Zinc supplementation for the prevention of pneumonia in children aged 2 months to 59 months (Review)

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[Intervention Review]

Zinc supplementation for the prevention of pneumonia in children aged 2 months to 59 months

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ABSTRACT

Background

Pneumonia is a leading cause of morbidity and mortality in children younger than five years of age. Most deaths occur during infancy and in low-income countries. Daily regimens of zinc have been reported to prevent acute lower respiratory tract infection and reduce child mortality.

Objectives

To evaluate the effectiveness of zinc supplementation in the prevention of pneumonia in children aged two to 59 months.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2010, Issue 2), which contains the Acute Respiratory Infections Group's Specialised Register, MEDLINE (1966 to January Week 2, 2010), EMBASE (1974 to January 2010) and LILACS (1985 to January 2010).

Selection criteria

Randomised controlled trials (RCTs) evaluating supplementation of zinc for the prevention of pneumonia in children aged 2 to 59 months of age.

Data collection and analysis

Two review authors independently assessed trial quality and extracted data.

Main results

We included six trials and 7850 participants in the meta-analysis. Analysis showed that zinc supplementation reduced the incidence of pneumonia by 13% (risk ratio (RR) 0.87; 95% confidence interval (CI) 0.81 to 0.94, fixed-effect, six studies) and prevalence of pneumonia by 41% (RR 0.59; 95% CI 0.35 to 0.99, random-effects, one study). On subgroup analysis, we found that zinc reduced the incidence of pneumonia defined by specific clinical criteria by 21% (i.e. confirmation by chest examination or chest radiograph) (RR 0.79; 95% CI 0.0.71 to 0.88, fixed-effect, four studies, n = 4591) but had no effect on lower specificity pneumonia case definition (i.e. age specific fast breathing with or without lower chest indrawing) (RR 0.95; 95% CI 0.86 to 1.06, fixed-effect, four studies, n = 3259).

Authors' conclusions

Zinc supplementation in children is associated with a reduction in the incidence and prevalence of pneumonia, the leading cause of death in children.

PLAIN LANGUAGE SUMMARY

Zinc supplementation for the prevention of pneumonia in children aged two to 59 months

Zinc is an essential element for growth and development of children. Its deficiency is associated with increased risk of infection, particularly diarrhoea and pneumonia. Zinc supplementation in children has been reported to prevent pneumonia; however, its effect remains unclear. The aim of this review is to evaluate the role of zinc supplementation in the prevention of pneumonia in children of two to 59 months of age.

The review authors found six randomised controlled trials evaluating the impact of providing zinc supplementation for the prevention of pneumonia. The studies were conducted in Bangladesh, India, Peru, and South Africa. Children of two to 59 months of age were randomly assigned to receive zinc or a placebo. In two studies, the children were given vitamin A in both the groups. Analysis of the studies showed that zinc supplementation was significantly associated with reducing the incidence and prevalence of pneumonia among children of two to 59 months of age. Evidence provided so far from randomised controlled trials is sufficient to recommend zinc intake in deficient populations through supplementation, dietary improvements, or fortification, for enhancing child survival.

BACKGROUND

Description of the condition

Zinc deficiency is common amongst children in low-income countries, as defined by the World Bank (World Bank 2008) due to a variety of factors such as low food intake, particularly from animal sources; limited zinc bioavailability from local diets; and loss of zinc during recurrent diarrhoeal illnesses (Bhutta 1999; Black 1998). Zinc deficiency is associated with decreased immunocompetence (Shankar 1998) and increased rates of serious infectious diseases (Bahl 1998; Black 1998). The deficiency is widely recognised as contributing to limited growth of children in both low-income and high-income countries (Ploysangam 1997).

Acute lower respiratory tract infections (LRTIs) are among the leading causes of mortality in children under five years of age (Bryce 2005; Rudan 2008) and account for nearly two million deaths annually, the majority of which occur in low-income countries. Pneumonia is the largest cause of mortality, accounting for 19% of all childhood deaths in low-income countries (Bryce 2005; Rudan 2008). Interventions that affect mortality due to pneumonia are thus of great importance in any effort to improve childhood survival.

Description of the intervention

The effect of zinc supplementation on infections remains unclear. It is reported to prevent pneumonia (Bhutta 1999) and has also been found to be beneficial in reducing the duration and severity of diarrhoeal episodes in children with acute and persistent diarrhoea (Bhandari 1994; Zinc Group 2000). Trials of zinc supplementation vary with regard to the magnitude of the effect demonstrated and the presence of a differential effect according to sex, age, nutritional status or baseline plasma zinc concentration.

How the intervention might work

Zinc plays an important role in maintaining a normal immune function. Studies have suggested that zinc deficiency impairs cell regeneration, epithelial barrier functions and linear growth (Shankar 1998). Zinc deficiency also impairs immunocompetence with reduced cell-mediated immune responses, decreased T-lymphocytes, abnormal T-helper and/or suppressor functions, impaired macrophage function and reduced killer cells and antibody-dependent cytotoxicity (Ibs 2003; Ravaglia 2000). Zinc supplementation in children causes an increase in the levels of complement in the blood that modulate the function of monocytes, macrophages and neutrophils polymorphs. It also helps in the development and activation of T-lymphocytes. When zinc supplements are given to individuals with low levels of zinc, the numbers

of T-cell lymphocytes circulating in the blood increase and the ability of lymphocytes to fight against infection improves (Fraker 1993). Because zinc is not stored in the body, adequate zinc supplementations are required.

Why it is important to do this review

A previously published review in 1999 (Bhutta 1999) has shown that continuous zinc supplementation was associated with decreased rates of pneumonia. Since then, additional studies have been published that were larger in size and scope. In a review published in 2007 (Aggarwal 2007), recent studies were added, but they included children aged between 0 and 59 months who were given zinc supplements for at least a few months. Recently, Roth 2010 also assessed this topic and calculated the effect size by case definition of pneumonia. However, they also included studies that gave supplements to children aged between 0 and 59 months with zinc. We realised the need for a systematic review of children aged from two to 59 months and therefore conducted a meta-analysis of trials investigating supplemented zinc for at least three months.

