

Zinc supplements for preventing otitis media (Review)

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[Intervention Review]

Zinc supplements for preventing otitis media

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ABSTRACT

Background

Otitis media (inflammation of the middle ear, usually caused by infection) affects people of all ages, but is particularly common in young children. Around 164 million people worldwide have long-term hearing loss caused by this condition, 90% of them in low-income countries. Because zinc supplements prevent pneumonia in disadvantaged children, we wondered whether they prevent otitis media.

Objectives

To evaluate whether zinc supplements prevent otitis media in adults and children of different ages.

Search strategy

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2009, issue 2) which includes the Acute Respiratory Infection Groups' Specialised Register; MEDLINE (1950 to June Week 1 2009); and EMBASE (1974 to June 2009).

Selection criteria

Randomised, placebo-controlled trials of zinc supplements given at least once a week for at least a month for preventing otitis media.

Data collection and analysis

Two review authors assessed the eligibility and methodological quality of the included trials, extracted and analysed data and wrote the review. We summarised results using risk ratios or rate ratios for dichotomous data and mean differences for continuous data. We combined trial results where appropriate.

Main results

We identified 12 trials for inclusion, 10 of which contributed outcomes data. In trials of healthy children living in low-income communities, two trials did not demonstrate a significant difference between the zinc supplemented and placebo groups in the numbers of participants experiencing an episode of definite otitis media during follow up (3191 participants), while another trial showed a significantly lower incidence rate of otitis media in the zinc group (rate ratio 0.69, 95% confidence interval (CI) 0.61 to 0.79, n = 1621). A small trial of 39 infants undergoing treatment for severe malnutrition suggested a benefit of zinc on the mean number of episodes of otitis media (mean difference -1.12 episodes, 95% CI -2.21 to -0.03). Zinc supplements did not seem to cause any serious adverse events, but a small minority of children were reported to have vomited shortly after ingestion of the supplements.

Zinc supplements for preventing otitis media (Review)

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Authors' conclusions

Evidence on whether zinc supplementation can reduce the incidence of otitis media in healthy children under the age of five years living in low- and middle-income countries is mixed. There is some evidence of benefit in children being treated for marasmus, but this is based on one small trial and should therefore be treated with caution.

PLAIN LANGUAGE SUMMARY

Zinc supplements for preventing middle ear infections

Middle ear infections are common, especially among young children, usually causing earache and some temporary (occasionally permanent) hearing loss. Zinc is an essential micronutrient, which has a role in the optimal functioning of the immune system and resistance to infection. Some people, especially children in low- and middle-income countries, may not have adequate zinc intake from food alone. Researchers have therefore examined the potential role of zinc supplements in preventing infective illnesses, including middle ear infections.

The review authors searched the medical literature for studies which compared middle ear infections in people randomly selected to receive zinc supplements or not receive supplements. Ten eligible studies were found, all conducted among young children. The results of the studies provided no convincing evidence that zinc supplements reduce the occurrence of middle ear infections in healthy children. However, in one small study of severely malnourished children, those receiving zinc supplements had fewer middle ear infections.

BACKGROUND

Description of the condition

Acute otitis media (inflammation of the middle ear, usually caused by infection) affects people of all ages throughout the world, particularly young children under the age of three years, in whom it is very common. It causes acute pain for a day or so, and temporary conductive deafness for longer. Usually it resolves quickly but it can lead to chronic conditions. The greatest burden is from chronic suppurative otitis media (discharge through a perforation in the ear drum), which affects between 65 to 328 million people worldwide; around 164 million people have hearing loss caused by this condition, 90% of them in low-income countries (WHO 2004). Other complications of otitis media include meningitis and brain abscess, causing about 28,000 deaths worldwide, mostly in low-income countries (WHO 2004).

Description of the intervention

Zinc is an essential micronutrient important for immune function and resistance to infection. It must be consumed regularly as it cannot be stored in the body. Mild to moderate zinc deficiency impairs immune function but has no obvious symptoms (Walker 2004). Zinc is found in a variety of foods, including most animal

proteins, and some nuts, beans, and seeds. Absorption of zinc is inhibited by phytates, found in many cereals and legumes. Diarrhoea causes zinc loss from the body. Over 60% of children under the age of five have zinc deficiency from inadequate diets in some low-income countries (Caulfield 2004).

Zinc supplements are recommended by the World Health Organization (WHO)/United Nations International Children's Fund (UNICEF) as an adjunct in the treatment of diarrhoea (WHO/UNICEF 2004), based on an analysis of effectiveness and costs (Robberstad 2004). There have also been a number of successful trials using zinc supplements in the prevention and treatment of pneumonia and other respiratory infections (Bhutta 2004). A systematic review published in 1999 concluded that zinc supplements prevent pneumonia in economically disadvantaged children living in low- and middle-income countries (ZICG 1999).

How the intervention might work

Children who experience recurrent otitis media have lower zinc levels than healthy controls (Bondestam 1985). Zinc supplementation helps prevent and cure respiratory and diarrhoeal diseases, and so it might have a similar effect against otitis media.

Why it is important to do this review

There are currently no published reviews on zinc supplements for the prevention of otitis media, or hearing loss and other complications arising from otitis media. Although a preliminary search revealed no published zinc supplementation trials with otitis media as a primary outcome, some trials which assess zinc for the prevention of other acute respiratory infections also record otitis media as an outcome.

OBJECTIVES

To evaluate whether zinc supplements prevent otitis media in adults and children of different ages.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs).

Types of participants

People of all ages, male or female.

Types of interventions

Zinc salt supplements, at any dose, given at least once a week, for at least one month versus placebo. Trials giving other micronutrients in addition to zinc were included if the only difference between the two groups was zinc.

Types of outcome measures

Primary outcomes

1. Number of participants with at least one episode of definite acute otitis media during follow up, diagnosed by clinical assessment of the ear.
2. Number of episodes of definite acute otitis media per participant per year of follow up.
3. Number of days with definite otitis media (acute or chronic) per participant per year of follow up.

Secondary outcomes

1. Number of participants with at least one episode of probable acute otitis media during follow up, indicated by ear pain, ear discharge or other indicator as specified by the trial author.
2. Number of episodes of probable acute otitis media per participant per year of follow up.
3. Number of days with probable otitis media (acute or chronic) per participant per year of follow up.
4. Adverse events: any adverse events as reported by the trial authors.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2009, issue 2), which includes the Acute Respiratory Infection Groups' Specialised Register; MEDLINE (1950 to June Week 1 2009); and EMBASE (1974 to June 2009).

The following search terms were used to search MEDLINE and CENTRAL. We combined the MEDLINE search string with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximising version (2008 revision); Ovid format ([Lefebvre 2008](#)). The search string was modified for EMBASE (see [Appendix 1](#)).

MEDLINE (Ovid)

1. exp Zinc/
2. zinc.tw.
3. exp Dietary Supplements/
4. 1 or 2 or 3

Searching other resources

We attempted to contact trial authors and other researchers in the field to identify additional studies that may be eligible for inclusion. We also contacted the WHO for unpublished and ongoing trials. There were no language or publication restrictions. We handsearched the references of all identified studies.

The search strategy was designed to identify all trials using zinc supplementation as an intervention, as we were aware that otitis media was likely to be only a secondary outcome in the majority of trials recording this outcome.

Data collection and analysis

Selection of studies

One review author (KA) screened the citations identified by the search strategy to exclude those which obviously did not refer to a study assessing zinc supplementation for the prevention of illness. Where there was any doubt we did not exclude citations at this stage. Two review authors (KA, AG) independently screened the abstracts of the remaining citations; obtaining copies of the full text reports where abstracts were not available. Full reports of potentially eligible studies were obtained and assessed for inclusion in the review by the same two review authors using a pre-designed eligibility form based on the inclusion criteria. We contacted trial authors for clarification in the event that it was unclear whether a trial was eligible for the review. We resolved any differences in opinion by discussion. We excluded studies that did not meet the criteria and, with the exception of those excluded on the basis of the citation alone, documented the reasons for exclusion.

Data extraction and management

Two review authors (KA, AG) independently extracted data using a tailored data extraction form. We extracted data on study design, participant characteristics, interventions, and outcomes. For dichotomous data, we extracted the number of participants with the outcome, the total number randomised to each group, and the total number analysed. For continuous data, we planned to extract the arithmetic mean for each group and their standard deviations. If medians had been used, we planned also to extract ranges. We planned to extract geometric means if presented by the trial author because of skewed data. We resolved any discrepancies between the extracted data by discussion and, if required, by referral to a third review author (HS). If data were unclear or not presented in the paper, we attempted to contact the trial authors for further details.

Assessment of risk of bias in included studies

Two review authors (KA, AG) independently assessed the risk of bias of the included trials using a pro forma. We contacted trial authors if details were missing in the publications or if they were unclear. In case of disagreement, we planned to consult a third person. We categorised the generation of the allocation sequence and allocation concealment as adequate, unclear, or inadequate as in [Juni 2001](#). We assessed whether, for the primary outcome of otitis media, the participants, care providers and investigators were blinded to which participants received zinc supplements as described in [Higgins 2008](#). For otitis media outcomes, we assessed that incomplete outcomes data had been adequately addressed if 85% or more of the participants were included in the analysis, or if less than 85% were included but adequate steps were taken to

ensure or demonstrate that this did not bias the results. We also examined the trial reports for any evidence of selective reporting of outcomes or any other issues that may bias the results. We reported the results of the assessment in a table.

