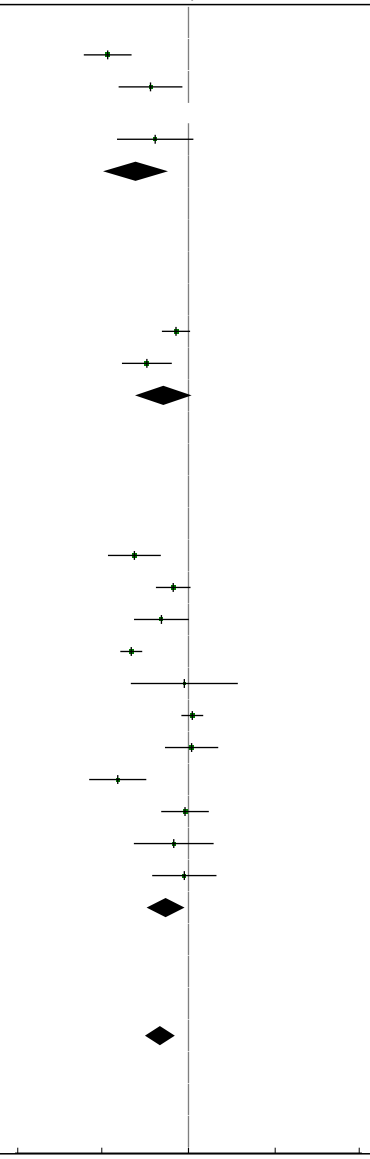



## Analysis 1.6. Comparison 1 Zinc versus placebo for children with acute diarrhoea, Outcome 6 Diarrhoea duration (hours): subgrouped by zinc dose.



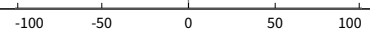
## Analysis 1.7. Comparison 1 Zinc versus placebo for children with acute diarrhoea, Outcome 7 Diarrhoea duration (hours): subgrouped by zinc type.

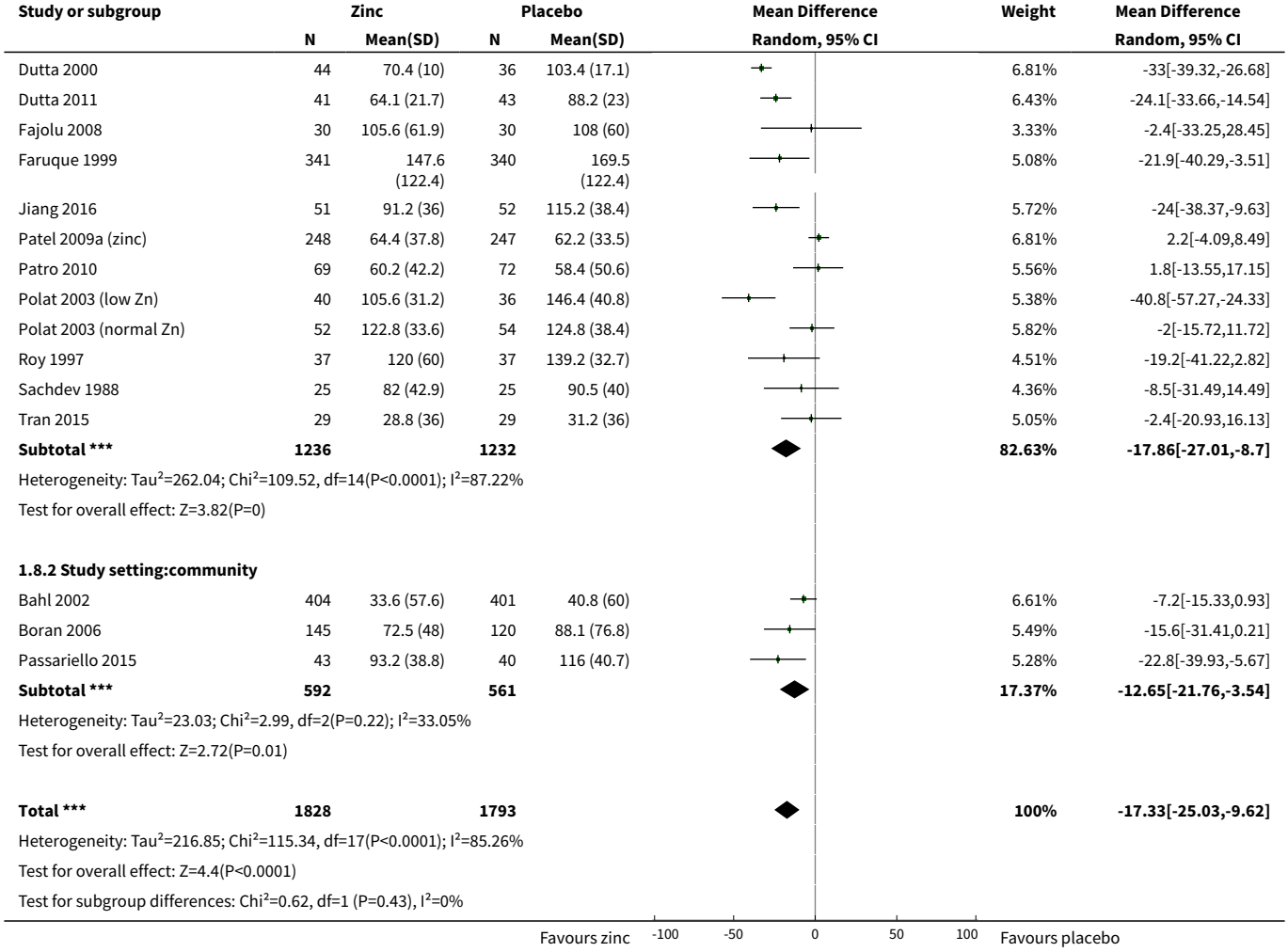
| Study or subgroup | Zinc N | Zinc Mean(SD) | Placebo N | Placebo Mean(SD) | Mean Difference Random, 95% CI | Weight | Mean Difference Random, 95% CI |
|---|---|---|---|---|---|---|---|
| **1.7.1 Zinc type: zinc acetate** | | | | | | | |
| Dalgic 2011 | 60 | 81.8 (33.1) | 60 | 128.4 (43.2) | | 6.56% | -46.6[-60.37,-32.83] |
| Faruque 1999 | 341 | 147.6 (122.4) | 340 | 169.5 (122.4) | | 5.8% | -21.9[-40.29,-3.51] |
| Roy 1997 | 37 | 120 (60) | 37 | 139.2 (32.7) | | 5.2% | -19.2[-41.22,2.82] |
| **Subtotal ***** | **438** | | **437** | | | **17.57%** | **-30.55[-49.29,-11.82]** |
| Heterogeneity: Tau²=189.79; Chi²=6.61, df=2(P=0.04); I²=69.76% | | | | | | | |
| Test for overall effect: Z=3.2(P=0) | | | | | | | |
| **1.7.2 Zinc type: gluconate** | | | | | | | |
| Bahl 2002 | 404 | 33.6 (57.6) | 401 | 40.8 (60) | | 7.37% | -7.2[-15.33,0.93] |
| Jiang 2016 | 51 | 91.2 (36) | 52 | 115.2 (38.4) | | 6.47% | -24[-38.37,-9.63] |
| **Subtotal ***** | **455** | | **453** | | | **13.84%** | **-14.51[-30.84,1.81]** |
| Heterogeneity: Tau²=105.64; Chi²=3.98, df=1(P=0.05); I²=74.86% | | | | | | | |
| Test for overall effect: Z=1.74(P=0.08) | | | | | | | |
| **1.7.3 Zinc type: zinc sulphate** | | | | | | | |
| Al-Sonboli 2003 | 37 | 28.8 (19.2) | 37 | 60 (43.2) | | 6.33% | -31.2[-46.43,-15.97] |
| Bhatnagar 2004a | 132 | 55.8 (37) | 134 | 64.6 (45.6) | | 7.14% | -8.8[-18.77,1.17] |
| Boran 2006 | 145 | 72.5 (48) | 120 | 88.1 (76.8) | | 6.23% | -15.6[-31.41,0.21] |
| Dutta 2000 | 44 | 70.4 (10) | 36 | 103.4 (17.1) | | 7.57% | -33[-39.32,-26.68] |
| Fajolu 2008 | 30 | 105.6 (61.9) | 30 | 108 (60) | | 3.92% | -2.4[-33.25,28.45] |
| Patel 2009a (zinc) | 248 | 64.4 (37.8) | 247 | 62.2 (33.5) | | 7.57% | 2.2[-4.09,8.49] |
| Patro 2010 | 69 | 60.2 (42.2) | 72 | 58.4 (50.6) | | 6.31% | 1.8[-13.55,17.15] |
| Polat 2003 (low Zn) | 40 | 105.6 (31.2) | 36 | 146.4 (40.8) | | 6.12% | -40.8[-57.27,-24.33] |
| Polat 2003 (normal Zn) | 52 | 122.8 (33.6) | 54 | 124.8 (38.4) | | 6.57% | -2[-15.72,11.72] |
| Sachdev 1988 | 25 | 82 (42.9) | 25 | 90.5 (40) | | 5.05% | -8.5[-31.49,14.49] |
| Tran 2015 | 29 | 28.8 (36) | 29 | 31.2 (36) | | 5.78% | -2.4[-20.93,16.13] |
| **Subtotal ***** | **851** | | **820** | | | **68.59%** | **-13.21[-24.16,-2.27]** |
| Heterogeneity: Tau²=277.38; Chi²=85.63, df=10(P<0.0001); I²=88.32% | | | | | | | |
| Test for overall effect: Z=2.37(P=0.02) | | | | | | | |
| **Total ***** | **1744** | | **1710** | | | **100%** | **-16.5[-25.11,-7.89]** |
| Heterogeneity: Tau²=244.5; Chi²=111.81, df=15(P<0.0001); I²=86.58% | | | | | | | |
| Test for overall effect: Z=3.76(P=0) | | | | | | | |
| Test for subgroup differences: Chi²=2.56, df=1 (P=0.28), I²=21.82% | | | | | | | |



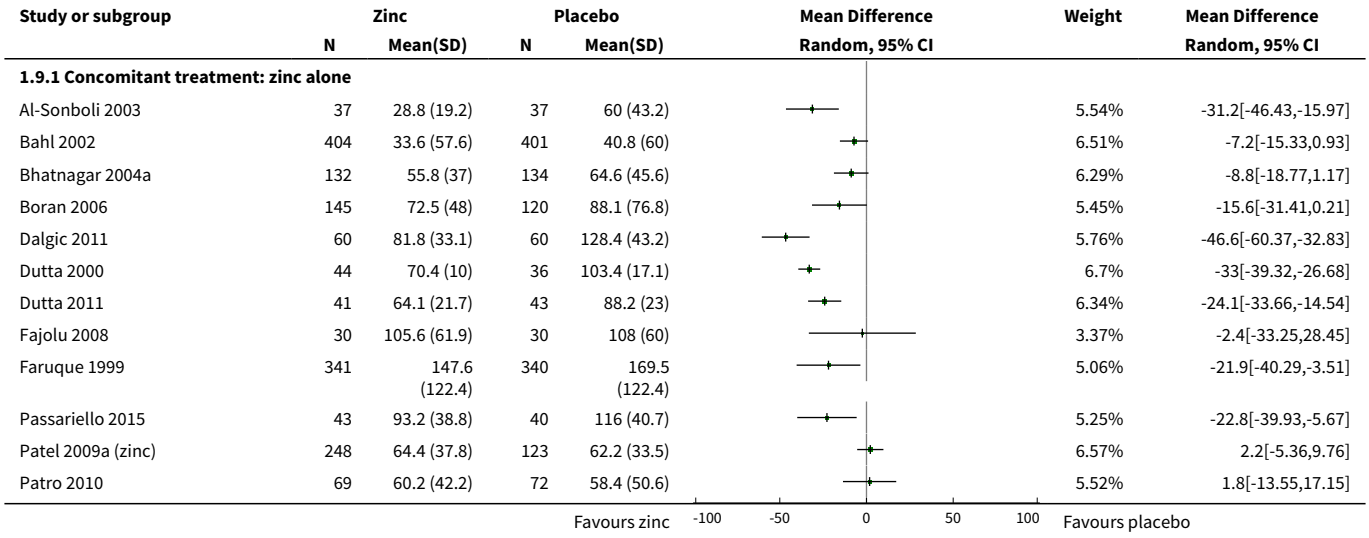

## Analysis 1.8. Comparison 1 Zinc versus placebo for children with acute diarrhoea, Outcome 8 Diarrhoea duration (hours): subgrouped by study setting.

| Study or subgroup | Zinc N | Zinc Mean(SD) | Placebo N | Placebo Mean(SD) | Mean Difference Random, 95% CI | Weight | Mean Difference Random, 95% CI |
|---|---|---|---|---|---|---|---|
| **1.8.1 Study setting: hospital** | | | | | | | |
| Al-Sonboli 2003 | 37 | 28.8 (19.2) | 37 | 60 (43.2) | | 5.58% | -31.2[-46.43,-15.97] |
| Bhatnagar 2004a | 132 | 55.8 (37) | 134 | 64.6 (45.6) | | 6.37% | -8.8[-18.77,1.17] |
| Dalgic 2011 | 60 | 81.8 (33.1) | 60 | 128.4 (43.2) | | 5.81% | -46.6[-60.37,-32.83] |

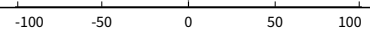





## Analysis 1.9. Comparison 1 Zinc versus placebo for children with acute diarrhoea, Outcome 9 Diarrhoea duration (hours): subgrouped by concomitant treatment.