OBJECTIVES

To evaluate the effectiveness of zinc supplementation in the prevention of pneumonia in children aged two to 59 months.

METHODS

Criteria for considering studies for this review

Types of studies

We included RCTs evaluating supplementation of zinc for the prevention of pneumonia in children aged two to 59 months. We included studies that define an episode of pneumonia in the following ways.

1. Reported cough or difficulty in breathing with a respiratory rate above the WHO-defined age-specific values (respiratory rate of 50 breaths per minute or more for children aged two to 11 months, or respiratory rate of 40 breaths per minute or more for children aged 12 to 59 months), and either documented fever of above 38^{o}C or chest in-drawing (WHO 1990).
2. A diagnosis of pneumonia based on chest examination by a physician.
3. A diagnosis of pneumonia based on a chest radiograph.

We included trials published in languages other than English. We excluded quasi-RCTs.

Types of participants

Children aged from two to 59 months.

Types of interventions

Oral supplement containing at least the United States' recommended daily allowance (RDA) of zinc versus either an oral supplement without zinc or placebo. Supplementation of zinc was the only difference between the intervention and the control group. We excluded trials in which individuals were given additional supplements unless the co-interventions other than zinc was the same in both groups. The RDA for infants is 5 mg of elemental zinc per day and for children aged from one to five years, it is 10 mg per day (RDA 1989). We included trials in which supplements were administered for at least three months and outcome surveillance was carried out for at least four weeks.

Types of outcome measures

Outcome measures included the number of new episodes of pneumonia and the prevalence (number of days of illness per total days of observation) of pneumonia in children aged two to 59 months.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2010, issue 2), which contains the Acute Respiratory Infections Group's Specialised Register, MEDLINE (1966 to January Week 2, 2010), EMBASE (1974 to January 2010) and LILACS (1985 to January 2010).

We used the following search strategy to search MEDLINE and CENTRAL. The search strategy incorporates the search strategy devised by Boluyt 2008 to identify child studies. Due to the small number of search results we chose not to use a search filter to identify randomised trials. We adapted the search strategy to search EMBASE (see Appendix 1) and LILACS (see Appendix 2).

1 exp Pneumonia/
2 pneumon*.tw.
3 lower respiratory tract infection*.tw.
4 lower respiratory infection*.tw.
5 lrti.tw.
6 or/1-5
7 Zinc/
8 (zinc or zn).tw,nm.
9 or/7-8
10 exp Infant/
11 (infant* or infancy or newborn* or baby* or babies or neonat* or preterm* or prematur*).tw.
12 exp Child/

13 (child* or schoolchild* or school age* or preschool* or kid or kids or toddler*).tw.
14 Adolescent/
15 (adoles* or teen* or boy* or girl*).tw.
16 Minors/
17 Puberty/
18 (minor* or pubert* or pubescen*).tw.
19 exp Pediatrics/
20 (pediatric* or pediatric*).tw.
21 exp Schools/
22 (nursery school* or kindergar* or primary school* or secondary school* or elementary school* or high school* or highschool*).tw.
23 or/10-22
24 6 and 9 and 23

Searching other resources

We imposed no language or publication restrictions. We also searched related conference proceedings for relevant abstracts. We contacted organisations and researchers in the field and pharmaceutical companies for information on unpublished and ongoing trials. We also checked the reference lists of all trials identified by the above methods.

Data collection and analysis

Selection of studies

Two review authors (ZSL, BAH) independently assessed for inclusion all the potential studies we identified as a result of the search strategy. We resolved any disagreement through discussion and, if required, we consulted the third review author (ZAB).

Data extraction and management

We designed a data extraction form. Two review authors (ZSL, BAH) extracted the data using the agreed form. We resolved discrepancies through discussion and, if required, we consulted the third review author (ZAB). We entered data into Review Manager software (RevMan 2008) and checked for accuracy.

Assessment of risk of bias in included studies

Two review authors (ZSL, BAH) independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008). We resolved any disagreement by discussion with the third review author (ZAB).

(1) Sequence generation (checking for possible selection bias)

We described for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups. We assessed the method as:

- adequate (any truly random process, for example, random number table; computer random number generator);
- inadequate (any non random process, for example, odd or even date of birth; hospital or clinic record number); or
- unclear.

(2) Allocation concealment (checking for possible selection bias)

We described for each included study the method used to conceal the allocation sequence in sufficient detail and determine whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment. We assessed the methods as:

- adequate (for example, telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- inadequate (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth); or
- unclear.

(3) Blinding (checking for possible performance bias)

We described for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We judged studies at low risk of bias if they were blinded, or if we judged that the lack of blinding could not have affected the results. We assessed blinding separately for different outcomes or classes of outcomes. We assessed the methods as:

- adequate, inadequate or unclear for participants;
- adequate, inadequate or unclear for personnel; and
- adequate, inadequate or unclear for outcome assessors.

(4) Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations)

We described for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We stated whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported, or could be supplied by the trial authors, we re-included missing data in the analyses which we undertook. We assessed methods as:

- adequate;

- inadequate; or
- unclear.

(5) Selective reporting bias

We described for each included study how we investigated the possibility of selective outcome reporting bias and what we found. We assessed the methods as:

- adequate (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- inadequate (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported); or
- unclear.

(6) Other sources of bias

We described for each included study any important concerns we have about other possible sources of bias. We assessed whether each study was free of other problems that could put it at risk of bias:

- yes;
- no; or
- unclear.

(7) Overall risk of bias

We made explicit judgements about whether studies are at high risk of bias, according to the criteria given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008). With reference to (1) to (6) above, we assessed the likely magnitude and direction of the bias and whether we consider it is likely to impact on the findings. We also explored the impact of the level of bias through undertaking sensitivity analyses.

Measures of treatment effect

For dichotomous outcomes, we extracted the total number of participants for each group and the number of participants experiencing an event. We used the risk ratio (RR) and 95% confidence intervals (CIs).

Unit of analysis issues

We carried out statistical analysis using the Review Manager software (RevMan 2008). Initially, we used fixed-effect inverse variance meta-analysis for combining data where trials were examining the same intervention, and the trials' populations and methods were judged sufficiently similar. Where we suspected clinical or methodological heterogeneity between studies sufficient to suggest that treatment effects may differ between trials, we used random-effects meta-analysis. When we identified substantial heterogeneity in a fixed-effect meta-analysis, we noted this and repeated the analysis using a random-effects method.