Measures of treatment effect

We analysed the data using Review Manager 5 ([RevMan 2008](#)). For dichotomous data, we calculated the risk ratio or rate ratio and if appropriate we combined results from different trials. We calculated mean differences for continuous data. All results were presented with 95% confidence interval (CI). Data presented by the trial authors in other formats were described in the text.

Assessment of heterogeneity

We planned to assess heterogeneity between the trials by examining the forest plot to check for overlapping CIs, using the Chi² test for heterogeneity with a 10% level of significance, and the I² statistic using a value of 50% to represent moderate levels of heterogeneity. If heterogeneity was detected and it remained clinically meaningful to combine the trials, we planned to use the random-effects model. We planned to explore heterogeneity using the following subgroups: type of supplement; length of supplementation; and participant age (adults, children, children of different ages). However, there were insufficient trials with similar outcome measures to undertake these analyses.

Assessment of reporting biases

We planned to assess the likelihood of small study effects, such as publication bias, by examining the funnel plot for asymmetry. However, there were insufficient trials reporting on the same outcomes to do this.

Sensitivity analysis

Providing there were sufficient trials, we planned also to conduct a sensitivity analysis to investigate the robustness of the results taking into account the quality components. However, there were insufficient trials to do this analysis.

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#); [Characteristics of studies awaiting classification](#).

Results of the search

The search identified 5678 records. After an initial scan of the titles, we identified 144 citations that could not be excluded from the review on the basis of title alone. From this list, we identified 12 trials that met the inclusion criteria. The excluded studies, and the reasons for their exclusion, are documented in the [Characteristics of excluded studies](#) table. Of the 12 included trials, two had extremely small sample sizes (21 and 49 participants respectively) and did not have any reported cases of otitis media in their participants, either in the intervention or control groups (Prasad 1999; Prasad 2007). These two trials are presented in the [Characteristics of included studies](#) table, but as they have no relevant outcome, they do not contribute to the conclusions. A further three trials may have met the inclusion criteria, but we were unable to contact the trial authors for clarification; these trials are listed in the [Studies awaiting classification reference section](#).

Included studies

Location

Nine trials were conducted in low- and middle-income countries, including Bangladesh (Brooks 2005), India (Bhandari 2002), South Africa (Bobat 2005), Burkina Faso (Muller 2001), Chile (Schlesinger 1992), Peru (Penny 2004), Ecuador (Wuehler 2008), Jamaica (Gardner 2005), and Indonesia (Lind 2004); and one trial was conducted in the USA (Heinig 2006). Two further trials were conducted in the USA; these are excluded from the analysis because no cases of otitis media were identified (Prasad 1999; Prasad 2007).

Participants

All the trial participants included in the analysis were children aged under five years at the start of the trials. All but one (Bobat 2005) included only children under the age of three years. All trials included both males and females. One trial included only children who had HIV infection and were not receiving antiretroviral therapy (Bobat 2005), and one included only infants with marasmus (Schlesinger 1992), one enrolled only children with persistent diarrhoea (Penny 2004), while others included only healthy children or children from the general population. The two trials excluded from the analysis involved adults with sickle cell disease (Prasad 1999) and elderly adults attending a senior citizens' centre (Prasad 2007). The trials varied widely in size; one trial had fewer than 50 participants (Schlesinger 1992), two had more than 50 but less than 100 participants (Bobat 2005; Heinig 2006), two had more than 100 but less than 250 (Gardner 2005; Penny 2004), three had around 600 to 700 participants (Lind 2004; Muller 2001; Wuehler 2008), and the two largest trials had 1621 (Brooks 2005) and 2482 (Bhandari 2002) participants respectively.

Interventions

Zinc supplements were provided in the form of zinc sulphate (Bobat 2005; Gardner 2005; Heinig 2006; Lind 2004; Muller 2001; Wuehler 2008), zinc gluconate (Bhandari 2002; Penny 2004; Prasad 2007), zinc acetate (Prasad 1999; Brooks 2005), and zinc chloride (Schlesinger 1992). Supplements were given for periods of 105 days (during nutritional rehabilitation) (Schlesinger 1992), four months (Bhandari 2002), six months (Bobat 2005; Gardner 2005; Heinig 2006; Lind 2004; Muller 2001; Penny 2004; Wuehler 2008), and 12 months (Brooks 2005). Zinc or placebo was given daily (or six days a week) in all trials, except one which gave supplements weekly (Brooks 2005).

Outcomes

Primary

Two trials reported on the number of children having at least one episode of otitis media during follow up, diagnosed by clinical assessment of the ear (Bhandari 2002; Muller 2001); one trial also reported on the number of children with more than one episode during follow up (Bhandari 2002).

Three trials reported on the number of episodes of diagnosed otitis media with ear suppuration per participant per year of follow up (Brooks 2005; Heinig 2006; Schlesinger 1992), although one trial (Heinig 2006) presented these data only in graph form, and the exact numbers could not be extracted.

No trials reported on the number of days with definite otitis media. Two trials in adults reported individual infections, and described the type of infections. None of the infections reported in these trials were otitis media (Prasad 1999; Prasad 2007).

Secondary

Two trials reported on the number of participants with at least one episode of probable otitis media, defined as ear discharge reported by the mother (Bhandari 2002; Gardner 2005), although one trial did not present any numerical data for this comparison (Gardner 2005).

One trial reported on the mean number of days with reported ear discharge (Bhandari 2002). Another reported on the total number of days with ear discharge for the entire population within each group (Lind 2004); these data are not presented in meta-analysis because of the potential that it may be skewed by a small number of children with chronic otitis media. Another recorded mean proportion of days with earache or ear discharge, and presented the conclusion but not the actual data (Wuehler 2008).

Adverse events

Three trials reported on vomiting following supplementation (Bhandari 2002; Lind 2004; Penny 2004), and one trial reported on

withdrawals from the study due to regurgitation of the supplement syrup (Bobat 2005).

Other

One trial, involving only children with HIV infection attending an HIV clinic but not receiving antiretroviral treatment, reported on the number of clinic attendances, and the number of attendances where otitis media was diagnosed.

Risk of bias in included studies

This section reports only on the included trials that contributed to data in the analysis.

Allocation

Seven of the trials included in the analysis reported an adequate method of random sequence generation and of concealment of the allocation sequence. One trial reported adequate sequence generation but did not describe allocation concealment (Wuehler 2008). In the remaining two trial reports the methods of sequence generation and allocation sequences were not described (Gardner 2005; Schlesinger 1992).

Blinding

Seven of the trials included in the analysis reported that knowledge of the allocated interventions was adequately concealed during the trial (blinding of all relevant individuals involved in the trial); the remaining three trials (Gardner 2005; Schlesinger 1992; Wuehler 2008) did not provide details of blinding, although Schlesinger 1992 and Wuehler 2008 were stated to be 'double-blind' and 'double-masked', respectively.

Incomplete outcome data

All ten of the trials included in the analysis had either almost complete outcome data, or had adequately addressed any incomplete outcome data.

Selective reporting

None of the trials included in the analysis showed any evidence of selective reporting, although this was difficult to assess because the outcomes of interest were not the primary outcomes of any of the trials.

Other potential sources of bias

There was no clear evidence of any other bias in any of the trials included in the analysis, although one trial (Heinig 2006) did not give clear information on how the trial sample was selected, and another (Schlesinger 1992) did not provide sufficient methodological details to judge the risk of other bias.

Effects of interventions

Definite otitis media

In two trials conducted in community settings (Bhandari 2002; Muller 2001), there was no significant difference between zinc or placebo in the number of children with at least one episode of definite otitis media during follow up (3191 participants, two trials, Analysis 1.1). There was also no significant difference between zinc and placebo groups in the numbers experiencing more than one definite episode (2482 participants, one trial, Analysis 1.2). One community trial (Brooks 2005) reported a lower incidence rate of diagnosed otitis media with zinc supplements compared with placebo (rate ratio 0.69, 95% CI 0.61 to 0.79, Analysis 1.4). This trial included a younger age group than the two trials described above (60 days to six months, compared with six to 36 months and six to 31 months).

In a small trial involving infants with marasmus (Schlesinger 1992), there was a significant benefit of zinc on mean number of episodes of otitis media (mean difference -1.12 episodes, 95% CI -2.21 to -0.03, 39 participants, Analysis 1.3). Another trial, involving breast fed infants in the USA, presented data on episodes of diagnosed otitis media per 100 days at risk, in graph form only (Heinig 2006); although it was not possible to extract numerical data, it was apparent from the graph that there was no significant difference between the zinc and placebo groups, the rate in each group being approximately 0.6 episodes per 100 days at risk.

In a trial involving 96 children with HIV infection and not receiving antiretroviral therapy (Bobat 2005), ear infection was diagnosed in 39 of 360 (10.8%) scheduled clinic visits and 46 of 407 (11.3%) total visits of children in the zinc group; while in the placebo group, ear infection was diagnosed in 52 of 370 (14.1%) scheduled visits and 65 of 447 (14.5%) total visits. The trial authors reported that this represented no significant differences between the groups.

Probable otitis media

In a trial within a community setting (Bhandari 2002), there was no significant difference between the zinc and placebo groups in the number of children who had at least one episode of probable otitis media of any duration (2482 participants, one trial, Analysis 1.5). This trial also reported no significant difference between the zinc and placebo groups in mean days with ear discharge (3145

participants, [Analysis 1.6](#)). In another community trial ([Gardner 2005](#)), there was no difference between the zinc supplemented and placebo groups in the median number of episodes of diagnosed ear infection (0.2 (range 0 to 5) compared with 0.0 (range 0 to 2)), or median time with ear infection (0.0 (range 0 to 28) compared with 0.0 (range 0 to 15)).