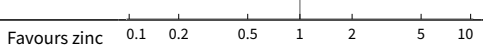


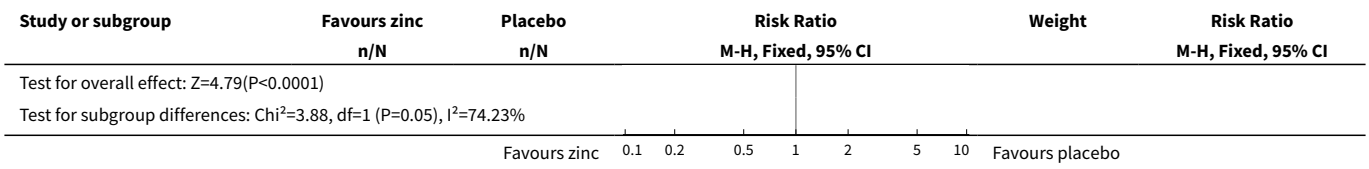
| Study or subgroup | Zinc N | Zinc Mean(SD) | Placebo N | Placebo Mean(SD) | Mean Difference Random, 95% CI | Weight | Mean Difference Random, 95% CI |
|---|---|---|---|---|---|---|---|
| Polat 2003 (low Zn) | 40 | 105.6 (31.2) | 36 | 146.4 (40.8) | | 5.35% | -40.8[-57.27,-24.33] |
| Polat 2003 (normal Zn) | 52 | 122.8 (33.6) | 54 | 124.8 (38.4) | | 5.77% | -2[-15.72,11.72] |
| Roy 1997 | 37 | 120 (60) | 37 | 139.2 (32.7) | | 4.51% | -19.2[-41.22,2.82] |
| Sachdev 1988 | 25 | 82 (42.9) | 25 | 90.5 (40) | | 4.37% | -8.5[-31.49,14.49] |
| Tran 2015 | 29 | 28.8 (36) | 29 | 31.2 (36) | | 5.04% | -2.4[-20.93,16.13] |
| **Subtotal *** ** | **1777** | | **1617** | | | **93.4%** | **-16.95[-24.85,-9.05]** |
| Heterogeneity: $Tau^2$=213.55; $Chi^2$=103.69, df=16(P<0.0001); $I^2$=84.57% | | | | | | | |
| Test for overall effect: Z=4.21(P<0.0001) | | | | | | | |
| **1.9.2 Concomitant treatment: zinc plus copper** | | | | | | | |
| Patel 2009b (zinc + copper) | 259 | 64.4 (35) | 124 | 62.2 (33.5) | | 6.6% | 2.2[-5.08,9.48] |
| **Subtotal *** ** | **259** | | **124** | | | **6.6%** | **2.2[-5.08,9.48]** |
| Heterogeneity: Not applicable | | | | | | | |
| Test for overall effect: Z=0.59(P=0.55) | | | | | | | |
| **Total *** ** | **2036** | | **1741** | | | **100%** | **-15.68[-23.53,-7.82]** |
| Heterogeneity: $Tau^2$=229.42; $Chi^2$=127.13, df=17(P<0.0001); $I^2$=86.63% | | | | | | | |
| Test for overall effect: Z=3.91(P<0.0001) | | | | | | | |
| Test for subgroup differences: $Chi^2$=12.22, df=1 (P=0), $I^2$=91.82% | | | | | | | |



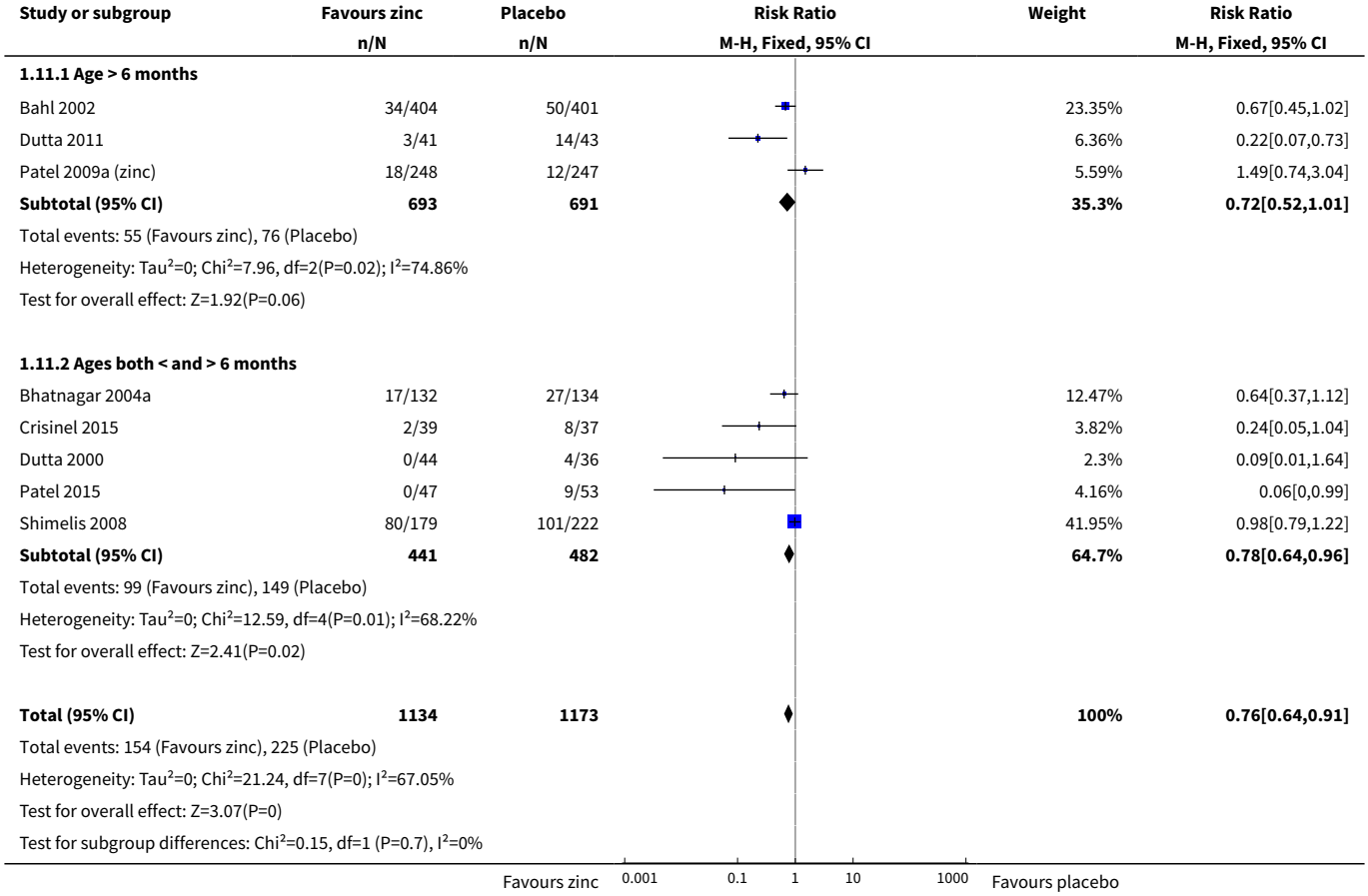

## Analysis 1.10. Comparison 1 Zinc versus placebo for children with acute diarrhoea, Outcome 10 Diarrhoea on day 3.

| Study or subgroup | Favours zinc n/N | Placebo n/N | Risk Ratio M-H, Fixed, 95% CI | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|
| **1.10.1 Age > 6 months** | | | | | |
| Jin 2013 | 42/65 | 49/65 | | 10.91% | 0.86[0.68,1.08] |
| Passariello 2015 | 21/43 | 29/40 | | 6.69% | 0.67[0.47,0.97] |
| Patel 2009a (zinc) | 69/248 | 66/247 | | 14.73% | 1.04[0.78,1.39] |
| Strand 2002 | 118/442 | 159/449 | | 35.14% | 0.75[0.62,0.92] |
| **Subtotal (95% CI)** | **798** | **801** | | **67.48%** | **0.83[0.72,0.94]** |
| Total events: 250 (Favours zinc), 303 (Placebo) | | | | | |
| Heterogeneity: $Tau^2$=0; $Chi^2$=4.63, df=3(P=0.2); $I^2$=35.17% | | | | | |
| Test for overall effect: Z=2.87(P=0) | | | | | |
| **1.10.2 Ages both < and > 6 months** | | | | | |
| Crisinel 2015 | 17/39 | 19/40 | | 4.18% | 0.92[0.57,1.49] |
| Jiang 2016 | 30/51 | 40/52 | | 8.82% | 0.76[0.58,1.01] |
| Patel 2015 | 10/47 | 19/53 | | 3.98% | 0.59[0.31,1.15] |
| Polat 2003 (low Zn) | 16/40 | 29/36 | | 6.8% | 0.5[0.33,0.75] |
| Polat 2003 (normal Zn) | 23/52 | 40/54 | | 8.74% | 0.6[0.42,0.84] |
| **Subtotal (95% CI)** | **229** | **235** | | **32.52%** | **0.66[0.56,0.79]** |
| Total events: 96 (Favours zinc), 147 (Placebo) | | | | | |
| Heterogeneity: $Tau^2$=0; $Chi^2$=5.14, df=4(P=0.27); $I^2$=22.21% | | | | | |
| Test for overall effect: Z=4.6(P<0.0001) | | | | | |
| **Total (95% CI)** | **1027** | **1036** | | **100%** | **0.77[0.69,0.86]** |
| Total events: 346 (Favours zinc), 450 (Placebo) | | | | | |
| Heterogeneity: $Tau^2$=0; $Chi^2$=13.23, df=8(P=0.1); $I^2$=39.55% | | | | | |