Dealing with missing data

For included studies, we noted levels of attrition. For all outcomes, we carried out analyses, as far as possible, on an intention to treat (ITT) basis, i.e. we attempted to include all participants randomised to each group in the analyses.

Assessment of heterogeneity

We measured heterogeneity among the trials by calculating the I^2 statistic, Chi^2 P value and by visual inspection of the forest plots. If I^2 statistic exceeds 50%, Chi^2 P value is less than 0.1, and visual inspection of the forest plots is indicative, then we considered heterogeneity to be substantial. We did not find any heterogeneity; therefore, we did not attempt to undertake subgroup analyses based on differences in zinc dosage, age, supplementation in healthy children against that of children recovering from an episode of illness, and pre-intervention zinc levels. However, we attempted to look for the differential effect of zinc supplementation on the case definition of ALRI.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.
See Characteristics of included studies, Table 1 and Characteristics of excluded studies tables.

Results of the search

Through the search strategy we identified six trials that fulfilled the eligibility criteria of inclusion.

Included studies

We included six trials in the pooled analysis. However, we included Sazawal and Bhandari twice in the analysis, because the investigators in the trials reported ALRI in two different ways.
The trial from Lima, Peru, Penny 2004, was a randomised, double-masked, placebo-controlled community-based trial. Children aged six to 36 months with diarrhoea for more than 14 days were

randomly assigned and were given zinc daily for two weeks. Characteristics of the children at baseline was similar except for sex and length-for-age Z scores.

Brooks 2005 was also conducted in a poor population in an urban setting of Dhaka, Bangladesh. The study included 1665 children aged 60 days to 12 months who were randomly allocated to the zinc (70 mg) or placebo orally once weekly group. In this study, children were assessed every week by field research assistants at their homes. On finding children with suggestive respiratory disease or diarrhoea, children were referred to clinics where medical officers and nurses were involved in their assessment and diagnosis was made based on the WHO criteria. At the outset, no significant demographic differences were found between the two groups, except for a slightly higher proportion of boys in the zinc group.

The trial from the urban slums of New Delhi, India (Bhandari 2002a; Bhandari 2002b) included 2482 children aged six to 30 months. These children were given daily elemental zinc, 10 mg to infants and 20 mg to older children, or placebo for four months. Both these groups also received a single massive dose of vitamin A (100,000 IU for infants and 200,000 IU for older children) at enrolment. Both these groups were comparable in age, anthropometry, child feeding practices, morbidity in the previous 24 hours, socioeconomic characteristics, and plasma zinc concentration.

The trial from the KwaZulu-Natal Province of South Africa by Luabeya 2007 included children four to six months of age and was divided into two intervention arms and one control arm. In the control arm, children were given vitamin A alone; in the first intervention arm they were given vitamin A plus zinc; and in the second intervention arm they were given vitamin A, zinc and multiple micronutrients. Children in this study were given supplements until 24 months of age, thus each child was given with supplement for the period of 18 to 20 months. In the study sample 32 children were born with HIV positive status, while 154 were born without HIV infection to HIV positive mothers. Baseline characteristics of the treatment groups in the three cohorts did not significantly differ with the exception of weight-for-length.

The trial conducted by Sazwal et al (Sazawal 1998a; Sazawal 1998b) was in a low socioeconomic population of urban India. It was a double-blind controlled trial in which 609 children (zinc, n = 298; control, n = 311) aged six to 35 months were recruited and assigned to supplementation and placebo groups. The treatment group received 10 mg elemental zinc and the placebo group a substance similar in colour and taste. The fixed dose of 5 mL per child was given daily for six months to the all enrolled children, while it was increased to 10 mL in the case of diarrhoeal illnesses. The baseline characteristics of children included into the two groups were similar for age, sex, nutritional status, and baseline plasma zinc.

The trial from South Africa by Bobat et al (Bobat 2005) was a randomised, double-blind placebo-controlled equivalence trial of zinc supplementation at Grey's Hospital in Pietermaritzburg. In this trial 96 children aged from six to 60 months with HIV 1 infection were randomly assigned to receive 10 mg of elemental zinc as sulphate or placebo daily for six months. Baseline characteristics of included children assigned into the two treatment groups were similar.

Please refer to the Characteristics of included studies table for more details.

Excluded studies

We excluded 19 studies as they did not satisfy the inclusion criteria for this review. Five studies included children outside the age limits of our review criteria (Lira 1998; Osendarp 2002; Sur 2003; Taneja 2009; Tielsch 2007). We excluded another five studies as they supplemented their participants for less than three months (Baqui 2002; Castillo-Duran 1987; Rahman 2001; Roy 1999; Sempértegui 1996). We found eight studies that had a case definition for ALRI/pneumonia which was different from what we had reported (Baqui 2003; Long 2006; Lind 2004; Ninh 1996; Reul 1997; Richard 2006; Rosado 1997; Umeta 2000). We excluded one study because the investigators supplemented children by using a fortified drink (Bates 1993).

Please refer to the Characteristics of excluded studies table for more details.

Risk of bias in included studies

Figure 1 and Figure 2 provide a graphical summary of the results of risk of bias for the six included studies.