In one community trial including infants from birth to 12 months ([Lind 2004](#)), the zinc supplemented group spent a total of 21 of 30,275 days of follow up with ear discharge, compared with 37 of 30,423 days in the placebo group (risk ratio 0.57, 95% CI 0.33 to 0.97, 340 participants, [Analysis 1.7](#)). This appears to represent a significant risk reduction in the zinc supplemented group in the number of days spent with ear discharge; however it is unclear from these data how many children were affected by ear discharge, and whether the data were skewed by one or two individuals who may have developed chronic ear discharge.

A further community trial reported that the overall proportion of days spent with earache or ear discharge was less than 1% in the zinc and placebo groups, and that there was no significant difference between the groups ([Wuehler 2008](#)).

Adverse events

One trial reported no difference between zinc and placebo in the proportion of doses given where vomiting followed within 15 minutes (0.6% in each group, 246 participants, [Penny 2004](#)), while another ([Bhandari 2002](#)) reported more days of vomiting with zinc than placebo (mean difference 1.70 days, 95% CI 1.31 to 2.09, 2842 participants, one trial, [Analysis 1.8](#)).

One trial ([Lind 2004](#)) reported no significant difference between the zinc and placebo groups in the number of children who vomited after ingesting the supplement (100 participants, [Analysis 1.9](#)). One ([Bhandari 2002](#)) reported that 8 of 1421 children in the zinc group discontinued supplementation because of vomiting, compared with 0 of 1421 in the placebo group; however, this difference was not significant ([Analysis 1.10](#)).

One trial reported that 9.1% of the participants dropped out before the end of the study ([Bobat 2005](#)). The most common reason in both the zinc and placebo groups was a reaction to the taste of the syrup resulting in regurgitation; this was most common in the youngest participants.

No trials reported any serious adverse events.

DISCUSSION

Summary of main results

Six of the included trials showed no evidence of a difference between zinc supplements and placebo on otitis media incidence or prevalence in children. These included a small trial of children with

HIV/AIDS, another small trial of breast fed infants in the USA, and three larger trials conducted within poor communities in low- or middle-income countries. One trial conducted within a community setting showed a possible benefit of zinc in infants from birth to 12 months, but the findings were difficult to interpret. However, two trials appeared to demonstrate a definite significant benefit of zinc supplementation; one of these trials involved only infants with marasmus, the other involved healthy infants aged 60 days to 12 months living in a poor urban community. While the two trials including only infants under the age of 12 months appeared to show a beneficial effect of zinc, and other trials including also the older age groups showed no beneficial effect, it is not possible to assess whether this effect is due to age differences as analyses stratified by age were not available for the other studies included in the review.

Overall completeness and applicability of evidence

All of the trials included in the analysis involved only young children under the age of five years, and most included only children under the age of three years, the age group in which otitis media is most common. Nine of the 10 trials were conducted in low- and middle-income countries, where zinc deficiency among young children is common, and supplements most likely to be beneficial. Therefore these trials were applicable to real life situations where the use of supplements to prevent otitis media and other adverse health outcomes may be considered. In all the included trials, otitis media was a secondary outcome; the primary outcomes usually being more serious illnesses such as pneumonia, malaria, diarrhoea, lower respiratory tract infection, or death. However, as data on otitis media were collected using the same methods as the primary outcomes, this should not have adversely affected the quality of the data collected. The main weakness of the data is that most trials, when presenting data, did not differentiate between acute otitis media and chronic suppurative otitis media, which may have more severe consequences including permanent deafness.

Quality of the evidence

The trial evidence included is generally of good quality, with a low risk of bias. Seven of the nine trials included in the analysis reported adequate allocation concealment, seven reported blinding the participants and trial staff, and all ten reported a low rate of loss to follow up. The majority were carefully conducted community trials, with active mechanisms to promote adherence to the intervention, and active case finding.

Potential biases in the review process

All the included trials, as expected, included otitis media only as a secondary outcome. There was therefore the potential to miss trials which were less publicised or less well indexed within the electronic databases. We tried to avoid this by conducting a wide search and assessing the relevance of each paper identified in that search carefully. However, only one author was able to find the time to assess all 5678 titles identified in the search, so there is a small possibility that relevant trials may have been inappropriately excluded at this stage. There are no other obvious sources of potential bias.

Agreements and disagreements with other studies or reviews

We are unaware of any similar reviews covering this topic.

AUTHORS' CONCLUSIONS

Implications for practice

Evidence on whether zinc supplementation can reduce the incidence of otitis media in healthy children under the age of five years living in low- and middle-income countries is mixed. Three out of the five trials assessing this outcome demonstrated no significant effect, with point estimates close to no effect; another trial suggested a possible benefit of zinc, but the findings were difficult to interpret, and another trial appeared to demonstrate a significant benefit. The trial demonstrating a benefit of zinc included only children aged 60 days to 12 months. There were no trials in adults or older children, but both otitis media and zinc deficiency are much less common in these groups.

There is no clear evidence on whether zinc supplements can reduce otitis media specifically in children with HIV/AIDS, as only one small study was conducted among this group, and involved only children not receiving antiretroviral treatment.

There is some evidence that zinc supplements may reduce otitis media in infants being treated for marasmus. However, this conclusion is based only on one small trial, so must be viewed with caution.

Implications for research

Although initial results do not seem promising, it is still unclear whether zinc supplements can prevent otitis media in poor community settings, and if so, which particular types of communities may benefit, and which age groups.

Future trials assessing zinc supplements for the prevention of morbidity in childhood could incorporate otitis media as an outcome. Such trials should take care to collect and code data on otitis media outcomes accurately, including differentiating between different forms of otitis media, and to analyse and present the data in manner that is appropriate and suitable for combining with other trial data in meta-analyses.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Bhandari 2002

Methods	Randomised controlled trial (simple randomisation in blocks of 8) Duration: February 1998 to September 2000	
Participants	Number: 2482 enrolled Inclusion criteria: aged 6 to 30 months, male and female Exclusion criteria: consent refused, likely to move out of the study area within the next 4 months, needed urgent admission to hospital on the enrolment day, received a massive dose of vitamin A within last 2 months	
Interventions	Group 1: zinc gluconate syrup taken daily for 4 months (contained 10 mg elemental zinc for infants and 20 mg for older children) Group 2: placebo syrup	
Outcomes	<p>Included in the review</p> <p>In passive surveillance at clinics: acute suppurative otitis media defined as pus draining from ear for less than 2 weeks duration plus otoscopic examination reveals redness, decreased mobility and/or bulging of ear drum. Two episodes of otitis media separated by ≥ 6 weeks</p> <p>Chronic suppurative otitis media defined as pus discharge from ear for more than 2 weeks and/or recurrent ear discharge</p> <p>In active surveillance: reported discharge from the ear, obtained during weekly surveillance visit by field workers</p> <p>Measures include children with at least 1 episode of clinically diagnosed otitis media during follow up, children with at least 1 episode of reported ear discharge during follow up, and mean number of days with reported ear discharge at follow up</p> <p>Not included in the review</p> <p>Acute lower respiratory infections Pneumonia Diarrhoea</p>	
Notes	Location: India Setting: community setting (urban slum) Source of funding: Indian Council for Medical Research	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Quote: "The randomisation scheme was generated by a statistician at Statens Serum Institute using SAS software" Comment: done

Bhandari 2002 (Continued)

Allocation concealment?	Yes	Quote: "The randomisation scheme was generated by a person not otherwise involved with this study" Comment: done
Blinding? All outcomes	Yes	Quote: "The zinc and placebo syrups were similar in appearance, taste and packaging. Masking was maintained during analysis by coding the groups A and B" Comment: done
Incomplete outcome data addressed? Otitis media	Yes	2226 of 2482 (89%) participants followed up for 4 months, a similar percentage in the placebo (91%) and zinc (88%) groups. Only 8 children (all in the zinc group) discontinued the trial because of vomiting
Free of selective reporting?	Yes	No evidence of selective reporting
Free of other bias?	Yes	No evidence of other bias

Bobat 2005

Methods	Randomised controlled trial. Randomised in blocks of 8 in 3 age strata Duration: March 2003 to September 2004
Participants	Number: 96 enrolled Inclusion criteria: HIV-1 infection, aged 6 to 60 months (age strata 6 to 23, 24 to 42, and 42 to 60 months), male or female, hospital outpatients, not receiving antiretroviral therapy. Children receiving a single dose of nevirapine to prevent transmission were included Exclusion criteria: none stated
Interventions	Group 1: zinc sulphate tablets (10 mg elemental zinc) daily for 6 months Group 2: placebo
Outcomes	Included in the review Presence of otitis media diagnosed by history and examination, including otoscopy, at routine and additional visits to the HIV clinic Not included in the review Watery diarrhoea Pneumonia Upper respiratory tract infection HIV-1 viral load and CD4 + T lymphocyte %
Notes	Location: South Africa Setting: hospital outpatients Source of funding: Johns Hopkins Family Health and Child Survival Cooperative Agree-

Bobat 2005 (Continued)

	ment with the Office of Health, Infectious Diseases and Nutrition, Global Health Bureau, US Agency for International Development	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Quote: "Randomisation lists were computer generated" Comment: done
Allocation concealment?	Yes	Quote: "Randomisation lists were generated at the WHO" Comment: done
Blinding? All outcomes	Yes	Quote: "The investigators were unaware of the treatment allocation until follow-up was completed" Comment: done
Incomplete outcome data addressed? Otitis media	Yes	85 of 96 children (89%) completed the protocol. Of the 11 that did not complete the study, 2 dropped out and 9 died
Free of selective reporting?	Yes	No evidence of selective reporting
Free of other bias?	Yes	No evidence of other bias