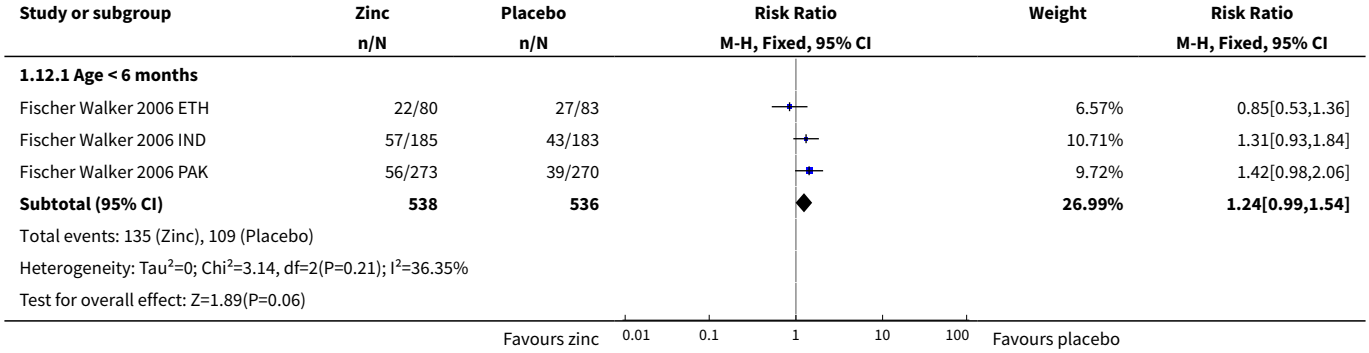


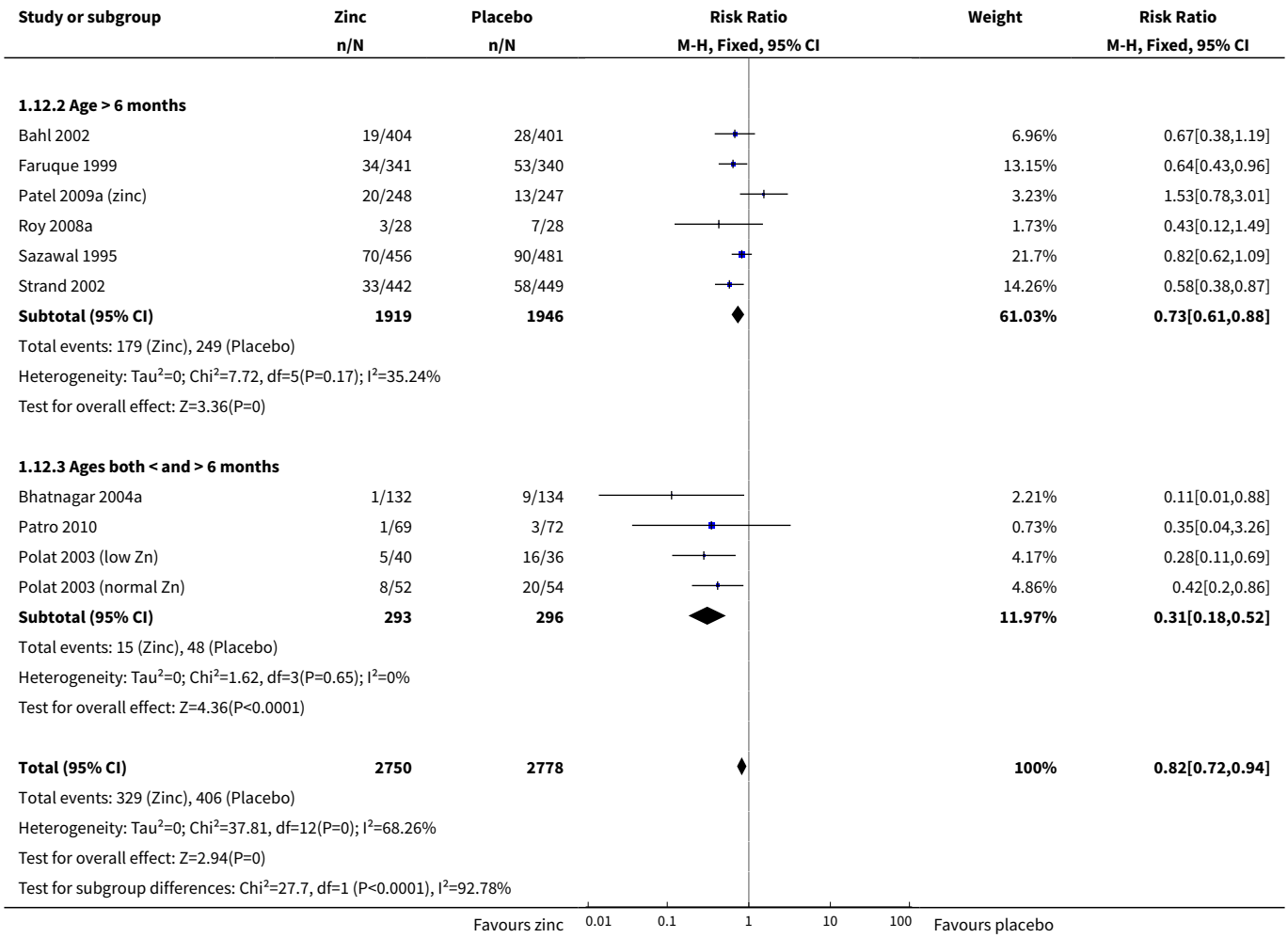



## Analysis 1.11. Comparison 1 Zinc versus placebo for children with acute diarrhoea, Outcome 11 Diarrhoea on day 5.

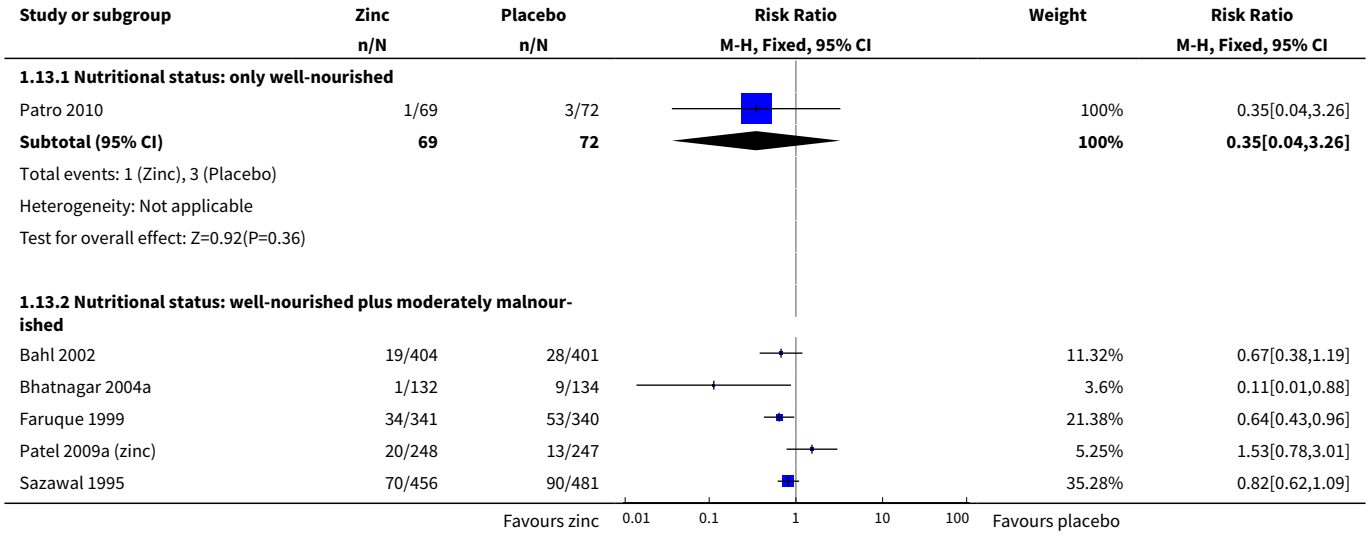


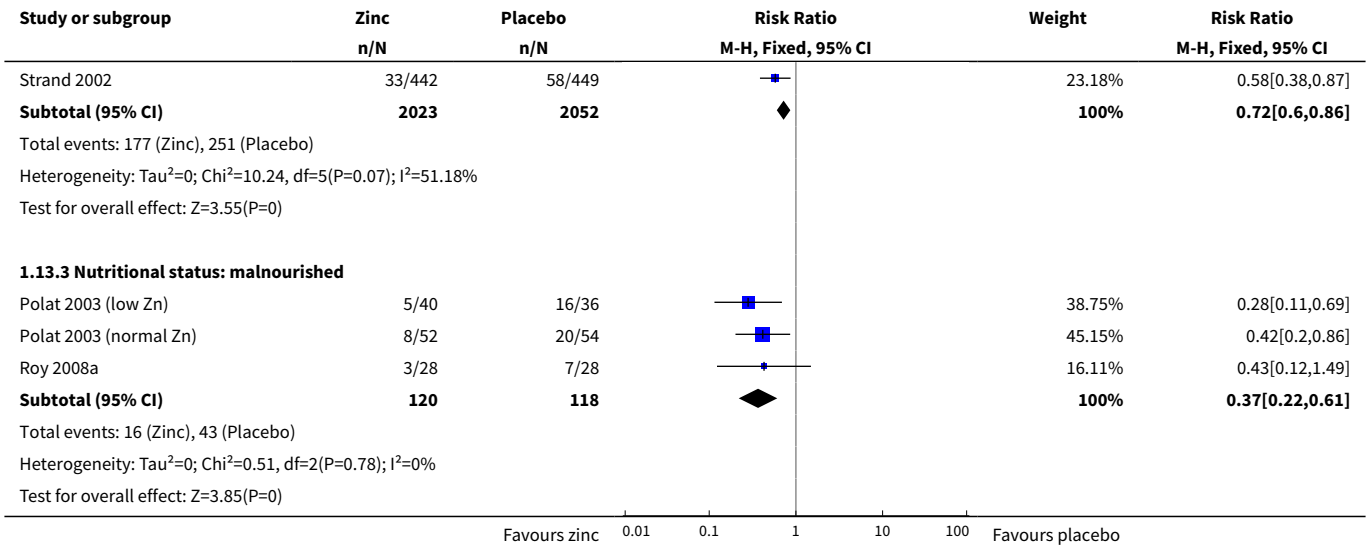

## Analysis 1.12. Comparison 1 Zinc versus placebo for children with acute diarrhoea, Outcome 12 Diarrhoea on day 7.



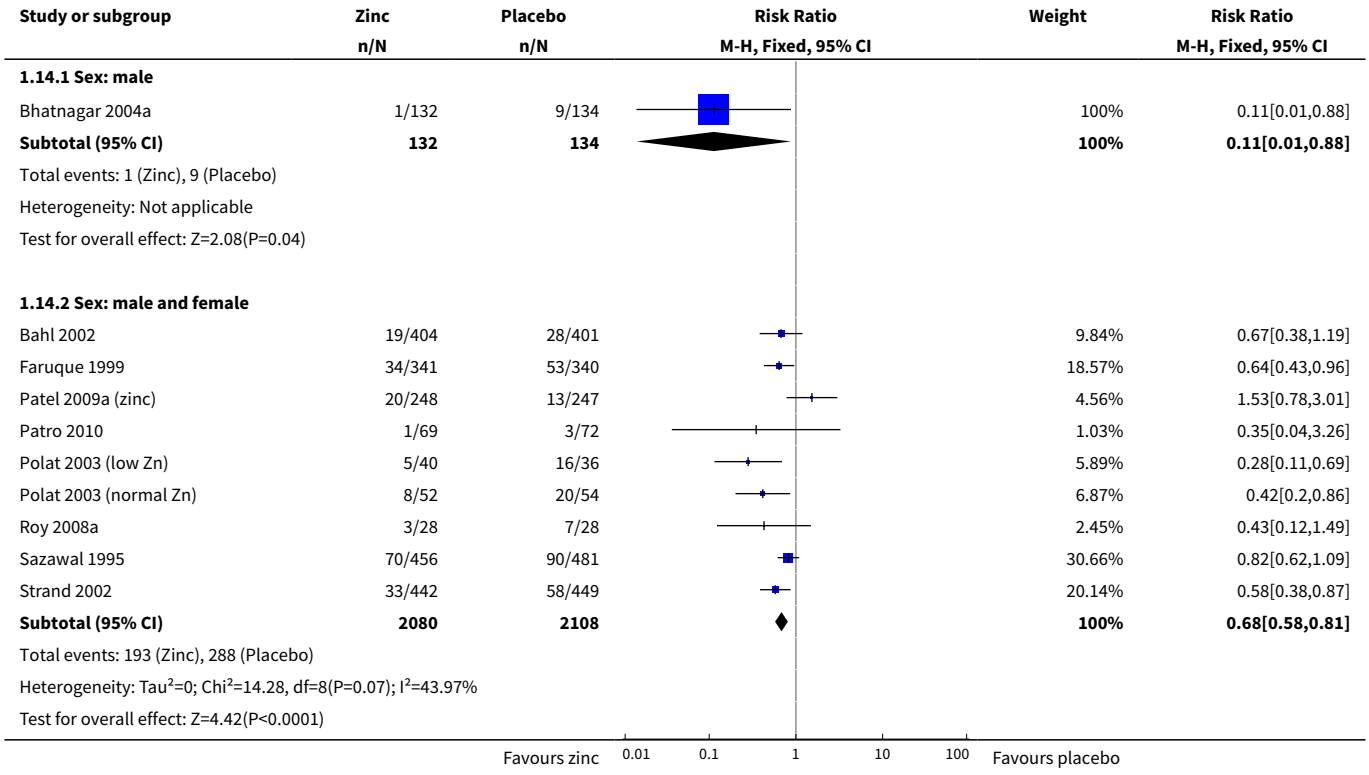



## Analysis 1.13. Comparison 1 Zinc versus placebo for children with acute diarrhoea, Outcome 13 Diarrhoea on day 7: subgrouped by nutritional status.