Figure 1. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

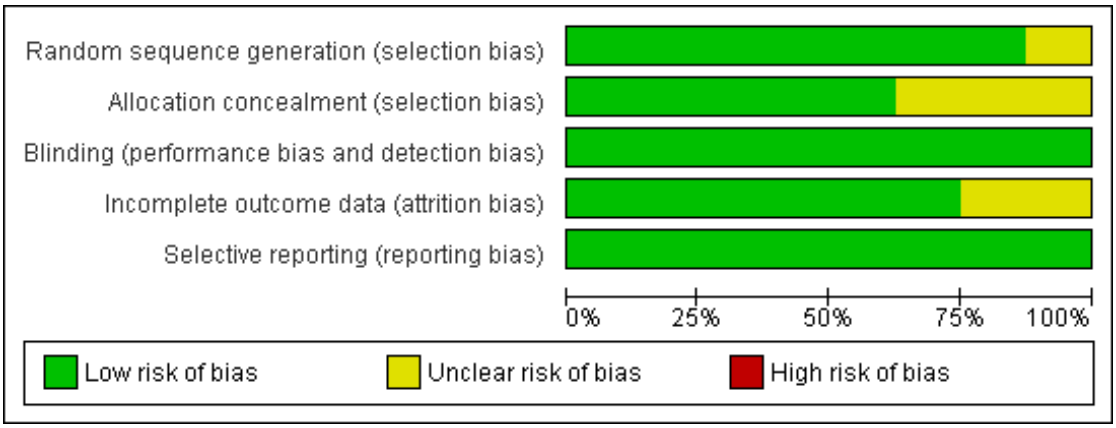
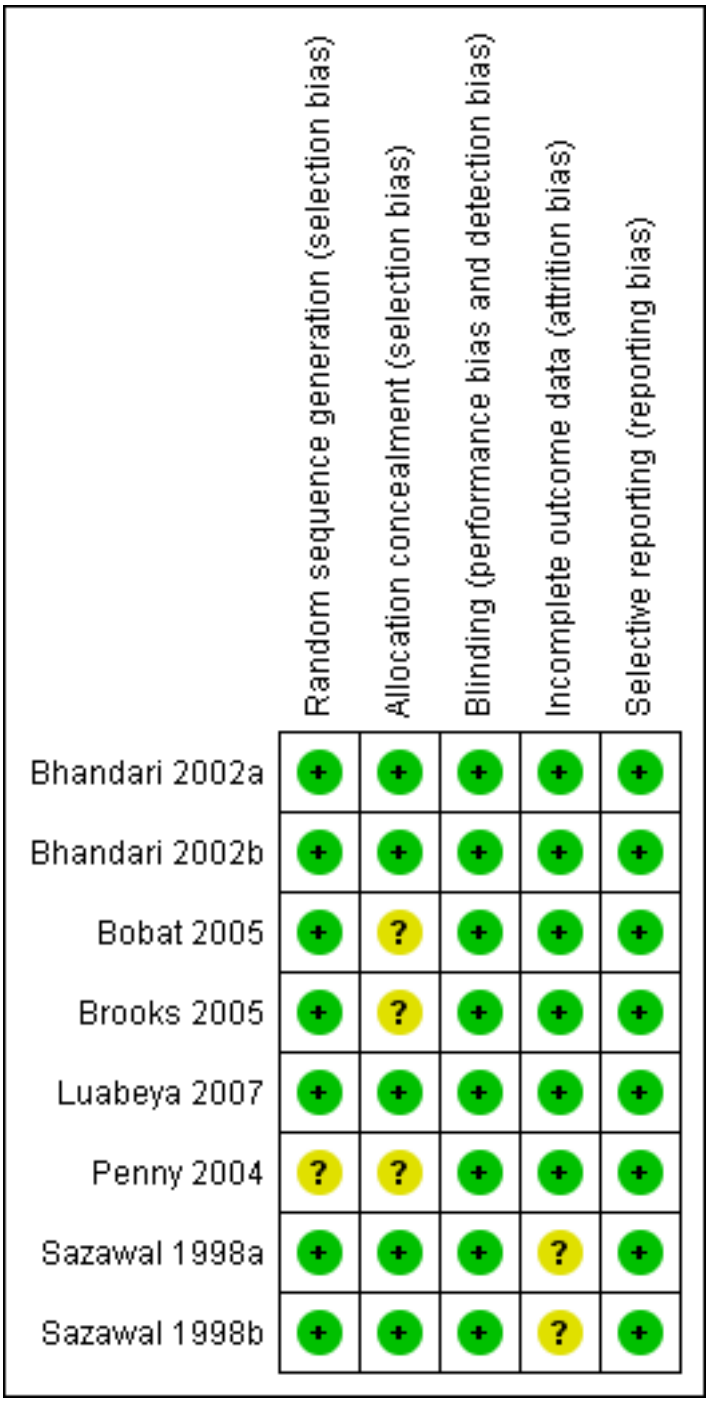


Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Allocation

All included studies, except one (Penny 2004), have adequate sequence generation (Bhandari 2002a; Bhandari 2002b; Bobat 2005; Brooks 2005; Luabeya 2007; Sazawal 1998a; Sazawal 1998b). Allocation concealment was also adequate in all, except for Bobat 2005, Brooks 2005 and Penny 2004 which had insufficient information to permit judgement.

Blinding

Blinding of participants, study personnel and outcome assessors was achieved in all seven included studies. Blinding of participants, study personnel and outcome assessors was achieved in one study (Sazawal 1998a; Sazawal 1998b), whereas in Bhandari (Bhandari 2002a; Bhandari 2002b), participants and outcome assessors were blinded to the assignment but we are unsure of the blinding of study personnel. In Brooks 2005 participants and study personnel were blinded to the assignment but we are unsure of the blinding of outcome assessors.

Incomplete outcome data

Attrition and exclusions were the reasons described in all except Sazawal (Sazawal 1998a; Sazawal 1998b).

Selective reporting

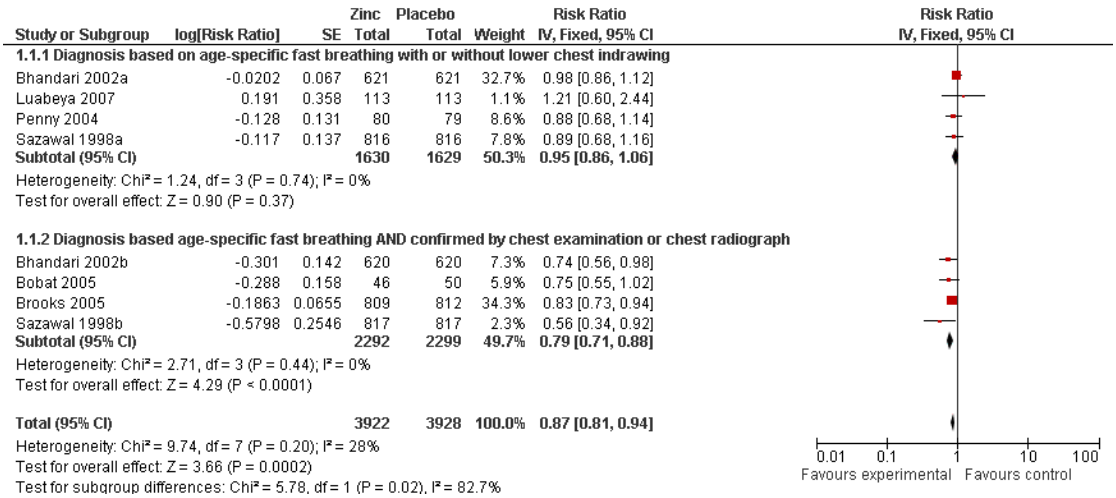
All the included studies appeared to be free of reporting bias.