Brooks 2005

Methods	Randomised controlled trial. Random assignment with permuted blocks of variable length between 2 and 8 Duration: April 1999 to August 2000 for recruitment
Participants	Number: 1655 enrolled, 1621 randomised Inclusion criteria: aged 60 days to 12 months, male or female Exclusion criteria: known or suspected tuberculosis, chronic respiratory or congenital heart disease, severe malnutrition requiring hospital admission
Interventions	Group 1: zinc acetate 70 mg once weekly for 12 months Group 2: placebo identical in colour odour and taste once weekly for 12 months
Outcomes	Included in the review Mean number of episodes of suppurative otitis media defined as 'purulent ear discharge'. Suspected cases were found during once-weekly home visits by trained research assistants using a standardised calendar questionnaire, then referred to the clinic for a definite diagnosis Not included in the review

Brooks 2005 (Continued)

	Episodes of diagnosed diarrhoea, upper respiratory tract infection, reactive airways disease or bronchiolitis, pneumonia, and severe pneumonia. Cases were found during once-weekly home visits by trained research assistants using a standardised calendar questionnaire Death Height and weight Serum zinc and copper, blood haemoglobin and white blood cells	
Notes	Location: Kamalapur, southeastern Dhaka, Bangladesh Setting: poor, urban community Source of funding: Johns Hopkins Family Health and Child Survival Cooperative Agreement with the US Agency for International Development, the Swiss Development Corporation, and a co-operative agreement between US Agency for International Development and core donors to the Centre for Health and Population Research	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Quote: "Random assignment...was done with permuted blocks of variable length between two and eight" Comment: probably done
Allocation concealment?	Yes	Quote: "ACME Laboratories, Ltd prepared, labelled and masked the identity of both preparations" Comment: done
Blinding? All outcomes	Yes	Quote: "The placebo was designed to be identical to the zinc syrup in colour, odour and taste" Comment: done
Incomplete outcome data addressed? Otitis media	Yes	Data were included in the analysis up the point of a child's withdrawal, even if they did not complete the observation period. Exit interviews were done for all drop-outs, to determine any possible biases
Free of selective reporting?	Yes	No evidence of selective reporting
Free of other bias?	Yes	No evidence of other bias

Gardner 2005

Methods	Randomised controlled trial. Stratified randomisation in 2 age groups Duration: not stated
Participants	Number: 126 enrolled Inclusion criteria: age 9 to 30 months (stratified 9 to 18 months and 19 to 30 months), male or female, weight for age z-score below -1.5 SDs of the National Centre for Health Statistics references, weight for age below -2 SDs of the National Centre for Health Statistics references Exclusion criteria: twins, children with physical or mental impairments that could affect development
Interventions	Group 1: 10 mg elemental zinc as zinc sulphate were given daily, as a flavoured syrup, for 6 months Group 2: placebo with identical appearance, odour and taste The trial had a factorial design, with some children in the zinc and placebo groups also receiving psychosocial stimulation. All children in both zinc and placebo groups also received a brand of mixed micronutrients containing vitamins and iron
Outcomes	Included in the review Number of episodes of illness, and number of days ill. Pain or discharge from the ear recorded by a fieldworker visiting the families every 7th day Not included in the review Development using 4 sub-scales of the Griffiths Mental Development Scales at enrolment and at 6 months Weight, length, weight-for-age z-score, height-for-age z-score, at enrolment and at 6 months Number of episodes of illness, and number of days ill. Symptoms recorded by a fieldworker visiting the families every 7th day: apathy, anorexia, fever, coughing, nasal discharge, diarrhoea, vomiting, rapid or difficult breathing, any skin condition. Clinic visits for illness, and hospital admissions were also recorded
Notes	Location: the parishes of Kingston, St Andrew and St Catherine, Jamaica Setting: nutrition clinics (outpatients) Source of funding: the Nestle Foundation, The Grace Kennedy Foundation (Jamaica) . Dr Jeffrey Meeks and the Matalon and Methado families provided further financial assistance. Zinc supplement donated by Federated Pharmaceuticals Limited

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Quote: "...randomly assigned to receive zinc supplement or placebo" Comment: probably done, but methods not described
Allocation concealment?	Unclear	Not described

Gardner 2005 (Continued)

Blinding? All outcomes	Unclear	The participants were blinded using placebos, but blinding of investigators is not described
Incomplete outcome data addressed? Otitis media	Yes	114 of 126 participants (91%) completed the study and were included in the analysis. The trial authors report that the children who withdrew were not significantly different from those remaining in the study
Free of selective reporting?	Yes	No evidence of selective reporting
Free of other bias?	Yes	No evidence of other bias

Heinig 2006

Methods	Randomised controlled trial (individual randomisation stratified by sex) Duration: November 1994 to August 1997 for recruitment and data collection	
Participants	Number: 85 enrolled and randomised Inclusion criteria: healthy male or female term infant weighing > 2500 g, healthy non-smoking mother, mother planning to breast feed (without using formula milk on a daily basis) for ≥ 10 months, and not to introduce complementary food before 4 months. Infants were recruited within 3 months of birth, and included in the trial between the ages of 4 and 10 months Exclusion criteria: mother under 19 years old, chronic medical condition that may interfere with lactation, planning to leave the study area during the study period	
Interventions	Group 1: 5 mg elemental zinc (as zinc sulphate) in drops each day between the ages 4 and 10 months Group 2: placebo drops	
Outcomes	Included in the review Episodes of physician diagnosed otitis media per 100 child days at risk Not included in the review Length, weight, head circumference, midarm circumference, skinfold thickness at triceps, subscapular, flank and quadriceps at ages 4 and 10 months Plasma zinc, iron, copper, ferritin, immunoglobulin G ₂ and G ₄ , and erythrocyte superoxide dismutase at ages 4 and 10 months Timing of introduction of complementary foods, nutrient intake from complementary foods Respiratory illness, diarrhoea, fever (without other symptoms), other illness Motor development measured using Alberta Infant Motor Scale	
Notes	Location: USA Setting: community setting, recruitment through local paediatrician's offices Source of funding: US Department of Agriculture	

Heinig 2006 (Continued)

Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Quote: "Random assignment to groups was done by using the Moses-Oakford algorithm" Comment: done
Allocation concealment?	Yes	Quote: "An assistant who was not in contact with the study subjects labelled the bottles with 1 of 4 colours" Comment: done
Blinding? All outcomes	Yes	Quote: "Each mother-infant pair was assigned to a colour group so that neither the primary investigator nor the mothers would know whether the infants received the zinc supplement" Comment: done
Incomplete outcome data addressed? Otitis media	Yes	70 of 85 participants (82%) were included in the analysis. Of these, 3 were lost to follow up and 12 became ineligible because of consumption of formula milk. The analysis was undertaken both including and excluding the 12 ineligible participants and the findings were the same; therefore data are presented only for the 70 infants who completed the trial
Free of selective reporting?	Yes	No evidence of selective reporting
Free of other bias?	Unclear	Not clear how participants were originally selected

Lind 2004

Methods	Randomised controlled trial Duration: July 1997 to May 1999
Participants	Number: 680 randomised Inclusion criteria: healthy male or female singleton infants under 6 months of age Exclusion criteria: metabolic or neurological disorders; handicaps affecting development, feeding or activity; severe or protracted illness; haemoglobin < 90 g/L

Lind 2004 (Continued)

Interventions	<p>Group 1: 10 mg iron as ferrous sulphate Group 2: 10 mg zinc as zinc sulphate Group 3: 10 mg iron plus 10 mg zinc Group 4: placebo All interventions given as a sweet-tasting syrup, given daily for 6 months</p>
Outcomes	<p>Included in the review Total number of days (for entire trial treatment groups) with ear discharge recorded by a fieldworker visiting families every 3rd day</p> <p>Not included in the review Weight, length, and knee-heel length, head circumference and mid arm circumference at 12 months of age Infant development, measured using the Bayley Scales of Infant Development, at 12 months of age Symptoms recorded by a fieldworker visiting the families every third day: fever (mothers own definition), coryza, cough, difficult or rapid breathing, diarrhoea or vomiting. Incidence of diarrhoeal disease and lower respiratory infections during the 6 months of the trial were the primary outcomes Perceived side effects of the intervention</p>
Notes	<p>Location: Purworejo, Central Java, Indonesia Setting: community setting, in a health and demographic surveillance area. Authors reported a high prevalence of child stunting and micronutrient deficiencies Source of funding: the Swedish Agency for Research Cooperation with Developing Countries, the Swedish Medical Research Council, the Swedish Foundation for International Cooperation in Research and Education, the Swedish Medical Society, the Maud and Birger Gustavsson Foundation, and Umea University Foundation</p>

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Quote: "Randomization was planned and generated by an independent statistician and performed in blocks of 20" Comment: done
Allocation concealment?	Yes	Quote: "Randomization was planned and generated by an independent statistician"... "The pharmaceutical company marked the 4 different supplements with letter codes to which the researchers and participants were blinded" Comment: done
Blinding? All outcomes	Yes	Quote: "Researchers and field staff were blinded to the information on group assignment, because this information was kept in safes at the administrative offices.."