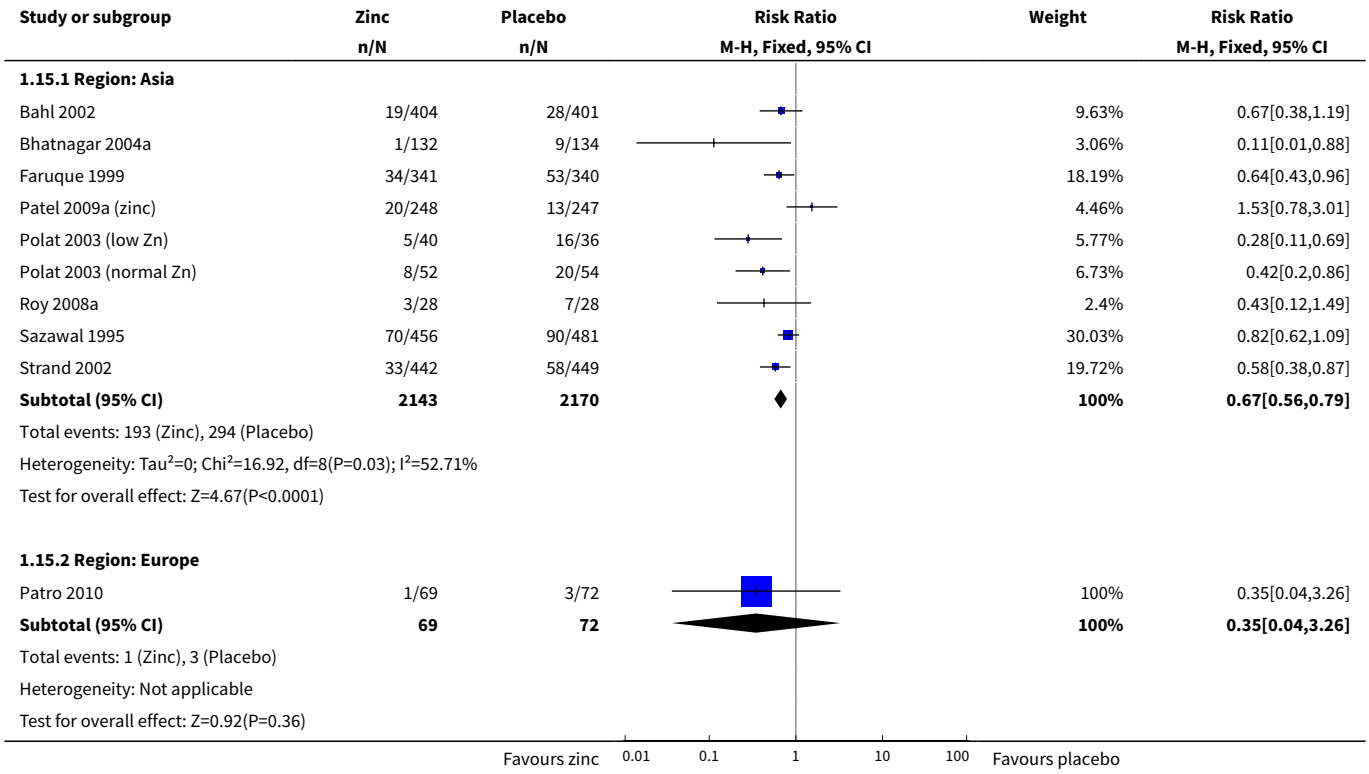




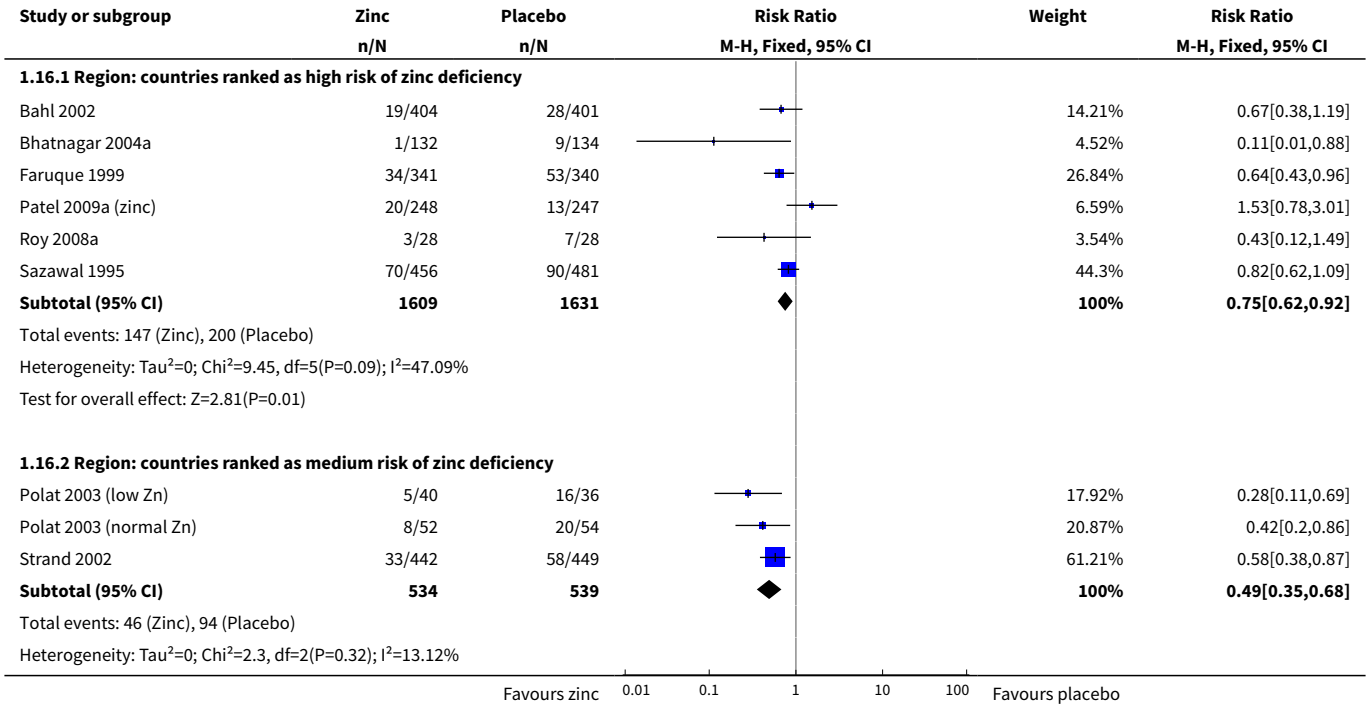

## Analysis 1.14. Comparison 1 Zinc versus placebo for children with acute diarrhoea, Outcome 14 Diarrhoea on day 7: subgrouped by sex.

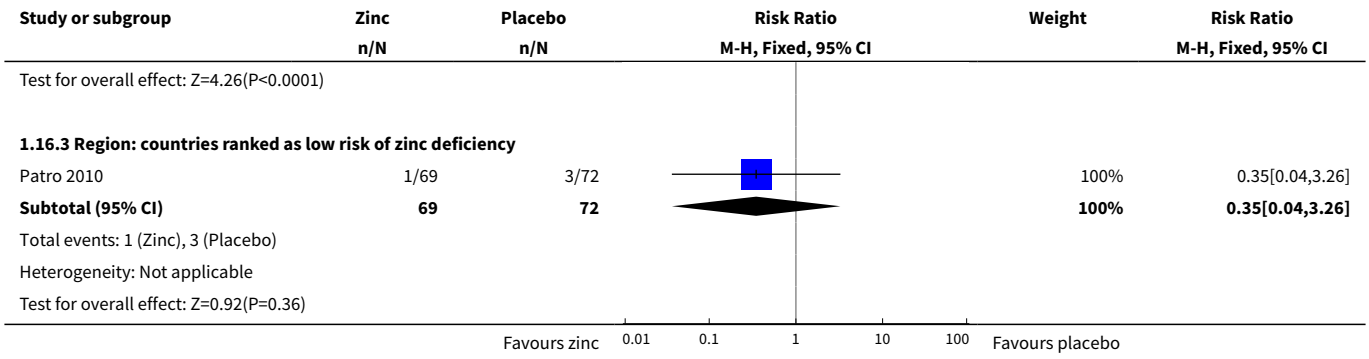


## Analysis 1.15. Comparison 1 Zinc versus placebo for children with acute diarrhoea, Outcome 15 Diarrhoea on day 7: subgrouped by continent.

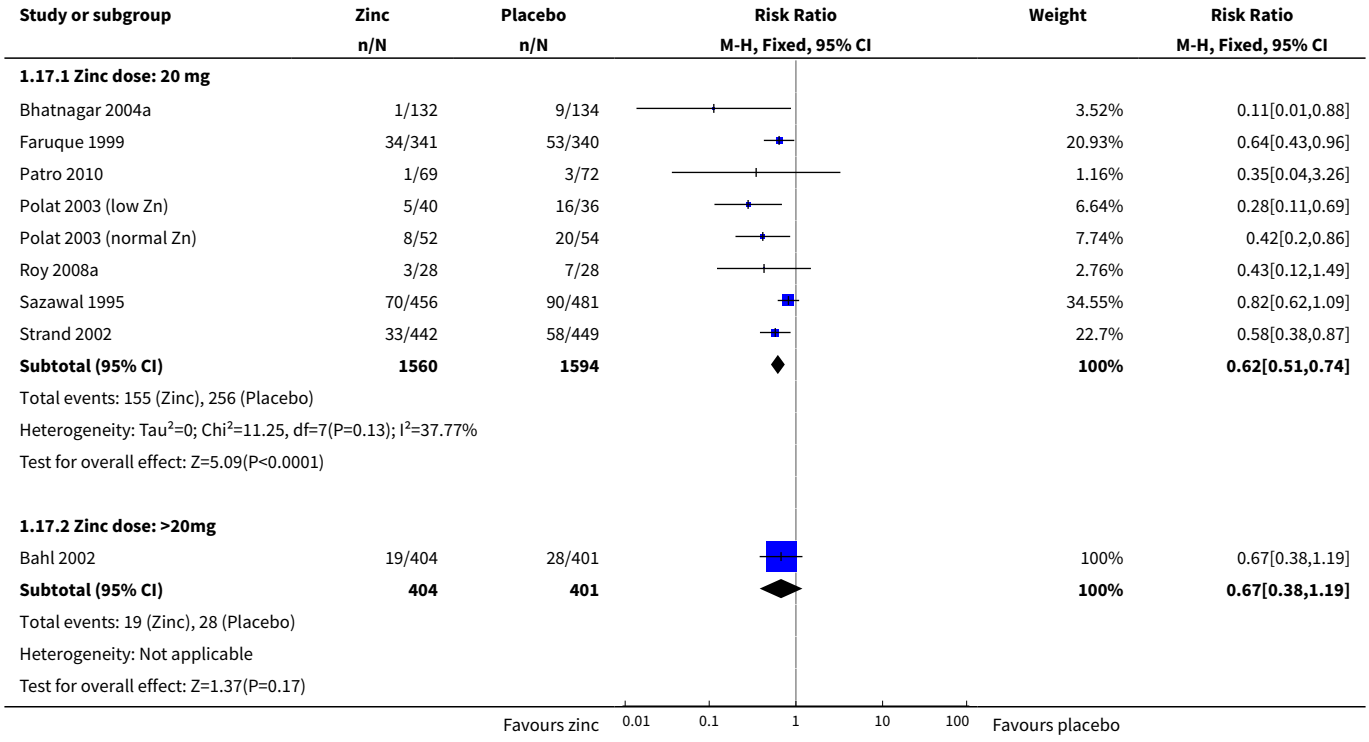



## Analysis 1.16. Comparison 1 Zinc versus placebo for children with acute diarrhoea, Outcome 16 Diarrhoea on day 7: subgrouped by national risk of zinc deficiency.