Effects of interventions

Incidence of pneumonia

Administration of zinc supplementation showed a statistically significant impact on reducing the incidence of pneumonia by 13% (RR 0.87; 95% CI 0.81 to 0.94, fixed-effect model, six studies, n = 7850), and there was no heterogeneity (I^2 statistic = 28% and Chi^2 test P value = 0.20) (Analysis 1.1; Figure 3). We then separately pooled studies using a similar case definition. Studies that used clinical definitions of age-specific fast-breathing with or without lower chest indrawing did not find any impact of zinc supplementation on reducing the incidence of pneumonia (RR 0.95; 95% CI 0.86 to1.06, fixed-effect model, four studies, n = 3259) and there was no heterogeneity (I^2 statistic = 0% and Chi^2 test P value = 0.74). On the other hand, studies that used the above-mentioned case definitions with chest examination or chest radiograph found a significant impact of zinc supplementation on reducing incidence pf pneumonia by 21% (RR 0.79; 95% CI 0.0.71 to 0.88, fixed-effect model, four studies, n = 4591) and there was no heterogeneity (I^2 statistic = 0% and Chi^2 test P value = 0.44).

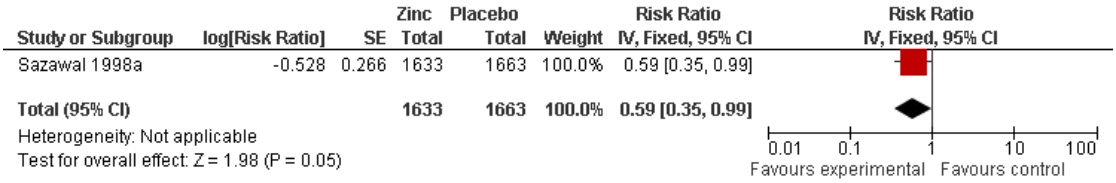
Figure 3. Forest plot of comparison: 1 Zinc supplementation versus placebo, outcome: 1.1 Pneumonia incidence. (LCI = lower chest indrawing)



Prevalence of pneumonia

Administration of zinc supplementation showed a statistically significant impact on reducing the prevalence of pneumonia among children aged two to 59 months by 41% (RR 0.59; 95% CI 0.35 to 0.99, fixed-effect model, one study, n = 3296) (Analysis 1.2; Figure 4).

Figure 4. Forest plot of comparison: 1 Zinc supplementation vs placebo, outcome: 1.5 Pneumonia Prevalence.



DISCUSSION

Summary of main results

We found six RCTs evaluating the impact of zinc supplementation in children aged two to 59 months. Our meta-analysis indicated that zinc supplementation for children between two to 59 months of age led to reductions in the incidence of pneumonia by 13% and pneumonia prevalence by 41%. The reason for the greater overall reduction of pneumonia prevalence is probably because the prevalence data originated from one study.

Regarding subgroup analysis, we found that zinc reduced the incidence of pneumonia (defined by specific clinical criteria) by 21% (i.e. confirmation by chest examination or chest radiograph) compared to no effect on lower specificity pneumonia case definition (i.e. age-specific fast-breathing with or without lower chest indrawing). We found an expected association of ALRI case definition with an effect size (P = 0.02) since it has been known that low specificity takes the biases towards the null as poor specificity leads to high false positive diagnoses in outcome ascertainment (non-differential error) (White 1986). We found benefits of zinc supplementation when the ALRI case was diagnosed, for example, clinical examination or chest radiograph that suggested infection. The reduction of pneumonia incidence by 21% would support the use of zinc supplements among children two to 59 months of age. Because zinc, unlike vitamin A, is not stored in the body after a large oral dose, it has been thought that adequate zinc must be available in the daily diet (Sanstead 1995). Therefore, children, particularly those from low-income countries who have an inadequate intake of foods that contain zinc (mainly foods of animal origin) should be given supplements to recover this deficiency.

Overall completeness and applicability of evidence

Participants in the majority of the included studies were from urban slums of low-income countries like Bangladesh, India and South Africa. In two selected studies, either children or their mothers had HIV positive status (Bobat 2005; Luabeya 2007). In most of the studies children were excluded if they had other co-morbidities like tuberculosis, congenital heart diseases, < 60% median weight-for-age Z score, and nutritional oedema, while in Penny 2004 children were selected based on their breastfeeding status. The use of strict definitions of pneumonia, with emphasis on clinical documentation of key sign or radiographic diagnosis, avoids misclassification and leads to greater confidence in the findings.

Quality of the evidence

In order to combine studies it is important that the outcome measures are comparable to avoid measurement bias. Of note, half of the trials included in this analysis reported pneumonia by using the WHO definition (WHO 1990), while the other half included clinical examination and chest radiographs. We therefore looked for the differential effect on outcome estimates with respect to case

definition and reported their impacts separately. Adequate allocation concealment, on the other hand, can avoid selection bias in controlled trials and there is evidence that inadequate allocation concealment leads to an overestimation of the treatment effect. In our included trials, allocation concealment was adequately described in all except for Penny 2004, which supports the evidence of lower risk of bias from selective reporting. All included studies were deemed to be adequately blinded for treatment assignment. Completion rates were greater than 90% in all but one study in which it was 16% (Penny 2004) and one study did not report the numbers of participants who dropped out (Sazawal 1998a). Due to the low levels of missing data, we did not choose to look for its impact on the overall estimates as it was not expected to cause a significant bias in the study results.