Lind 2004 (Continued)

		until after the intention-to-treat analyses” Comment: done
Incomplete outcome data addressed? Otitis media	Yes	662 of 680 participants (97%) had complete morbidity data. Analysis showed no differences between those who completed the trial and those who did not
Free of selective reporting?	Yes	No evidence of selective reporting
Free of other bias?	Yes	No evidence of other bias

Muller 2001

Methods	Randomised controlled trial (randomisation in blocks of 30) Duration: June 1999 to December 1999
Participants	Number: 709 enrolled and randomised Inclusion criteria: aged between 6 and 31 months, male or female, permanent residents in participating villages Exclusion criteria: serious underlying disease, absence for more than 14 consecutive days during the study period
Interventions	Group 1: 12.5 mg zinc sulphate, in tablet form, daily (except Sundays) for 6 months Group 2: placebo identical in appearance and taste
Outcomes	Included in the review Number of children with at least 1 episode of clinically diagnosed otitis media, at period cross-sectional surveys Not included in the review Daily reports, for 6 months, from the parents on reported symptoms other than earache, visits to healthcare providers, and any treatments received Incidence of malaria, detected by daily temperature monitoring and testing of children with a temperature of 37.5 C or higher At baseline, 3 months and 6 months, cross-sectional survey data including: personal characteristics and risk factors (age, sex, ethnicity, use of mosquito nets), clinical data (including diagnosed otitis media), anthropometric data (weight, height or length, mid arm circumference) and malaria parasite density from thick and thin blood films. Packed cell volumes and serum zinc concentrations were measured in a random sample of 100
Notes	Location: 18 villages in rural northwestern Burkina Faso Setting: community setting, in rural area where malaria is common Source of funding: the World Health Organization and Deutsche Forschungsgemeinschaft

Risk of bias

Item	Authors' judgement	Description
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Muller 2001 (Continued)

Adequate sequence generation?	Yes	Quote: "Children were allocated zinc or placebo in blocks of 30 by computer generated random permuted codes" Comment: done
Allocation concealment?	Yes	Quote: "Children were allocated by computer generated random permuted codes (prepared by the World Health Organization)" Comment: done
Blinding? All outcomes	Yes	Quote: "The tablets were identical in appearance and taste" "The randomization code was broken after the database was closed" Comment: done
Incomplete outcome data addressed? Otitis media	Yes	685 of 709 (97%) children were included in the analysis. Children absent from the trial for more than 14 consecutive days were excluded
Free of selective reporting?	Yes	No evidence of selective reporting
Free of other bias?	Yes	Participants selected for the study randomly

Penny 2004

Methods	Randomised controlled trial. Block randomisation, stratified by current breastfeeding status Duration: not stated
Participants	Number: 246 enrolled Inclusion criteria: aged 6 to 36 months with diarrhoea for ≥ 14 days, male or female, intending to remain in the study area the next 6 months Exclusion criteria: none stated
Interventions	Group 1: 20 mg zinc per day as zinc gluconate Group 2: 20 mg zinc per day as zinc gluconate plus a mixture of other micronutrients Group 3: placebo The 3 interventions were indistinguishable by taste and appearance. They were in the form of a dry powder with added sugar, flavouring and colouring, and were administered by dissolving in boiled water in the participants' homes All interventions were given daily for 6 months after the episode of diarrhoea had ended
Outcomes	Included in the review Incidence and prevalence of ear infection, assessed by field workers who made daily visits

Penny 2004 (Continued)

	<p>to the children's home, asked the caregivers about symptoms and examined the child if new symptoms or worsening of existing symptoms was reported. (Awaiting data from author)</p> <p>Not included in the review</p> <p>Incidence and prevalence of various illnesses and symptoms, assessed by field workers who made daily visits to the children's home, asked the caregivers about symptoms and examined the child if new symptoms or worsening of existing symptoms were reported. Illnesses reported on included diarrhoea, cough, lower respiratory infection, pneumonia, fever, anorexia</p> <p>Weight, length, mid-upper arm circumference, and skinfold thicknesses on biceps, triceps, suprailiac, subscapular. Measured at baseline, 15 days, then monthly</p> <p>Haemoglobin, haematocrit and plasma zinc measured at baseline, 15 days, and 6 months</p>	
Notes	<p>Location: Canto Grande, a shanty town on the outskirts of Lima, Peru</p> <p>Setting: community setting</p> <p>Source of funding: Thrasher Research Fund and the World Health Organization; additional funds were provided by the University of California Pacific Rim Programme</p>	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Quote: "With the use of a computer-generated, block randomization scheme..." Comment: done
Allocation concealment?	Yes	Quote: "Each study number had been linked previously to 1 of 9 letter codes, each of which indicated one of the three treatment groups" Comment: done
Blinding? All outcomes	Yes	Quote: "The identities of the codes were not available to the field staff or investigators until after the data had been cleaned and analysed" Comment: done
Incomplete outcome data addressed? Otitis media	Yes	6/246 (2%) children were withdrawn from the study by their parents. For the remaining children, information on morbidity was available for > 90% of days during the period of supplementation
Free of selective reporting?	Yes	No evidence of selective reporting
Free of other bias?	Yes	No evidence of other bias

Prasad 1999

Methods	Randomised controlled trial Duration: 4 years
Participants	Number: 21 enrolled Inclusion criteria: adults (male or female) with sickle cell disease, sickle cell haemoglobin C, or sickle cell beta thalassaemia, who were attending a clinic, and who were identified as zinc-deficient using cellular zinc levels and immunological parameters Exclusion criteria: non-ambulatory, receiving more than 6 transfusions per year, drug dependent, neurological or psychiatric deficits, taking immunosuppressive drugs, HIV positive, hepatitis B, already taking zinc supplements
Interventions	Group 1: no supplement for 1 year, placebo for 1 year, followed by 50 mg elemental zinc as zinc acetate daily for 2 years Group 2: 50 mg elemental zinc as zinc acetate daily for 3 years
Outcomes	Infections, classified by type and diagnosed at the clinic
Notes	Location: Detroit, USA Source of funding: FDA grant

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Mentioned "randomized groups"
Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	Yes	"Acutely symptomatic, febrile patients were evaluated by an infectious disease consultant who was a blinded observer"
Incomplete outcome data addressed? Otitis media	Yes	No loss to follow up
Free of selective reporting?	Yes	No evidence of selective reporting
Free of other bias?	Yes	No evidence of other bias

Prasad 2007

Methods	Randomised controlled trial Duration: 12 months
Participants	Number: 50 enrolled Inclusion criteria: elderly men and women attending a senior citizens' centre Exclusion criteria: life expectancy less than 8 months, progressive neoplastic disease, significant kidney disease, significant liver disease, people self-supplementing with zinc, people unable to provide informed consent for participation

Prasad 2007 (Continued)

Interventions	Group 1: one capsule zinc gluconate (15 mg elemental zinc) every day for 12 months Group 2: placebo capsules every day in the same manner	
Outcomes	Any infection, classified by type of infection, diagnosed by a nurse practitioner	
Notes	Location: Detroit, USA Source of funding: NIH grant and Labcatal Laboratories, France	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Quote: "Elderly subjects were randomly assigned in pairs to the zinc supplemented or the placebo group with the use of envelopes that each contained two smaller envelopes" Comment: done
Allocation concealment?	Yes	Quote: "Elderly subjects were randomly assigned in pairs to the zinc supplemented or the placebo group with the use of envelopes that each contained two smaller envelopes" Comment: done
Blinding? All outcomes	Yes	Quote: "The nurse practitioner was blinded to the treatment assignment" Quote: "The persons caring for the patient...were blinded to the assignment"
Incomplete outcome data addressed? Otitis media	Unclear	One participants dropped out of the study on day 2. There was no other loss to follow up
Free of selective reporting?	Yes	No evidence of selective reporting
Free of other bias?	Yes	No evidence of any other bias

Schlesinger 1992

Methods	Randomised controlled trial Duration: not stated
Participants	Number: 39 enrolled Inclusion criteria: marasmic infants, male or female Exclusion criteria: none stated

Schlesinger 1992 (Continued)

Interventions	Group 1: zinc fortified (zinc chloride 15 mg/L) nutritional recovery formula, based on full fat powdered cow milk Group 2: identical nutritional recovery formula, but without the zinc Interventions were given daily for 105 days
Outcomes	Included in the review Mean number of episodes of ear suppuration, detected by daily recording of signs and symptoms Not included in the review Haemoglobin, ferritin, plasma zinc and copper, anaemia and iron stores at admission, 30 days, 60 days and 105 days Height for age, weight for age and height for weight z-scores at admission, 30 days, 60 days and 105 days Positive skin tests indicating immunocompetence at admission and 105 days Mean number of episodes, mean duration of days of each episode and mean percentage of infected days with illness for upper respiratory infection, lower respiratory infection, acute diarrhoea, skin and mucous candidiasis, purulent conjunctivitis, within the 105 days duration. These were detected by daily recording of signs and symptoms
Notes	Location: Santiago, Chile Setting: nutritional recovery centre inpatients

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not described
Allocation concealment?	Unclear	No described
Blinding? All outcomes	Unclear	Quote: "controlled double blind design" Comment: probably done, but methods not described
Incomplete outcome data addressed? Otitis media	Yes	39 of 39 participants (100%) included in the analysis
Free of selective reporting?	Yes	No evidence of selective reporting
Free of other bias?	Unclear	Not enough information provided about the methods