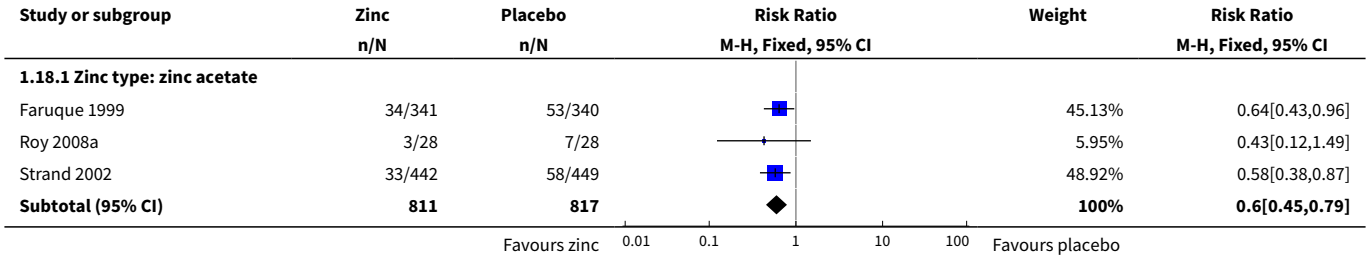


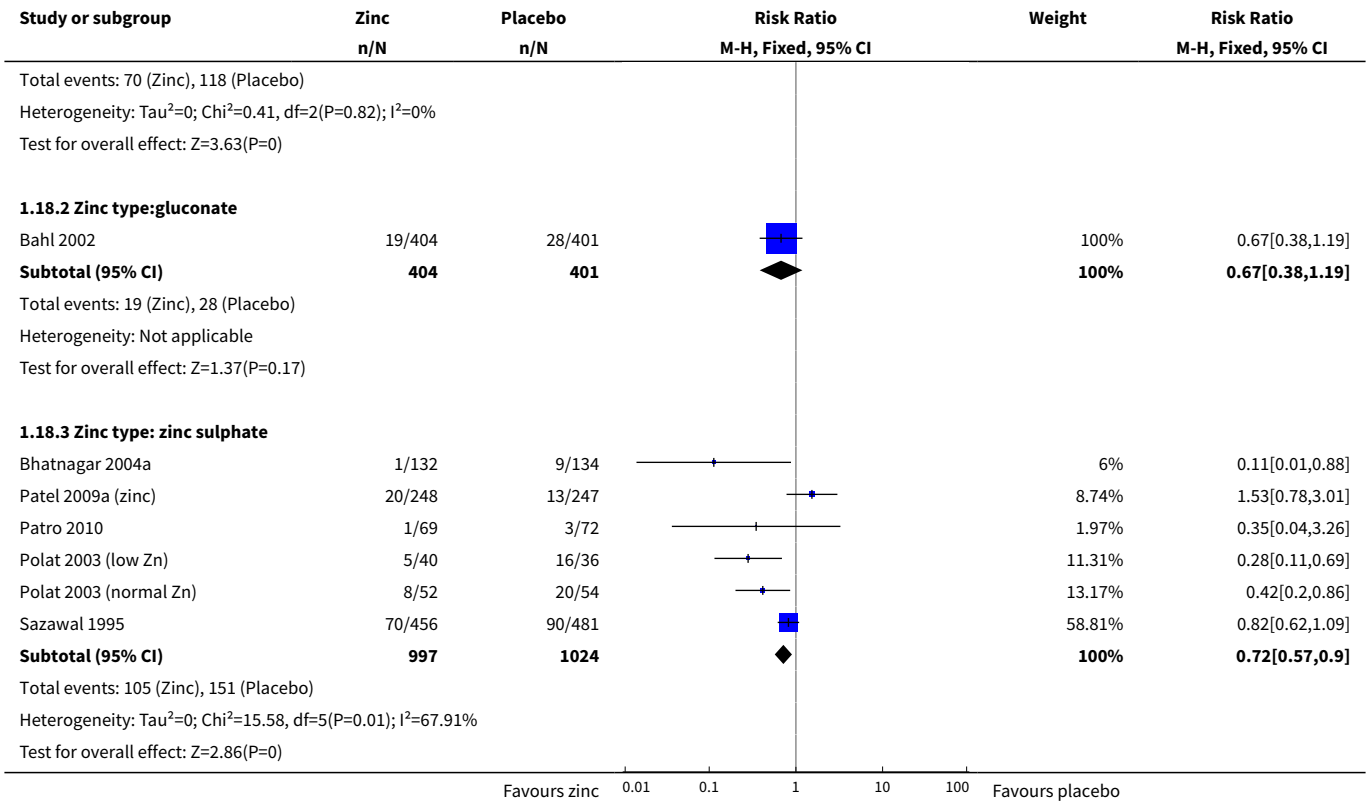



## Analysis 1.17. Comparison 1 Zinc versus placebo for children with acute diarrhoea, Outcome 17 Diarrhoea on day 7: subgrouped by zinc dose.

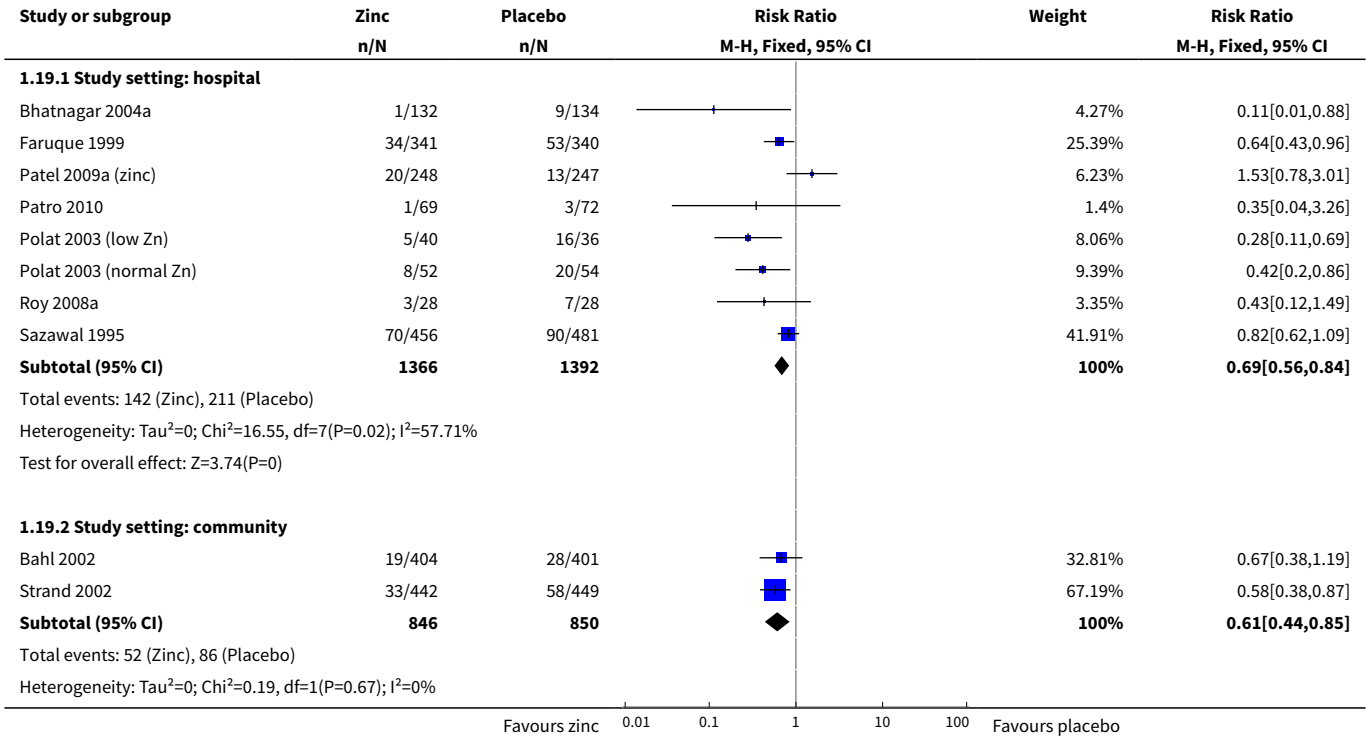



## Analysis 1.18. Comparison 1 Zinc versus placebo for children with acute diarrhoea, Outcome 18 Diarrhoea on day 7: subgrouped by zinc type.

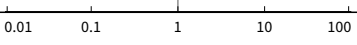





## Analysis 1.19. Comparison 1 Zinc versus placebo for children with acute diarrhoea, Outcome 19 Diarrhoea on day 7: subgrouped by study setting.

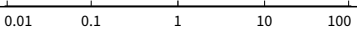


| Study or subgroup | Zinc n/N | Placebo n/N | Risk Ratio M-H, Fixed, 95% CI | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|
| Test for overall effect: Z=2.94(P=0) | | | | | |



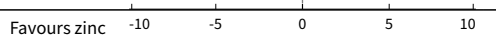

## Analysis 1.20. Comparison 1 Zinc versus placebo for children with acute diarrhoea, Outcome 20 Diarrhoea on day 7: subgrouped by concomitant treatment.

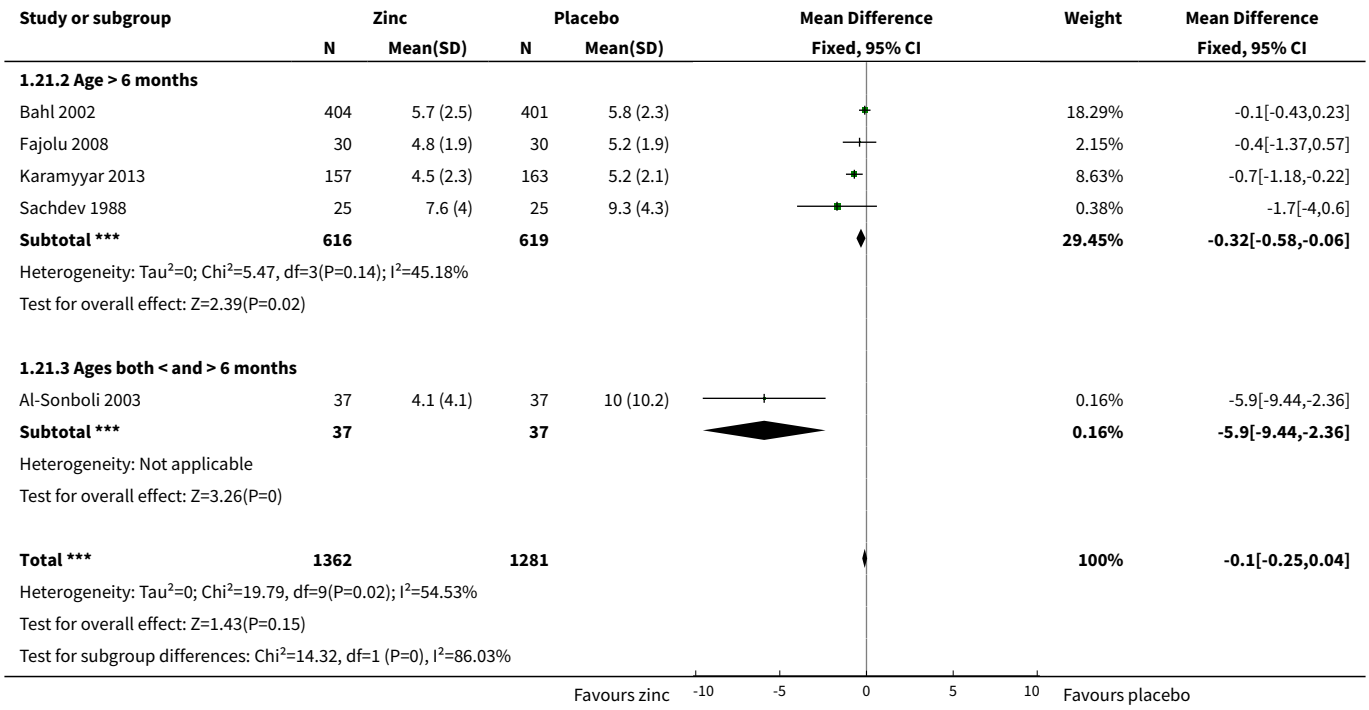
| Study or subgroup | Zinc n/N | Placebo n/N | Risk Ratio M-H, Fixed, 95% CI | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|
| **1.20.1 Concomitant treatment: zinc alone** | | | | | |
| Bahl 2002 | 19/404 | 28/401 | | 9.7% | 0.67[0.38,1.19] |
| Bhatnagar 2004a | 1/132 | 9/134 | | 3.08% | 0.11[0.01,0.88] |
| Faruque 1999 | 34/341 | 53/340 | | 18.32% | 0.64[0.43,0.96] |
| Patel 2009a (zinc) | 20/248 | 6/123 | | 2.77% | 1.65[0.68,4.01] |
| Patro 2010 | 1/69 | 3/72 | | 1.01% | 0.35[0.04,3.26] |
| Polat 2003 (low Zn) | 5/40 | 16/36 | | 5.81% | 0.28[0.11,0.69] |
| Polat 2003 (normal Zn) | 8/52 | 20/54 | | 6.77% | 0.42[0.2,0.86] |
| Roy 2008a | 3/28 | 7/28 | | 2.42% | 0.43[0.12,1.49] |
| Sazawal 1995 | 70/456 | 90/481 | | 30.24% | 0.82[0.62,1.09] |
| Strand 2002 | 33/442 | 58/449 | | 19.86% | 0.58[0.38,0.87] |
| **Subtotal (95% CI)** | **2212** | **2118** | | **100%** | **0.65[0.55,0.78]** |
| Total events: 194 (Zinc), 290 (Placebo) | | | | | |
| Heterogeneity: $Tau^2$=0; $Chi^2$=15.48, df=9(P=0.08); $I^2$=41.87% | | | | | |
| Test for overall effect: Z=4.87(P<0.0001) | | | | | |
| **1.20.2 Concomitant treatment: zinc plus copper** | | | | | |
| Patel 2009b (zinc + copper) | 15/259 | 7/124 | | 100% | 1.03[0.43,2.45] |
| **Subtotal (95% CI)** | **259** | **124** | | **100%** | **1.03[0.43,2.45]** |
| Total events: 15 (Zinc), 7 (Placebo) | | | | | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Z=0.06(P=0.95) | | | | | |