Potential biases in the review process

We undertook a systematic, thorough search of the literature to identify all studies meeting the inclusion criteria for this review and we are confident that all trials meeting the inclusion criteria are included in this review. Study selection and data extraction were done in duplicate and independently and we reached consensus by discussing any discrepancies.

Agreements and disagreements with other studies or reviews

Over the past two decades, we have found strong evidence from multiple RCTs, in both high-income and low-income countries, showing an effect of zinc in decreasing morbidity and mortality in children due to gastrointestinal and respiratory infections (Hambidge 1999; Sazawal 1998a; Sazawal 1998b). This effect of zinc against infectious diseases is therapeutic as well as preventive. Consistent findings were drawn from previous reviews by the Zinc Investigators' Collaborative Group in 1999 (Bhutta 1999) and by Aggarwal 2007 that have studied the effect of zinc supplementation on diarrhoeal and respiratory morbidity. In the review by the Zinc Investigators' Collaborative Group (Bhutta 1999) the zinc supplemented children had an odds ratio (OR) of 0.59 (95% CI 0.41 to 0.83) for pneumonia. Moreover, that review included trials which administered zinc supplementation with a therapeutic intent which might have led to an overestimation of the potential preventive effects of zinc. Aggarwal 2007 included trials that recruited children aged from 0 to 59 months and provided zinc supplementation for at least three months, and showed a 20% decreased incidence of respiratory illness among children supplemented with zinc compared to a placebo. Similar findings were also reported by Roth 2010, who also assessed specific case definitions for impact evaluation on children between zero and five years of age. They reported that zinc reduced the incidence of ALRI defined by specific clinical criteria (IRR 0.65, 95% CI: 0.52 to 0.82), compared to no effect on lower-specificity ALRI case definitions based on the caregiver reports (IRR 1.01; 95% CI: 0.91 to 1.12) or World Health Organization 'non-severe pneumonia' (IRR 0.96; 95% CI: 0.86 to 1.08).

AUTHORS' CONCLUSIONS

Implications for practice

Evidence to date is sufficient to recommend the use of zinc supplementation for children aged two to 59 months of age for the prevention of pneumonia. To conclude, our analysis supports the inclusion of preventive zinc supplementation in public health programmes to improve child health.

Implications for research

More well-designed, large-scale RCTs are needed to establish the benefit of zinc supplementation for the prevention of pneumonia among children aged two to 59 months. The development of effective and feasible interventions to improve the zinc status in children is essential. Enhancement of bioavailable zinc in foods by genetic engineering and plant breeding and period supplementation are other possible intervention strategies that should be evaluated.

Given the rising burden of child mortality due to respiratory infections, particularly pneumonia, and considering its decreasing impact with zinc supplementation, further reviews should be considered in the near future in which effectiveness of zinc supplementation should be assessed for severe pneumonia provided cases are well-defined by strict clinical criteria.

ACKNOWLEDGEMENTS

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REFERENCES

References to studies included in this review

Bhandari 2002a *{published data only}*

Bhandari N, Bahl R, Taneja S, Strand T, Mølbak K, Ulvik RJ, et al.Effect of routine zinc supplementation on pneumonia in children aged 6 months to 3 years: randomised controlled trial in an urban slum. *BMJ* 2002; **324**:1358.

Bhandari 2002b *{published data only}*

Bhandari N, Bahl R, Taneja S, Strand T, Mølbak K, Ulvik RJ, et al.Effect of routine zinc supplementation on pneumonia in children aged 6 months to 3 years: randomised controlled trial in an urban slum. *BMJ* 2002; **324**:1358.

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;**26**(366 (9500)):1862–7.

Brooks 2005 *{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**:999–1004.

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 diarrhoea and respiratory disease in South African children: a randomised controlled trial. *PLoS ONE* 2007;**2**(6):e541.

Penny 2004 *{published data only}*

Duggan C, Penny ME, Hibberd P, Gil A, Huapaya A, Cooper A, et al.Oligofructose-supplemented infant cereal: two randomised, blinded, community-based trials in Peruvian infants. *American Journal of Clinical Nutrition* 2003;**77**:937–42.

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

* 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.

Sazawal 1998a *{published data only}*

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

Sazawal S, Black RE, Bhan MK, Jalla S, Bhandari N, Sinha A, et al.Zinc supplementation reduces the incidence of persistent diarrhoea and dysentery among low socioeconomic children in India. *Journal of Nutrition* 1996; **126**:443–50.

* Sazawal S, Black RE, Jalla S, Mazumdar S, Sinha A, Bhan MK. Zinc supplementation reduces the incidence of acute lower respiratory infections in infant and preschool children: a double-blind controlled trial. *Pediatrics* 1998;**102**:1–5.

Sazawal 1998b *{published data only}*

Sazawal S, Black RE, Jalla S, Mazumdar S, Sinha A, Bhan MK. Zinc supplementation reduces the incidence of acute lower respiratory infections in infant and preschool children: a double-blind controlled trial. *Pediatrics* 1998;**102**:1–5.

References to studies excluded from this review

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**: 1059.

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 diarrhoea and acute lower respiratory infection in Bangladeshi infants. *Journal of Nutrition* 2003;**133**:4150-7.

Bates 1993 *{published data only}*

Bates CJ, Evans PH, Dardenne M, Prentice A, Lunn PG, Northrop-Clewes CA, et al.A trial of zinc supplementation in young rural Gambian children. *British Journal of Nutrition* 1993;**69**:243-55.

Castillo-Duran 1987 *{published data only}*

Castillo-Duran C, Heresi G, Fisberg M, Uauy R. Controlled trial of zinc supplementation during recovery from malnutrition:effects on growth and immune function. *American Journal of Clinical Nutrition* 1987;**45**:602-8.

Lind 2004 *{published data only}*

Lind T, Lonnerdal 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**:729-36.

Lira 1998 *{published data only}*

Lira PIC, 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**: 418–24.

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**: 693-700.

Ninh 1996 *{published data only}*
Ninh NX, Thissen JP, Collette L, Gerard G, Khoi HH, Ketelslegers JM. Zinc supplementation increases growth and circulating insulin-like growth factor I (IGF-I) in growth-retarded Vietnamese children. *American Journal of Clinical Nutrition* 1996;**63**:514-9.