Wuehler 2008

Methods	Randomised controlled trial Duration: November 2001 to April 2005
Participants	Number: 631 enrolled Inclusion criteria: children 12 to 29 months old, male or female, length for age z-score < -1.3 for children 12 to 20 months old, < -1.5 for children 21 to 29 months old (stunted) , assessed by comparison with WHO/NCHS international reference data. All received iron supplements for 1 month before the start of the trial Exclusion criteria: anaemia assessed by haemoglobin < 10.5 g/dL, adjusted for altitude, chronic disease or congenital defect that restricts normal growth
Interventions	Group 1: placebo Group 2: 3 mg zinc per day Group 3: 7 mg zinc per day Group 4: 10 mg zinc per day Group 5: 10 mg zinc plus 0.5 mg copper per day Zinc was given as zinc sulphate and copper given as copper sulphate. All supplements were given for 6 months
Outcomes	Included in the review Earache or discharge from the ear during each day, recorded during home visits 3 to 5 times per week using a systematic, symptom-based questionnaire and observation of the child Not included in the review Child's general health status, appetite, number and consistency of stools, symptoms of cough, fever, nasal discharge, vomiting Length and weight at 0, 3 and 6 months Zinc, iron and copper status as measured in blood samples
Notes	Location: Ecuador, various communities Source of funding: US Department of Agriculture, US Agency for International Development Micronutrient Program, the United Nations Children Fund, Bristol-Meyers/Squibb Freedom to Discover grant, and Grupo Farma del Ecuador

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Quote: "The randomization lists..were generated..by using a fixed block randomization procedure" Decision: done
Allocation concealment?	Unclear	Not described
Blinding? All outcomes	Unclear	Quote: "double -masked" Decision: unclear, probably done

Wuehler 2008 (Continued)

Incomplete outcome data addressed? Otitis media	Yes	30 days or more of morbidity data was obtained for 590 of 631 participants (94%)
Free of selective reporting?	Yes	No evidence of selective reporting
Free of other bias?	Yes	No evidence of other bias

Characteristics of excluded studies [ordered by study ID]

Abdulhamid 2008	No relevant outcomes
Al-Sonboli 2003	No relevant outcomes
Arsenault 2008	No relevant outcomes
Bacqui 2002	No relevant outcomes
Bacqui 2003	No relevant outcomes
Bates 1993	No relevant outcomes
Behrens 1990	No relevant outcomes
Bhandari 2007	No relevant outcomes
Bhutta 1999	No relevant outcomes
Bogden 1988	No relevant outcomes
Bogden 1990	No relevant outcomes
Boran 2006	No relevant outcomes
Brooks 2004	No relevant outcomes
Brooks 2005a	No relevant outcomes
Brown 2007	No relevant outcomes
Carcamo 2006	No relevant outcomes
Castillo-Duran 1987	No relevant outcomes
Castillo-Duran 1995	No relevant outcomes
Castillo-Duran 2001	No relevant outcomes

(Continued)

Cavan 1993	No relevant outcomes
Chang 2006	No relevant outcomes
Coles 2008	No relevant outcomes
Czerwinski 1974	No relevant outcomes
Dehbozorgi 2007	No relevant outcomes
Dijkhuizen 2001	No relevant outcomes
Dijkhuizen 2008	No relevant outcomes
Doherty 1998	No relevant outcomes
Duchateau 1981	Not a randomised controlled trial
Dutta 2000	No relevant outcomes
Eggert 1982	No relevant outcomes
Ertekin 2003	No relevant outcomes
Fahmida 2007	No relevant outcomes
Fajolu 2008	No relevant outcomes
Faruque 1999	No relevant outcomes
Fawzi 2005	No relevant outcomes
Fischer Walker 2007	No relevant outcomes (contacted trial author for clarification)
Fischer Walker 2009	No relevant outcomes
Floersheim 1980	Not a randomised controlled trial
Fortes 1998	No relevant outcomes
Friel 1993	No relevant outcomes
Friis 1997	No relevant outcomes
Giroden 1999	Intervention is not zinc alone (zinc plus selenium sulphide)
Golden 1978	Intervention is not oral zinc (topical zinc cream)

(Continued)

Goransson 1978	No relevant outcomes
Grazioso 1993	No relevant outcomes
Gupta 1995	No relevant outcomes
Gupta 2003	No relevant outcomes
Hambridge 1993	No relevant outcomes
Hemalatha 1993	No relevant outcomes
Hettiarachchi 2008	No relevant outcomes
Hodkinson 2007	No relevant outcomes
Intorre 2008	No relevant outcomes
Johnson 2007	No relevant outcomes
Jonsson 1996	No relevant outcomes
Khanum 1988	No relevant outcomes
Khatun 2001	No relevant outcomes
Kilic 1998	No relevant outcomes
Kurogol 2007	No relevant outcomes
Labadie 1986	No relevant outcomes
Lin 2008	No relevant outcomes
Linday 2004	Not a randomised controlled trial
Lira 1998	No relevant outcomes
Lockitch 1989	No relevant outcomes
Long 2006	No relevant outcomes
Mahomed 1989	No relevant outcomes
Makonnen 2003	No relevant outcomes
Mocchegiani 1995	No relevant outcomes
Mocchegiani 1999	Not a randomised controlled trial

(Continued)

Muller 2003	No relevant outcomes
Munguia 2003	No relevant outcomes
Naheed 2009	Zinc supplements given for less than 1 month
Osendarp 2002	No relevant outcomes
Osendarp 2007	No relevant outcomes
Oyoke 2008	Review article
Rahman 2002	No relevant outcomes
Rawer 1987	No relevant outcomes
Rivera 1998	No relevant outcomes
Rosado 1997	No relevant outcomes
Roy 1997	No relevant outcomes
Roy 1999	Supplements given for a shorter period than 1 month
Roy 2007	Intervention not zinc alone (zinc plus multivitamins)
Roy 2008	Supplements given for a period shorter than 1 month
Roy 2008b	No relevant outcomes
Ruel 1997	No relevant outcomes (checked with author)
Ruz 1997	No relevant outcomes
Sachdev 1990	No relevant outcomes
Safai-Kutti 1990	Not a randomised controlled trial
Safai-Kutti 1991	No relevant outcomes
Samman 1987	No relevant outcomes
Sancho Martinez 2007	Not a randomised controlled trial (review article)
Sazawal 1995	No relevant outcomes
Sazawal 1996	No relevant outcomes

(Continued)

Sazawal 2001	No relevant outcomes
Sazawal 2007	No relevant outcomes
Shankar 2000	No relevant outcomes
Silva 2006	No relevant outcomes
Simmer 1988	Not a randomised controlled trial
Simmer 1991	No relevant outcomes
Singh 1994	No relevant outcomes
Smith 1999	No relevant outcomes
Sur 2003	No relevant outcomes
Thu 1999	Intervention not zinc alone (multiple micronutrients)
Tielsch 2007	No relevant outcomes
Udomkesmalee 1992	No relevant outcomes
Valery 2005	No relevant outcomes
Van Horn 2003	Intervention not zinc (promotion of diet low in saturated fat)
Vasudevan 1997	No relevant outcomes
Walravens 1976	No relevant outcomes
Walravens 1989	No relevant outcomes
Walravens 1992	No relevant outcomes
Wasantwisut 2006	No relevant outcomes
Wazewska-Czyzewska 1978	No relevant outcomes
Weismann 1978	No relevant outcomes
Weismann 1979	No relevant outcomes
Wieringa 2007	No relevant outcomes
Yang 2002	No relevant outcomes
Zeba 2008	Intervention not zinc alone (zinc plus vitamin A)

(Continued)

Zemel 2002	No relevant outcomes
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Characteristics of studies awaiting assessment [ordered by study ID]

Berger 2006

Methods	Randomised controlled trial Duration: March to November 1998
Participants	Number: 933 enrolled Inclusion criteria: singleton breast fed infants, between 4 and 7 months of age Exclusion criteria: chronic or acute illness, severe malnutrition or congenital abnormality
Interventions	Group 1: 10 mg iron daily as ferrous sulphate Group 2: 10 mg zinc daily as zinc sulphate Group 3: 10 mg zinc daily as zinc sulphate plus 10 mg iron as ferrous sulphate Group 4: placebos Supplements were given 7 days per week for 6 months by trained field workers
Outcomes	Serum haemoglobin, ferritin, and zinc; anaemia; height and weight; number of episodes of and number of days with acute respiratory infection, cough, fever, and diarrhoea
Notes	Location: rural area of Vietnam Source of funding: UNICEF, New York

Ninh 1996

Methods	Randomised controlled trial Duration: 5 months (dates not stated)
Participants	Number: 210 enrolled Inclusion criteria: children aged 4 to 36 months with growth retardation evidenced by WAZ score below -2 and HAZ score below -2, and no obvious medical reasons for poor growth Exclusion criteria: none stated
Interventions	Group 1: 10 mg zinc as zinc sulphate Group 2: placebo Doses of zinc and placebo were given daily for 5 months
Outcomes	Height and weight, respiratory infections, diarrhoea
Notes	Location: rural area of Vietnam Source of funding: University of Louvain and the National Institute of Nutrition of Vietnam

Richard 2006

Methods	Randomised controlled trial Duration: February to September 1998
Participants	Number: 855 enrolled Inclusion criteria: children aged 6 months to 15 years of age Exclusion criteria: chronic illness or severe malnutrition
Interventions	Group 1: 15 mg iron as iron sulphate Group 2: 15 mg zinc as zinc sulphate Group 3: 15 mg iron as iron sulphate plus 15 mg zinc as zinc sulphate Group 4: placebos All supplements were given daily for 7 months
Outcomes	Height and weight; haemoglobin status; zinc status; diarrhoea, fever, vomiting, coughing, and a variety of other symptoms. Diagnoses of malaria, diarrhoea, and acute lower respiratory infection
Notes	Location: rural village in Peru Source of funding: United Nations Children's Fund and United States Agency for International Development