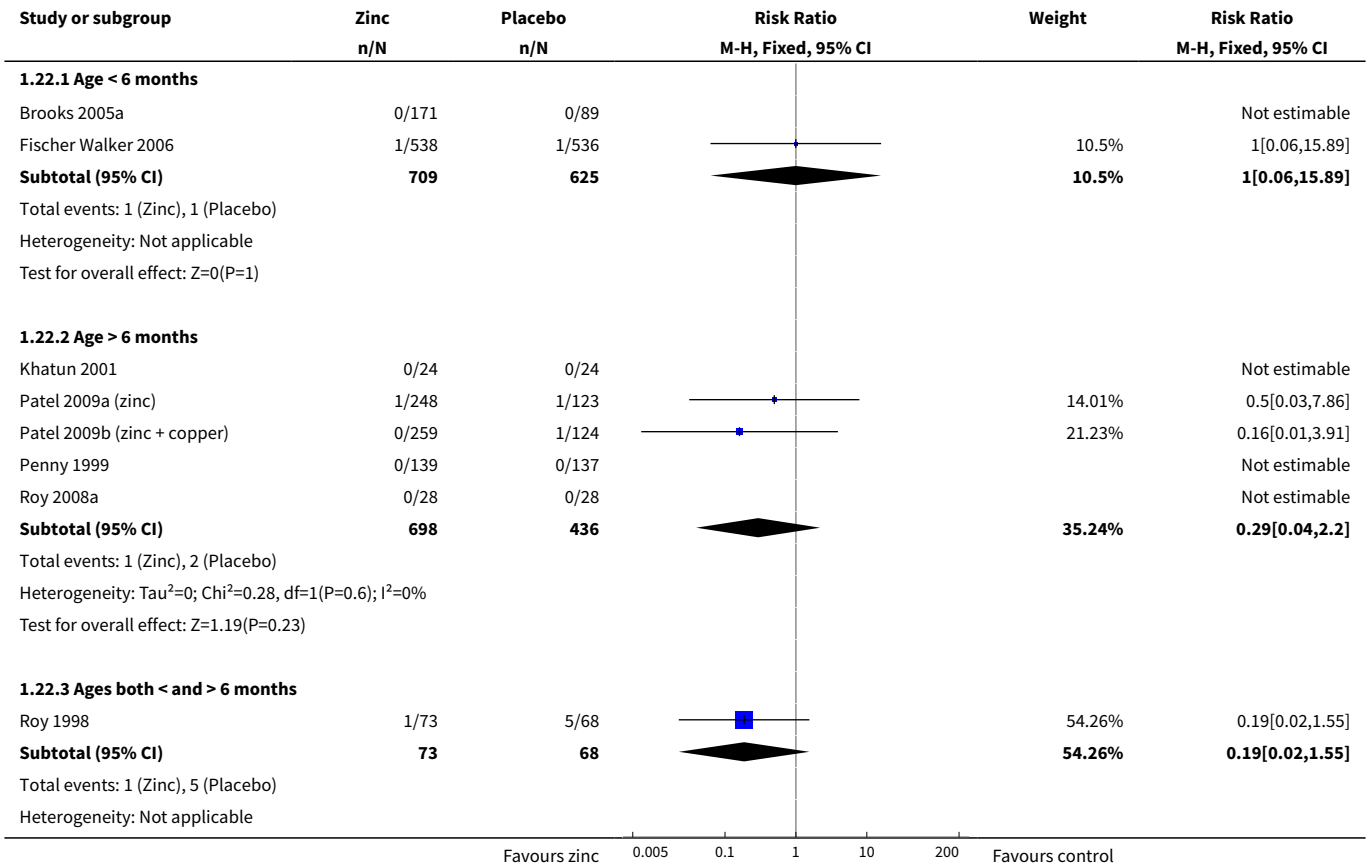

## Analysis 1.21. Comparison 1 Zinc versus placebo for children with acute diarrhoea, Outcome 21 Stool frequency (stools /day).

| Study or subgroup | Zinc N | Zinc Mean(SD) | Placebo N | Placebo Mean(SD) | Mean Difference Fixed, 95% CI | Weight | Mean Difference Fixed, 95% CI |
|---|---|---|---|---|---|---|---|
| **1.21.1 Age < 6 months** | | | | | | | |
| Brooks 2005a (20 mg) | 86 | 5 (4.7) | 44 | 5 (4.7) | | 0.69% | 0[-1.7,1.7] |
| Brooks 2005a (5 mg) | 85 | 5 (4.6) | 45 | 5 (4.7) | | 0.71% | 0[-1.69,1.69] |
| Fischer Walker 2006 ETH | 80 | 4 (0.8) | 83 | 4 (0.6) | | 42.48% | 0[-0.22,0.22] |
| Fischer Walker 2006 IND | 185 | 5.6 (3.1) | 183 | 5.6 (3.4) | | 4.55% | 0[-0.66,0.66] |
| Fischer Walker 2006 PAK | 273 | 4.9 (1.8) | 270 | 4.9 (1.8) | | 21.96% | 0[-0.3,0.3] |
| **Subtotal ***** | **709** | | **625** | | | **70.39%** | **0[-0.17,0.17]** |
| Heterogeneity: $Tau^2$=0; $Chi^2$=0, df=4(P=1); $I^2$=0% | | | | | | | |
| Test for overall effect: Not applicable | | | | | | | |






## Analysis 1.22. Comparison 1 Zinc versus placebo for children with acute diarrhoea, Outcome 22 Death.



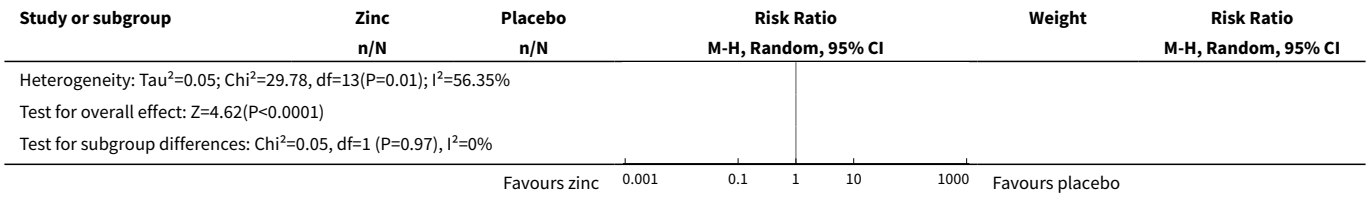
| Study or subgroup | Zinc n/N | Placebo n/N | Risk Ratio M-H, Fixed, 95% CI | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|
| Test for overall effect: Z=1.55(P=0.12) | | | | | |
| **Total (95% CI)** | **1480** | **1129** | | **100%** | **0.31[0.09,1.07]** |
| Total events: 3 (Zinc), 8 (Placebo) | | | | | |
| Heterogeneity: $Tau^2$=0; $Chi^2$=1.18, df=3(P=0.76); $I^2$=0% | | | | | |
| Test for overall effect: Z=1.85(P=0.06) | | | | | |
| Test for subgroup differences: $Chi^2$=0.9, df=1 (P=0.64), $I^2$=0% | | | | | |

Favours zinc 0.005 0.1 1 10 200 Favours control

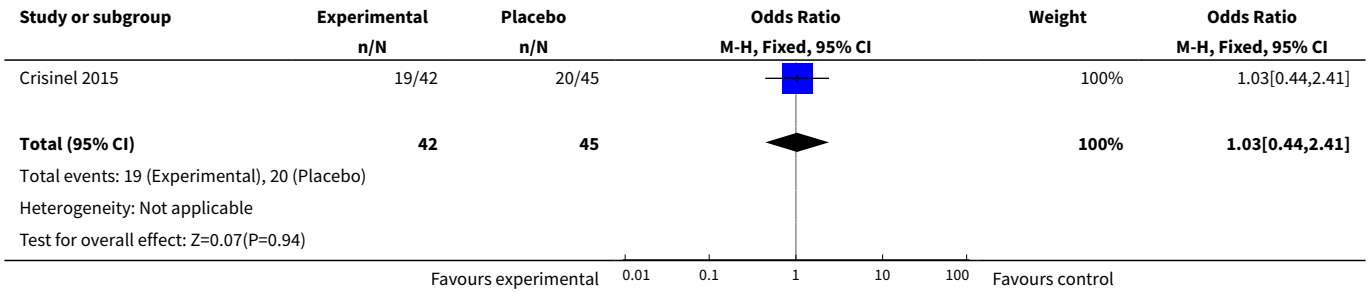
## Analysis 1.23. Comparison 1 Zinc versus placebo for children with acute diarrhoea, Outcome 23 Adverse events (vomiting).

| Study or subgroup | Zinc n/N | Placebo n/N | Risk Ratio M-H, Random, 95% CI | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|
| **1.23.1 Age < 6 months** | | | | | |
| Brooks 2005a (20 mg) | 12/86 | 3/44 | | 2.03% | 2.05[0.61,6.88] |
| Brooks 2005a (5 mg) | 15/85 | 4/45 | | 2.64% | 1.99[0.7,5.63] |
| Fischer Walker 2006 | 47/538 | 33/536 | | 8.91% | 1.42[0.92,2.18] |
| **Subtotal (95% CI)** | **709** | **625** | | **13.58%** | **1.54[1.05,2.24]** |
| Total events: 74 (Zinc), 40 (Placebo) | | | | | |
| Heterogeneity: $Tau^2$=0; $Chi^2$=0.58, df=2(P=0.75); $I^2$=0% | | | | | |
| Test for overall effect: Z=2.23(P=0.03) | | | | | |
| **1.23.2 Age > 6 months** | | | | | |
| Bahl 2002 | 74/193 | 55/209 | | 12.1% | 1.46[1.09,1.95] |
| Boran 2006 | 5/145 | 0/120 | | 0.4% | 9.12[0.51,163.22] |
| Fajolu 2008 | 17/30 | 14/30 | | 7.69% | 1.21[0.74,1.99] |
| Sachdev 1988 | 0/25 | 0/25 | | | Not estimable |
| Sazawal 1995 | 2/456 | 2/481 | | 0.84% | 1.05[0.15,7.46] |
| Strand 2002 | 145/442 | 85/449 | | 13.5% | 1.73[1.37,2.19] |
| **Subtotal (95% CI)** | **1291** | **1314** | | **34.52%** | **1.57[1.32,1.86]** |
| Total events: 243 (Zinc), 156 (Placebo) | | | | | |
| Heterogeneity: $Tau^2$=0; $Chi^2$=3.65, df=4(P=0.46); $I^2$=0% | | | | | |
| Test for overall effect: Z=5.21(P<0.0001) | | | | | |
| **1.23.3 Ages both < and > 6 months** | | | | | |
| Bhatnagar 2004a | 86/132 | 79/134 | | 14.6% | 1.11[0.92,1.33] |
| Crisinel 2015 | 30/42 | 26/45 | | 11.46% | 1.24[0.9,1.69] |
| Larson 2005 | 139/534 | 64/533 | | 12.56% | 2.17[1.65,2.84] |
| Polat 2003 (low Zn) | 8/40 | 2/36 | | 1.41% | 3.6[0.82,15.86] |
| Polat 2003 (normal Zn) | 12/52 | 3/54 | | 2.05% | 4.15[1.24,13.88] |
| Shimelis 2008 | 46/179 | 37/222 | | 9.82% | 1.54[1.05,2.27] |
| **Subtotal (95% CI)** | **979** | **1024** | | **51.9%** | **1.63[1.14,2.34]** |
| Total events: 321 (Zinc), 211 (Placebo) | | | | | |
| Heterogeneity: $Tau^2$=0.13; $Chi^2$=25.49, df=5(P=0); $I^2$=80.38% | | | | | |
| Test for overall effect: Z=2.65(P=0.01) | | | | | |
| **Total (95% CI)** | **2979** | **2963** | | **100%** | **1.54[1.28,1.85]** |
| Total events: 638 (Zinc), 407 (Placebo) | | | | | |