Osendarp 2002 *{published data only}*
Osendarp SJM, Santosham M, Black RE, Wahed MA, Van Raaij MA, Fuchs GJ. Effect of zinc supplementation between 1 and 6 months of life on growth and morbidity of Bangladeshi infants in urban slums. *American Journal of Clinical Nutrition* 2002;**76**:1401–8.

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**:314–8.

Reul 1997 *{published data only}*
Ruel MT, Rivera JA, Santizo MC, Lonnerdal B, Brown KH. Impact of zinc supplementation on morbidity from diarrhoea and respiratory infections among rural Guatemalan children. *Pediatrics* 1997;**99**:808-13.

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

Rosado 1997 *{published data only}*
Rosado JL, Lopez P, Munoz 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**:13-9.

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**:529-34.

Sempértegui 1996 *{published data only}*
Sempértegui F, Estrella B, Correa E, Aguirre L, Saa B, Torres M, et al.Effects of short-term zinc supplementation on cellular immunity, respiratory symptoms,and growth of malnourished Equadorian children. *European Journal of Clinical Nutrition* 1996;**50**:42-6.

Sur 2003 *{published data only}*
Sur D, Gupta DN, Mondal SK, Ghosh S, Manna B, Rajendran K, et al.Impact of zinc supplementation on diarrhoeal morbidity and growth pattern of low birth weight infants in Kolkata, India: a randomised, double-blind, placebo-controlled, community-based study. *Pediatrics* 2003;**112**:1327–32.

Taneja 2009 *{published data only}*
Taneja S, Bhandari N, Rongsen-Chandola T, Mahalanabis D, Fontaine O, Bhan MK. Effectof zinc supplementation on morbidity and growth in hospital-born, low-birth-weight infants. *American Journal of Clinical Nutrition* 2009; **90**:385–91.

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 southernNepal: a community-based, cluster randomised, placebo controlled trial. *Lancet* 2007; **370**: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**:2021-6.

Additional references

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

Bahl 1998
Bahl R, Bhandari N, Hambidge KM, Bhan MK. Plasma zinc as a predictor of diarrhoeal & respiratory morbidity in children in an urban slum setting. *American Journal of Clinical Nutrition* 1998;**68**(Suppl):414–7.

Bhandari 1994
Bhandari N, Bhan MK, Sazawal S. Impact of massive dose of vitamin A given to preschool children with acute diarrhoea on subsequent respiratory and diarrhoeal morbidity. *BMJ* 1994;**309**:1404–7.

Bhutta 1999
Bhutta ZA, Black RE, Brown KN, Gardner JM, Gore S, Hidayat A, et al.Zinc Investigators Collaborative Group. Prevention of diarrhoea & pneumonia by zinc supplementation in children in developing countries: pooled analysis of randomised controlled trials. *Journal of Paediatrics* 1999;**135**:689–97.

Black 1998
Black RE. Therapeutic & preventive effects of zinc on serious childhood infectious diseases in developing countries. *American Journal of Clinical Nutrition* 1998;**68** (Suppl 2):476–9.

Boluyt 2008
Boluyt N, Tjosvold L, Lefebvre C, Klassen TP, Offringa M. Usefulness of systematic review search strategies in finding child health systematic reviews in MEDLINE. *Archives of Pediatric and Adolescent Medicine* 2008;**162**(2):111–6.

Bryce 2005
Bryce J, Boschi-Pinto C, Shibuya K, Black R. WHO estimates of the causes of death in children. *Lancet* 2005; **365**(9465):1147–52.

Fraker 1993
Fraker PG, King LE, Gravy BA. *The immunopathology of zinc deficiency in humans and rodents: a possible role for programmed cell death*. New York, NY: In: Klurfeld DM, editor. Nutrition and Immunology, 1993.

Hambidge 1999
Hambidge M, Krebs N. Zinc, diarrhoea, and pneumonia. *Journal of Pediatrics* 1999;**135**(6):661–4.

Higgins 2008
Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions. Version 5.0.0 [updated February 2008]. The Cochrane Collaboration, 2008. Available from www.cochrane-handbook.org . Chichester, UK: Wiley–Blackwell.

Ibs 2003
Ibs KH, Rink L. Zinc-altered immune function. *Journal of Nutrition* 2003;**133**(5 Suppl 1):1452–6.

Ploysangam 1997
Ploysangam Afalciglia GA, Brehm BJ. Effect of marginal zinc deficiency on human growth and development. *Journal of Tropical Pediatrics* 1997;**43**:192–8.

Ravaglia 2000
Ravaglia G, Forti P, Maioli F, Bastagli L, Facchini A, Mariani E, et al.Effect of micronutrient status on natural killer cell immune function in healthy free-living subjects aged ≥90 y. *American Journal of Clinical Nutrition* 2000;**71**(2):590–8.

RDA 1989
Subcommittee on the tenth edition of the RDAs of the Food and Nutrition Board. *Recommended Dietary Allowances*. 10th Edition. Washington DC: National Academy Press, 1989.

RevMan 2008
The Nordic Cochrane Centre: The Cochrane Collaboration. The Cochrane Collaboration. Review Manager (RevMan). 5.0. Copenhagen: The Nordic Cochrane Centre: The Cochrane Collaboration, 2008.

Roth 2010
Roth DE, Richard SA, Black RE. Zinc supplementation for the prevention of acute lower respiratory infection in children in developing countries: meta-analysis and meta-regression of randomized trials. *International Journal of Epidemiology* 2010;**39**:795–808.

Rudan 2008
Rudan I, Boschi-Pinto C, Biloglav Z, Mulholland K, Campbelle H. Epidemiology and etiology of childhood pneumonia. *Bulletin of the World Health Organization* 2008; **86**:408-16.

Sanstead 1995
Sanstead HH. Is zinc deficiency a public health problem?. *Nutrition* 1995;**11**:87–92.

Shankar 1998
Shankar AH, Prasad AS. Zinc and immune function: the biological basis of altered resistance to infection. *American Journal of Clinical Nutrition* 1998;**68**(Suppl 2):44763.