HAZ: height-for-age z-score

WAZ: weight-for-age z-score

DATA AND ANALYSES

Comparison 1. Zinc versus placebo

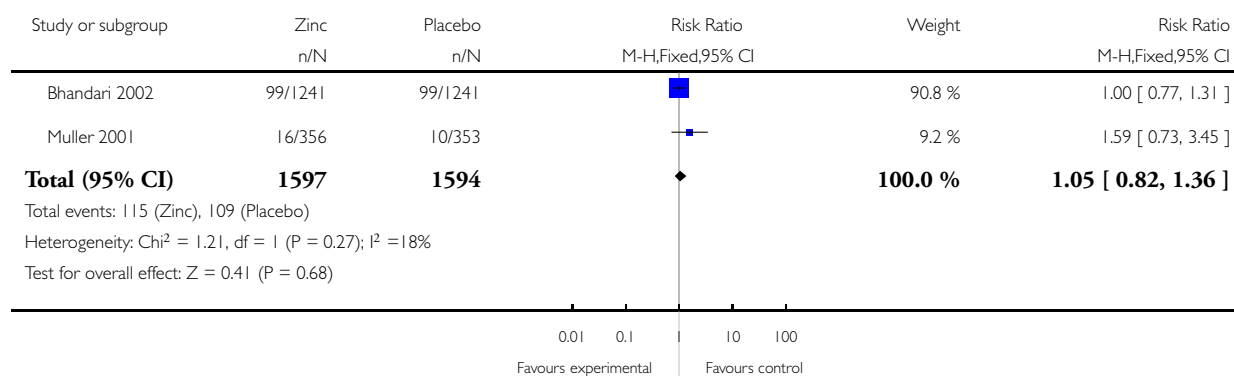
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Individuals who had at least one episode of definite otitis media of any duration	2	3191	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.82, 1.36]
2 Individuals who had more than one episode of definite otitis media	1	2482	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.50, 2.36]
3 Mean number of episodes of definite otitis media	1	39	Mean Difference (IV, Fixed, 95% CI)	-1.12 [-2.21, -0.03]
4 Rate ratio episodes of definite otitis media	1		Rate Ratio (Fixed, 95% CI)	0.69 [0.61, 0.79]
5 Individuals who had at least one case of probable otitis media	1	2482	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.80, 1.22]
6 Mean days with probable otitis media	1	3145	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.45, 0.65]
7 Total number of days with ear discharge	1	60698	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.33, 0.97]
8 Days with vomiting after supplementation	1	2482	Mean Difference (IV, Fixed, 95% CI)	1.70 [1.31, 2.09]
9 At least one episode of vomiting immediately after supplementation	1	326	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.93, 1.79]
10 Discontinued supplement due to vomiting	1	2482	Risk Ratio (M-H, Fixed, 95% CI)	17.0 [0.98, 294.21]

Analysis 1.1. Comparison 1 Zinc versus placebo, Outcome 1 Individuals who had at least one episode of definite otitis media of any duration.

Review: Zinc supplements for preventing otitis media

Comparison: 1 Zinc versus placebo

Outcome: 1 Individuals who had at least one episode of definite otitis media of any duration

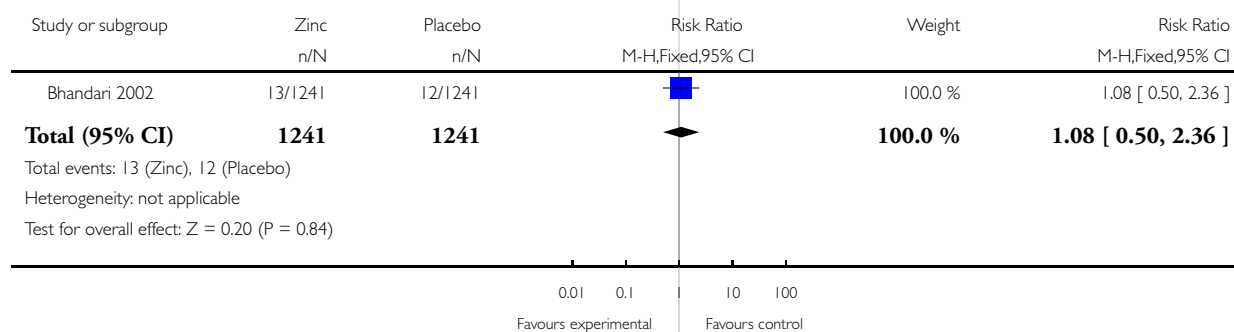


Analysis 1.2. Comparison 1 Zinc versus placebo, Outcome 2 Individuals who had more than one episode of definite otitis media.

Review: Zinc supplements for preventing otitis media

Comparison: 1 Zinc versus placebo

Outcome: 2 Individuals who had more than one episode of definite otitis media

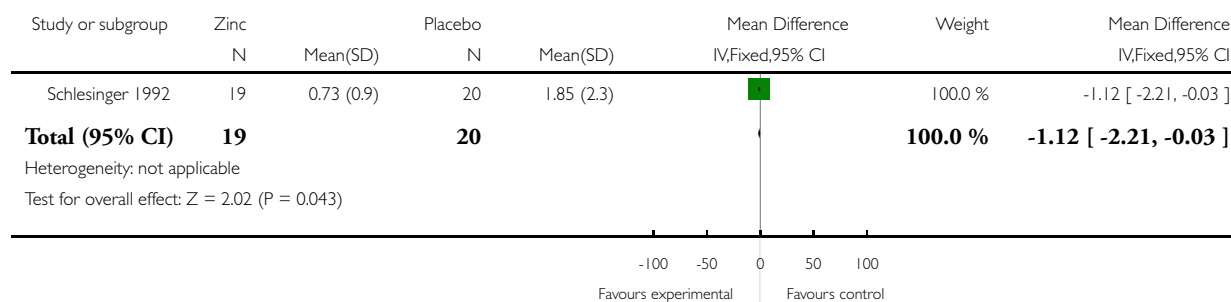


Analysis 1.3. Comparison 1 Zinc versus placebo, Outcome 3 Mean number of episodes of definite otitis media.

Review: Zinc supplements for preventing otitis media

Comparison: 1 Zinc versus placebo

Outcome: 3 Mean number of episodes of definite otitis media

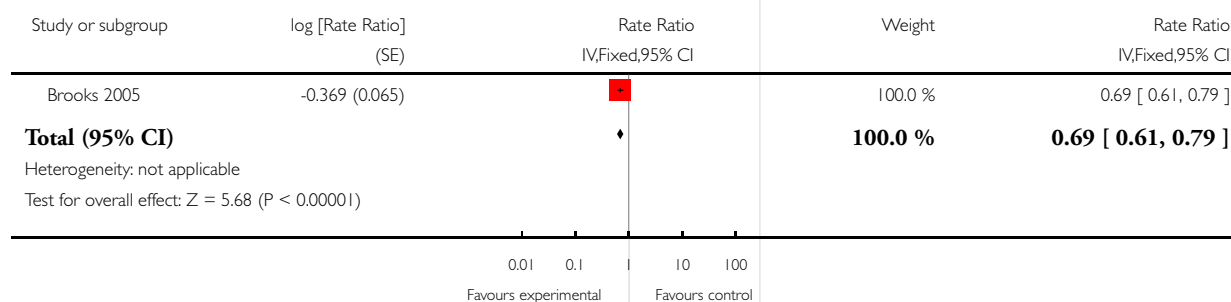


Analysis 1.4. Comparison 1 Zinc versus placebo, Outcome 4 Rate ratio episodes of definite otitis media.

Review: Zinc supplements for preventing otitis media

Comparison: 1 Zinc versus placebo

Outcome: 4 Rate ratio episodes of definite otitis media

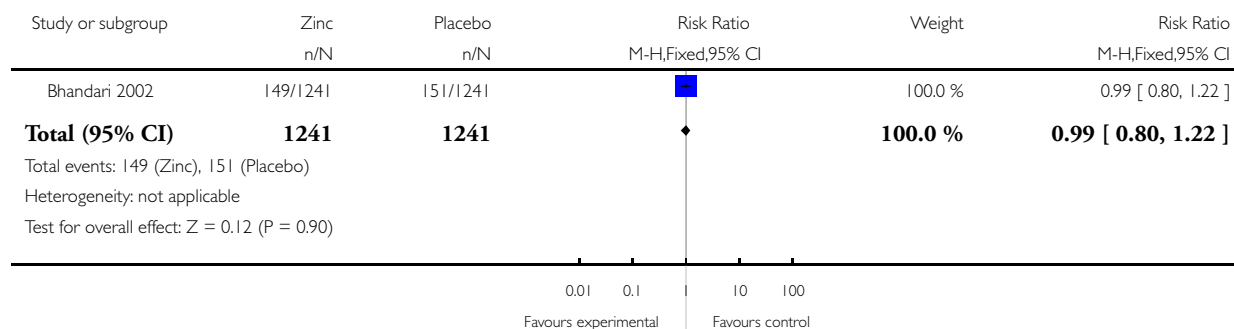


Analysis 1.5. Comparison 1 Zinc versus placebo, Outcome 5 Individuals who had at least one case of probable otitis media.