Favours zinc 0.001 0.1 1 10 1000 Favours placebo




**Analysis 1.24. Comparison 1 Zinc versus placebo for children with acute diarrhoea, Outcome 24 Difficulties in treatment administration.**




## Comparison 2. Zinc versus placebo for children with persistent diarrhoea

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Diarrhoea duration (hours) | 5 | 529 | Mean Difference (IV, Fixed, 95% CI) | -15.84 [-25.43, -6.24] |
| 1.1 Age > 6 months | 4 | 388 | Mean Difference (IV, Fixed, 95% CI) | -16.01 [-26.16, -5.86] |
| 1.2 Ages both < and > 6 months | 1 | 141 | Mean Difference (IV, Fixed, 95% CI) | -14.40 [-43.77, 14.97] |
| 2 Diarrhoea on day 3 | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 2.1 Age > 6 months | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 3 Diarrhoea on day 5 | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 3.1 Age > 6 months | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 4 Diarrhoea on day 7 | 2 | 221 | Risk Ratio (M-H, Fixed, 95% CI) | 0.52 [0.27, 1.02] |
| 4.1 Age > 6 months | 2 | 221 | Risk Ratio (M-H, Fixed, 95% CI) | 0.52 [0.27, 1.02] |
| 5 Stool frequency (stools/day) | 1 | | Mean Difference (IV, Fixed, 95% CI) | Totals not selected |
| 5.1 Age > 6 months | 1 | | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |

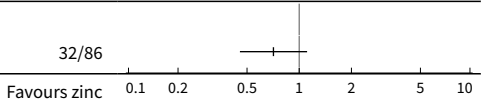
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 6 Adverse events (vomiting) | 4 | 505 | Risk Ratio (M-H, Fixed, 95% CI) | 1.97 [0.37, 10.59] |
| 6.1 Age > 6 months | 3 | 364 | Risk Ratio (M-H, Fixed, 95% CI) | 1.97 [0.37, 10.59] |
| 6.2 Ages both < and > 6 months | 1 | 141 | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |

## Analysis 2.1. Comparison 2 Zinc versus placebo for children with persistent diarrhoea, Outcome 1 Diarrhoea duration (hours).

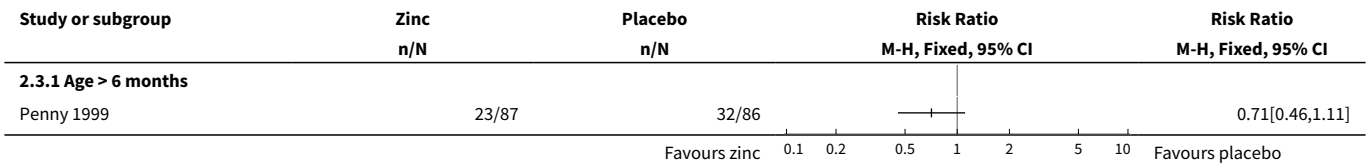
| Study or subgroup | Zinc N | Zinc Mean(SD) | Placebo N | Placebo Mean(SD) | Mean Difference Fixed, 95% CI | Weight | Mean Difference Fixed, 95% CI |
|---|---|---|---|---|---|---|---|
| **2.1.1 Age > 6 months** | | | | | | | |
| Bhutta 1999 | 43 | 122.4 (79.2) | 44 | 132 (64.8) | | 9.93% | -9.6[-40.05,20.85] |
| Khatun 2001 | 44 | 69.6 (33.6) | 44 | 84 (33.6) | | 46.7% | -14.4[-28.44,-0.36] |
| Penny 1999 | 87 | 69.4 (67.4) | 86 | 89.5 (92.2) | | 15.87% | -20.1[-44.19,3.99] |
| Sachdev 1990 | 20 | 88.2 (27.4) | 20 | 108.6 (45.8) | | 16.83% | -20.4[-43.79,2.99] |
| **Subtotal ***** | **194** | | **194** | | | **89.33%** | **-16.01[-26.16,-5.86]** |
| Heterogeneity: $Tau^2$=0; $Chi^2$=0.47, df=3(P=0.93); $I^2$=0% | | | | | | | |
| Test for overall effect: Z=3.09(P=0) | | | | | | | |
| **2.1.2 Ages both < and > 6 months** | | | | | | | |
| Roy 1998 | 73 | 153.6 (86.4) | 68 | 168 (91.2) | | 10.67% | -14.4[-43.77,14.97] |
| **Subtotal ***** | **73** | | **68** | | | **10.67%** | **-14.4[-43.77,14.97]** |
| Heterogeneity: $Tau^2$=0; $Chi^2$=0, df=0(P<0.0001); $I^2$=100% | | | | | | | |
| Test for overall effect: Z=0.96(P=0.34) | | | | | | | |
| **Total ***** | **267** | | **262** | | | **100%** | **-15.84[-25.43,-6.24]** |
| Heterogeneity: $Tau^2$=0; $Chi^2$=0.48, df=4(P=0.98); $I^2$=0% | | | | | | | |
| Test for overall effect: Z=3.24(P=0) | | | | | | | |
| Test for subgroup differences: $Chi^2$=0.01, df=1 (P=0.92), $I^2$=0% | | | | | | | |


## Analysis 2.2. Comparison 2 Zinc versus placebo for children with persistent diarrhoea, Outcome 2 Diarrhoea on day 3.

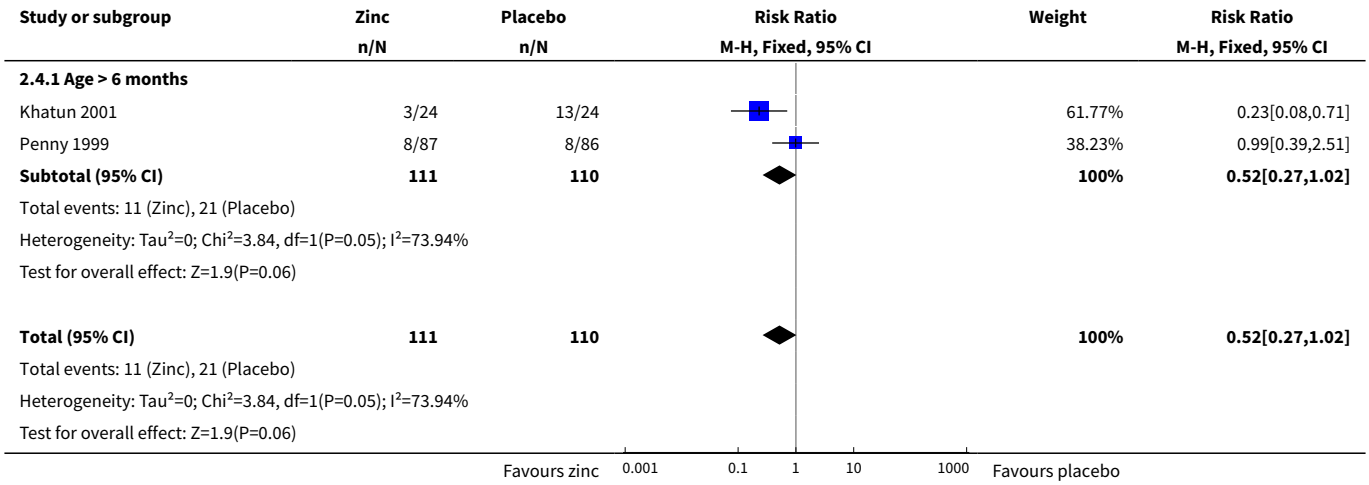
| Study or subgroup | Zinc n/N | Placebo n/N | Risk Ratio M-H, Fixed, 95% CI | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|
| **2.2.1 Age > 6 months** | | | | |
| Penny 1999 | 23/87 | 32/86 | | 0.71[0.46,1.11] |



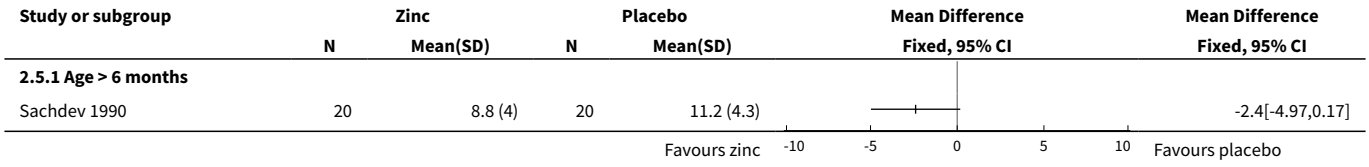
## Analysis 2.3. Comparison 2 Zinc versus placebo for children with persistent diarrhoea, Outcome 3 Diarrhoea on day 5.



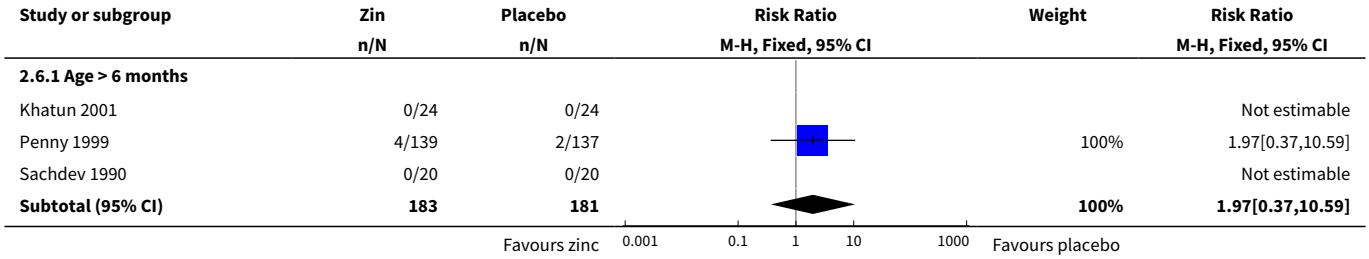

## Analysis 2.4. Comparison 2 Zinc versus placebo for children with persistent diarrhoea, Outcome 4 Diarrhoea on day 7.

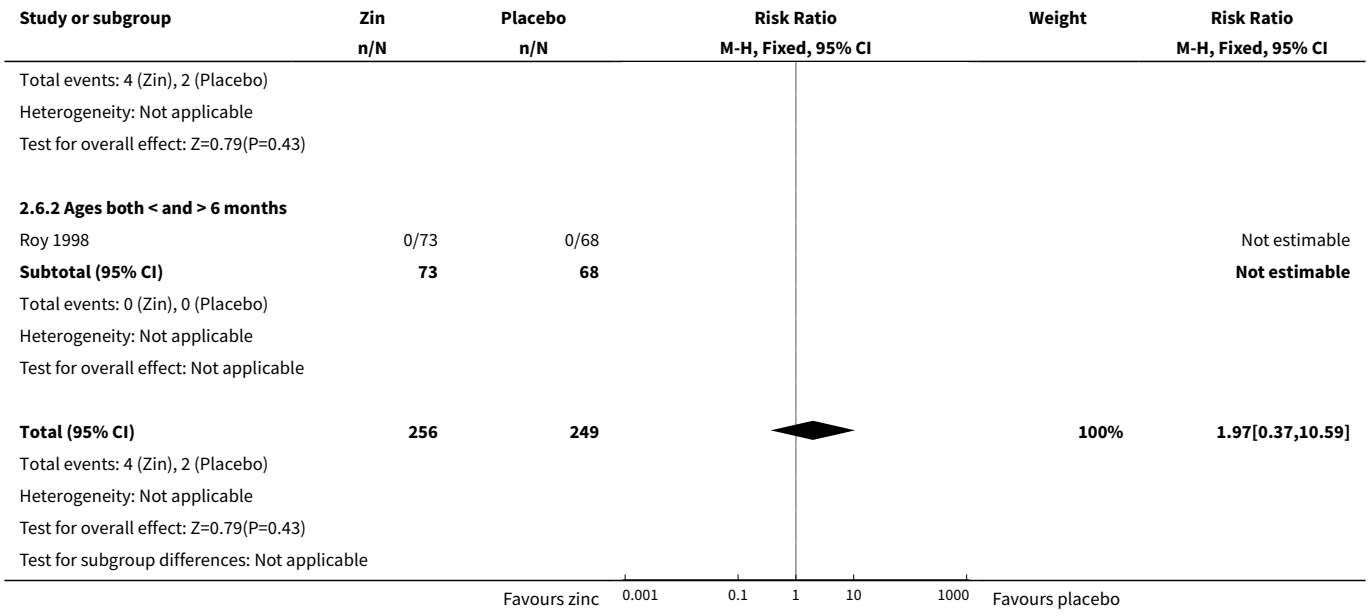



## Analysis 2.5. Comparison 2 Zinc versus placebo for children with persistent diarrhoea, Outcome 5 Stool frequency (stools/day).