Review: Zinc supplements for preventing otitis media

Comparison: 1 Zinc versus placebo

Outcome: 5 Individuals who had at least one case of probable otitis media

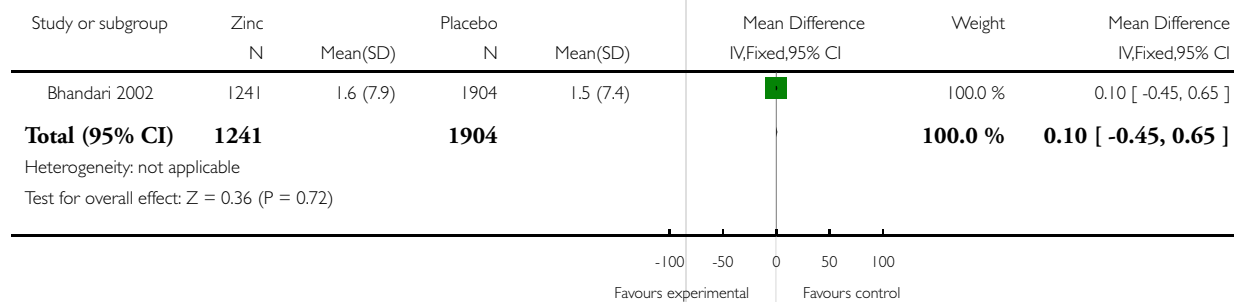


Analysis 1.6. Comparison 1 Zinc versus placebo, Outcome 6 Mean days with probable otitis media.

Review: Zinc supplements for preventing otitis media

Comparison: 1 Zinc versus placebo

Outcome: 6 Mean days with probable otitis media

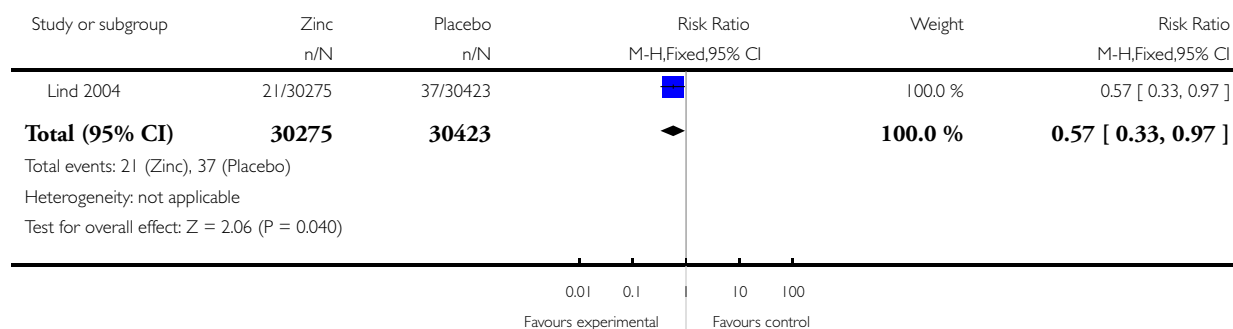


Analysis 1.7. Comparison 1 Zinc versus placebo, Outcome 7 Total number of days with ear discharge.

Review: Zinc supplements for preventing otitis media

Comparison: 1 Zinc versus placebo

Outcome: 7 Total number of days with ear discharge

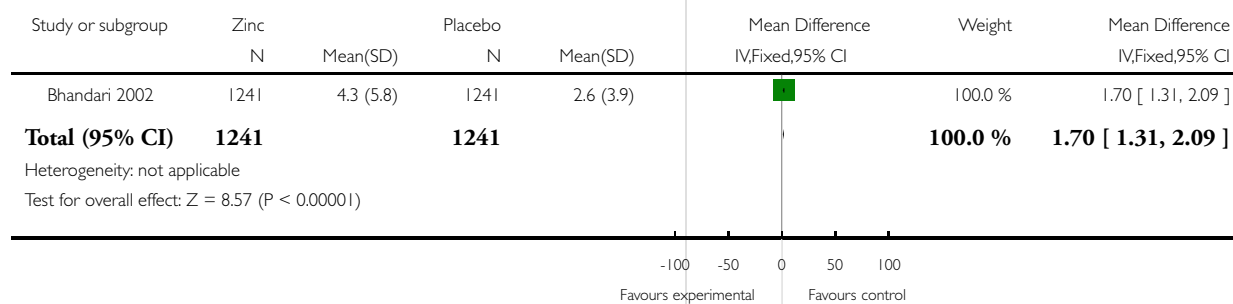


Analysis 1.8. Comparison 1 Zinc versus placebo, Outcome 8 Days with vomiting after supplementation.

Review: Zinc supplements for preventing otitis media

Comparison: 1 Zinc versus placebo

Outcome: 8 Days with vomiting after supplementation

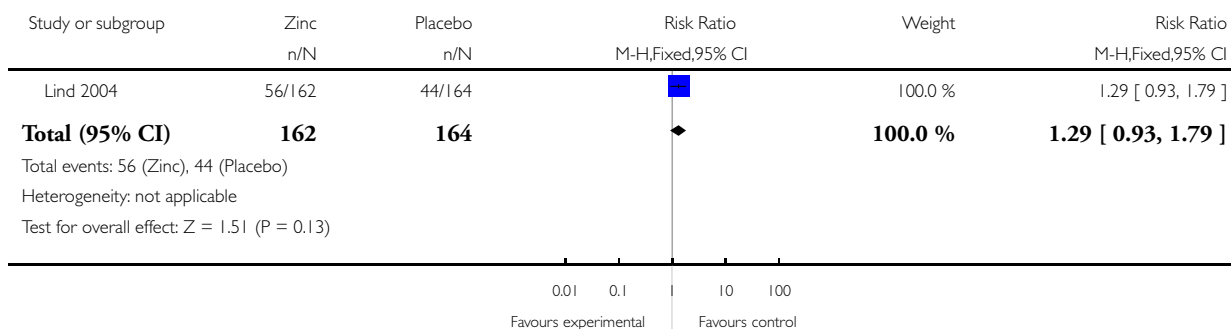


Analysis 1.9. Comparison 1 Zinc versus placebo, Outcome 9 At least one episode of vomiting immediately after supplementation.

Review: Zinc supplements for preventing otitis media

Comparison: 1 Zinc versus placebo

Outcome: 9 At least one episode of vomiting immediately after supplementation

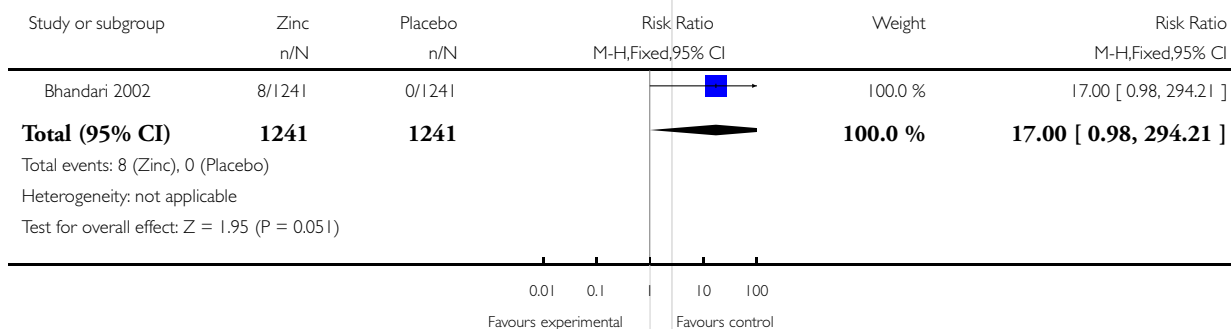


Analysis 1.10. Comparison 1 Zinc versus placebo, Outcome 10 Discontinued supplement due to vomiting.

Review: Zinc supplements for preventing otitis media

Comparison: 1 Zinc versus placebo

Outcome: 10 Discontinued supplement due to vomiting



APPENDICES

Appendix I. EMBASE search strategy

1. 'zinc'/exp
2. zinc:ti,ab
3. 'diet supplementation'/exp
4. #1 OR #2 OR #3
5. 'randomized controlled trial'/exp
6. 'single blind procedure'/exp
7. 'double blind procedure'/exp
8. 'crossover procedure'/exp
9. (random*:ti,ab OR factorial*:ti,ab OR crossover*:ti,ab OR placebo*:ti,ab OR assign*:ti,ab OR allocat*:ti,ab OR volunteer*:ti,ab) OR 'cross over':ti,ab OR 'single blind':ti,ab OR 'single blinded':ti,ab OR 'single blinding':ti,ab OR 'double blind':ti,ab OR 'double blinding':ti,ab OR 'double blinded':ti,ab
10. #5 OR #6 OR #7 OR #8 OR #9
11. #4 AND #10

HISTORY

Protocol first published: Issue 3, 2007

Review first published: Issue 2, 2010

30 November 2008	Amended	Converted to new review format.
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CONTRIBUTIONS OF AUTHORS

Katharine Abba (KA) wrote the protocol.

KA and Anjana Gulani (AG) selected the included studies, assessed their quality, undertook the analysis and drafted the review.

Harshpal Singh Sachdev (HS) provided advice and comments on the findings of the review and contributed to the writing.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Liverpool School of Tropical Medicine, UK.
- Sitaram Bhartia Institute of Science and Research, India.

External sources

- Department for International Development (DFID), UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There was a change in authorship between the protocol and the review. Paul Garner contributed to the protocol but did not participate in the review process. Anjana Gulani and Harshpal Singh Sachdev contributed to the review, but were not involved in the protocol.

INDEX TERMS

Medical Subject Headings (MeSH)

*Dietary Supplements; Chlorides [therapeutic use]; Developing Countries; Gluconates [therapeutic use]; Otitis Media [*prevention & control]; Randomized Controlled Trials as Topic; Trace Elements [*therapeutic use]; Zinc Acetate [therapeutic use]; Zinc Compounds [*therapeutic use]; Zinc Sulfate [therapeutic use]

MeSH check words

Child, Preschool; Female; Humans; Infant; Male