## Analysis 2.6. Comparison 2 Zinc versus placebo for children with persistent diarrhoea, Outcome 6 Adverse events (vomiting).





## ADDITIONAL TABLES

**Table 1. Detailed search strategies**

| Search set | CIDG SR[1] | CENTRAL | MEDLINE[2] | EMBASE[2] | LILACS[2] | CINAHL | CCT |
|---|---|---|---|---|---|---|---|
| 1 | zinc | zinc | zinc | zinc | zinc | zinc | zinc |
| 2 | diarrhoea | diarrhoea | ZINC | ZINC | diarrhoea | diarrhoea | diarrhoea |
| 3 | vomiting | morbidity | 1 or 2 | 1 or 2 | morbidity | morbidity | vomiting |
| 4 | adverse effects | 2 or 3 | diarrhoea | diarrhoea | 2 or 3 | 2 or 3 | adverse effects |
| 5 | — | 1 and 4 | diarrhoea | morbidity | 1 and 4 | 1 and 4 | — |
| 6 | — | vomiting | morbidity | 4 or 5 | vomiting | vomiting | — |
| 7 | — | adverse effects | MORBIDITY | 3 and 6 | adverse effects | adverse effects | — |
| 8 | — | 6 or 7 | 4 or 5 or 6 or 7 | Limit 7 to human | 6 or 7 | 6 or 7 | — |
| 9 | — | 1 and 2 and 8 | 3 and 8 | vomiting | 1 and 2 and 8 | 1 and 8 | — |
| 10 | — | — | Limit 9 to human | adverse effects | — | — | — |
| 11 | — | — | vomiting | 9 or 10 | — | — | — |
| 12 | — | — | adverse effects | 3 and 4 and 11 | — | — | — |
| 13 | — | — | 11 or 12 | — | — | — | — |
| 14 | — | — | 3 and (4 or 5) and 13 | — | — | — | — |

[1]Cochrane Infectious Diseases Group Specialized Register.
[2]Search terms used in combination with the search strategy for retrieving trials developed by Cochrane (Higgins 2006); upper case: MeSH or EMTREE heading; lower case: free text term.

**Table 2. Results of the study selection**

| | |
|---|---|
| Total number of studies identified through the search (up to 30 September 2016) | 306 trials |
| Total number of studies excluded as clearly did not concern the topic of interest | 126 trials |
| Studies further evaluated and excluded[1]<br>• Not RCTs: 25 trials<br>• Not placebo-controlled RCTs: 8 trials<br>• RCTs on prevention of diarrhoea, not on treatment: 51 trials<br>• Not concerning the population of interest (for example, studies on low birthweight, HIV): 13 trials<br>• Not concerning the interventions of interest (for example, studies on zinc in oral rehydration solution (ORS), multiple micronutrients, probiotics, food fortification): 19 trials<br>• Concerning different outcomes (for example, studies on serology, appetite, mental or motor development, malnutrition): 16 trials<br>• Could not be compared with other studies because of methodological problems (enrolling the same children more than once) and types of outcomes (episodes of diarrhoea and not children with diarrhoea): 1 trial<br>• Secondary analysis of other studies: 8 | 141 trials |
| Duplicates of included studies<br>• Folwaczny 1996; Darmon 1997 are review articles of the same trial (Sazawal 1995)<br>• Roy 1991 is a duplication of Roy 1997 and Roy 1998<br>• Roy 1998 is an abstract of Khatun 2001<br>• Cuevas 2000 is an abstract of Al-Sonboli 2003<br>• Patel 2013 is a cost effectiveness analysis based on data reported in Patel 2009 | 6 trials |
| Independent trials included in the review | 33 trials (10,841 participants) |

[1]See the 'Characteristics of excluded studies' section.
Abbreviations: HIV: human immunodeficiency virus; RCT: randomized controlled trial.

**Table 3. Stool output: acute diarrhoea**

| Trial ID | Outcome | Units | Zinc | | Placebo | | Mean difference | Statistical test |
|---|---|---|---|---|---|---|---|---|
| | | | N | Values | N | Values | | |
| **Age < 6 months** | | | | | | | | |
| Brooks 2005a (5 mg) | Total (mL) | Mean (95% CI) | 85 | 229 (180 to 256) | 45 | 202 (180 to 246) | 27 (−23.3 to 77.3)[1] | Not significant |
| Brooks 2005a (20 mg) | Total (mL) | Mean (95% CI) | 86 | 240 (200 to 266) | 44 | 202 (180 to 246) | 38 (−8.6 to 84.6)[1] | Not significant |
| **Age > 6 months** | | | | | | | | |
| Patel 2009a (zinc) | Total (g) | Mean (95% CI) | 248 | 972 (858 to 1087) | 247 | 877 (728 to 1026) | −95 (−283 to 92) | Not significant |
| Dutta 2011 | Total (L) | Mean (95% CI) | 41 | 1.2 (0.6 to 1.8) | 43 | 2.0 (1.3 to 2.7) | - 0.8 (-1.1 to 1.5) | P < 0.0001 |
| Dutta 2011 | Per day (ml/kg/day) | Mean (95% CI) | 41 | 51.22 (27.39 to 79.05) | 43 | 66.83 (42.41 to 71.25) | - 15.61 (-22.9 to -8.2) | P = 0.0001 |
| **Ages < and > 6 months** | | | | | | | | |
| Bhatnagar 2004a | Total (g/kg) | Geometric mean (95% CI) | 132 | 111 (86 to 147) | 134 | 148 (116 to 190) | 0.69 (0.48 to 0.99)[2] | P < 0.05 |
| | Per day (g/kg/day) | Geometric mean (95% CI) | 132 | 62 (51 to 78) | 134 | 78 (68 to 91) | 0.76 (0.59 to 0.98)[2] | P < 0.05 |
| Dutta 2000 | Total (kg) | Mean (95% CI) | 44 | 1.5 (1.3 to 1.7) | 36 | 2.4 (2.2 to 2.6) | −0.9 (−1.2 to −0.6)[1] | P = 0.0001 |
| Roy 1997 | Per day (g/kg/day) | Median (range) | 37 | 238 | 37 | 329 | −91 | P = 0.06 |

**Table 3. Stool output: acute diarrhoea** *(Continued)*

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | (35 to 2416) | | (32 to 1464) | (NA) | |

[1]Arithmetic mean difference (95% CI) for means.
[2]Geometric mean ratio (95% CI) for geometric means, adjusted for confounders. (Stool output using zinc is 0.69 and 0.76 times that of participants using placebo, which means a 31% and 24% less stool output under zinc treatment.)
Abbreviations: CI: confidence interval; NA: not applicable.

**Table 4. Stool output: persistent diarrhoea**

| Trial ID | Outcome | Zinc | | Placebo | | Mean difference [1] | Statistical test |
|---|---|---|---|---|---|---|---|
| | | N | Mean (95% CI) | N | Mean (95% CI) | | |
| **Age > 6 months** | | | | | | | |
| Bhutta 1999 | Per day of diarrhoea, day 1 (g/kg/day) | 43 | 116.8 (85.8 to 147.8) | 44 | 141.9 (91.2 to 192.6) | −25.1 (−84.5 to 34.3) | Not significant |
| | Per day of diarrhoea, day 7 (g/kg/day) | 43 | 66.7 (40.9 to 92.4) | 44 | 43.9 (32.1 to 55.7) | 22.8 (−5.5 to 51.1) | Not significant |
| | Per day of diarrhoea, day 14 (g/kg/day) | 43 | 24.9 (20.1 to 29.7) | 44 | 27.8 (18.5 to 37.1) | -2.9 (−13.4 to 7.6) | Not significant |
| Khatun 2001 | Cumulative day 1 (mg/kg) | 24 | 127 (113 to 141) | 24 | 137 (121 to 153) | −10 (−31.6 to 11.6) | Not significant |
| | Cumulative day 7 (mg/kg) | 24 | 528 (472 to 584) | 24 | 866 (815 to 917) | −338 (−413.6 to −262.4) | P ≤ 0.001 |

[1]Arithmetic mean difference (95% CI) for means.
Abbreviations: CI: confidence interval; ID: identification.

## WHAT'S NEW

| Date | Event | Description |
|---|---|---|
| 25 April 2017 | Amended | We have amended the GRADE assessment for two outcomes, duration of diarrhea and diarrhea on day 7 for children aged less than 6 months with acute diarrhoea and treated with zinc, which we had scored incorrectly in the review update. We had stated that these outcomes had a GRADE score of moderate. However, we had downgraded the certainty of the evidence by 2, and thus the certainty of the evidence was low. We have amended the certainty of the evidence for these two outcomes to low in 'Summary of findings' table 2 and the review text. |

## HISTORY

Protocol first published: Issue 3, 2005
Review first published: Issue 3, 2008

| Date | Event | Description |
|---|---|---|
| 19 December 2016 | New citation required but conclusions have not changed | We included 33 trials in total in this review update, of which nine were new trials. We updated the 'Summary of findings' tables according to the GRADE approach, and included a PRISMA study flow diagram and funnel plots. |
| 19 December 2016 | New search has been performed | We amended the author team. Luca Ronfani stepped down as an author, and Humphrey Wanzira joined as an author. We updated the literature search to 30 September 2016, and nine new trials met the inclusion criteria of the review update. |
| 6 December 2012 | New citation required but conclusions have not changed | We corrected the Abstract. |
| 6 December 2012 | Amended | An error was spotted in the abstract (number of participants and number of studies was incorrect). We have corrected this and republished the review to ensure the correct details are documented. |
| 22 March 2012 | New search has been performed | We updated the search on 20 February 2012, and included two new trials. We updated the Background and undertook a more detailed assessment of the risk of bias in all included trials. We updated the 'Summary of findings' tables according to the GRADE methodology. |
| 22 March 2012 | New citation required but conclusions have not changed | Update. |
| 11 February 2011 | New search has been performed | We updated the search on 1 December 2010, and included four new trials. We updated the Background and performed a more detailed assessment of the risk of bias in all included trials. We added 'Summary of findings' tables according to the GRADE methodology. |

## CONTRIBUTIONS OF AUTHORS

Both ML and HW contributed equally to the preparation of this Cochrane Review update.

## DECLARATIONS OF INTEREST

Marzia Lazzerini has no known conflicts of interest.
Humprey Wanzira has no known conflicts of interest.

## SOURCES OF SUPPORT

### Internal sources

- Liverpool School of Tropical Medicine, UK.

### External sources

- Department for International Development (DFID), UK.

  Grant: 5242

## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

### 2016

We included a PRISMA study flow diagram and funnel plots.

### 2011

We used GRADE profiler, version 3.2.2 to create 'Summary of findings' tables for the primary outcomes in the review.

### 2007, Issue 4 (first review version)

We made the following modifications to the review.

- We changed the inclusion criteria for participant age to "children over one month old" (rather than "two months") to avoid arbitrarily losing trials.
- We amended death to a secondary outcome measure following feedback from referees.
- We stratified the results by age categories since we observed significant heterogeneity when trials were pooled, and a clear difference in zinc effect was evident according to age.
- For subgroup analysis by nutritional status, it was not possible to refer to the definition of malnutrition given in the protocol (weight/height) as most included trials used another definition (weight/age), which is easier to measure. The difference between the two definition is that the first identifies children with acute weight loss or 'wasted', while the second includes both children with acute and chronic malnutrition ('wasted' and 'stunted').
- Two categories of 'zinc dose' were used (20 mg and > 20 mg) as most trials used zinc 20 mg/day, and only two trials used more than 20 mg/day.
- We added sex (male, female) as a subgroup as it was identified as a possible effect modifier (Garenne 2005).

## INDEX TERMS

### Medical Subject Headings (MeSH)

Acute Disease; Age Factors; Developing Countries; Diarrhea [*drug therapy] [mortality]; Diarrhea, Infantile [drug therapy] [mortality]; Randomized Controlled Trials as Topic; Time Factors; Trace Elements [adverse effects] [deficiency] [*therapeutic use]; Zinc [adverse effects] [deficiency] [*therapeutic use]

### MeSH check words

Child, Preschool; Humans; Infant