White 1986
White E. The effect of misclassification of disease status in follow-up studies: implications for selecting disease classification criteria. *American Journal of Epidemiology* 1986;**124**:816-25.

WHO 1990
World Health Organization. Acute respiratory infections in children: Case. Programme for the Control of Acute Respiratory Infections. World Health Organization. Geneva, 1990. [: WHO/ARI/90.5]

World Bank 2008
World Bank. Geographic classifications and data reported for geographic regions are for low-income and middle-income economies as defined by the World Bank. http://www.icce2010.org/docs/developingCountries.pdf (Accessed June 27, 2010) 2008.

Zinc Group 2000
Zinc Investigators Collaborative Group. Therapeutic effects of oral zinc in acute and persistent diarrhoea in children in developing countries: pooled analysis of randomised controlled trials. *American Journal of Clinical Nutrition* 2000;**72**:1516–22.

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Bhandari 2002a

Methods	RCT in which the children were individually randomised by a computer generated simple randomisation scheme in blocks of 8. Zinc or placebo bottles were labelled with a unique child identification number according to the randomisation scheme. 6 bottles, one for each month and 2 extra, for each child were produced and labelled before enrolment commenced. The supplies for each child were kept separately in labelled plastic bags. The zinc and placebo syrups were similar in appearance, taste, and packaging. Masking was maintained during analyses by coding the groups as A or B
Participants	The study included children aged 6 to 30 months. There were 1241 children in each group and after drop outs the number reduced to 1093 in the zinc and 1133 in the placebo group. Children were excluded if consent was refused, were likely to move out of the study area within the next four months, needed urgent admission to hospital on the enrolment day or had received a massive dose of vitamin A (100,000 IU for infants and 200,000 IU for older children) within the two months before enrolment
Interventions	Doses of elemental zinc were 10 mg for infants and 20 mg for older children (twice the recommended daily dosage) as zinc gluconate. Zinc or placebo was taken daily for four months. Both groups received single massive doses of vitamin A (100,000 IU for infants and 200,000 IU for older children) at enrolment. Immunisations and treatment for acute illnesses were provided as per World Health Organization (WHO) guidelines. Children with acute lower respiratory tract infections received cotrimoxazole. Amoxicillin was substituted if the child did not respond within three days. Children were sent to hospital if they had signs and symptoms that warranted referral according to WHO guidelines
Outcomes	Number of incidence of ALRI. ALRIs were defined by cough and fast-breathing or lower chest indrawing as assessed by the physician; other clinical signs were not taken into account. Fast breathing was defined as 2 counts of > 50 breaths/min for infants and > 40 breaths/min for older children
Notes	The study took place in the urban slum of Dakshinpuri in New Delhi, India. For episodes to be counted as individual, there had to be at least 14 intervening days. The children in the two groups were comparable for age, anthropometry, child feeding practices, morbidity in the previous 24 hours, socioeconomic characteristics and plasma zinc concentration

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "children were individually randomised by a simple randomisation scheme in blocks of eight. The randomisation scheme was generated by a statistician at Statens Serum Institut, not otherwise involved with this study, using the SAS soft-

Bhandari 2002a (*Continued*)

		ware" Comment: adequately done
Allocation concealment (selection bias)	Low risk	Quote: "zinc or placebo syrups were prepared and packaged in unbreakable bottles by GK Pharma ApS Koge, Denmark, who also labelled bottles with a unique child identification number according to the randomisation scheme. The supplies of each child were kept separately in labelled plastic bags. The Zinc and placebo were similar in appearances, taste and packaging. Masking was maintained during the analysis by coding the groups as A and B" Comment: adequately done
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "the supplies for each child were kept separately in labelled plastic bags". "Masking was maintained during analyses by coding the groups as A or B" Comment: participants and outcome assessors were blinded to the treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Exclusion (35%) with their reasons documented. Attrition was 12% in the zinc group and 8.7% in the control group
Selective reporting (reporting bias)	Low risk	The study appears to be free of selective reporting

Bhandari 2002b

Methods	Same as Bhandari 2002a
Participants	Same as Bhandari 2002a
Interventions	Same as Bhandari 2002a
Outcomes	Pneumonia was diagnosed either by a combination of cough with crepitations or bronchial breathing by auscultation or as an episode of acute lower respiratory tract infection associated with at least one of lower chest indrawing, convulsions, not able to drink or feed, extreme lethargy, restlessness or irritability, nasal flaring, or abnormal sleepiness
Notes	Same as Bhandari 2002a
Risk of bias	

Bhandari 2002b (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "children were individually randomised by a simple randomisation scheme in blocks of eight. the randomisation scheme was generated by a statistician at Statens Serum Institut, not otherwise involved with this study, using the SAS software" Comment: adequately done
Allocation concealment (selection bias)	Low risk	Quote: "zinc or placebo syrups were prepared and packaged in unbreakable bottles by GK Pharma ApS Koge, Denmark, who also labelled bottles with a unique child identification number according to the randomisation scheme. The supplies of each child were kept separately in labelled plastic bags. The Zinc and placebo were similar in appearances, taste and packaging. Masking was maintained during the analysis by coding the groups as A and B Comment: adequately done
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "the supplies for each child were kept separately in labelled plastic bags". "Masking was maintained during analyses by coding the groups as A or B" Comment: participants and outcome assessors were blinded to the treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Exclusion (35%) with their reasons documented. Attrition was 12% in the zinc group and 8.7% in the control group
Selective reporting (reporting bias)	Low risk	The study appears to be free of selective reporting

Bobat 2005

Methods	This was a randomised, double-blind controlled placebo controlled trial conducted in Grey's Hospital in Pietermaritxburg, South Africa. Baseline measurements of plasma HIV-1 viral load and the percentage of CD4T lymphocytes were established at two study visits before randomisation, and measurements were repeated 3, 6, and 9 months after the start of supplementation
Participants	96 children with HIV-1 infection between the ages of 6 months to 60 months, being cared for as outpatients at Grey's Hospital, and not receiving anti-retroviral therapy were recruited. Pneumonia was diagnosed by history and physical examination, including chest auscultation, and confirmed by chest radiograph
Interventions	Children either received 10 mg of elemental zinc as sulphate or placebo every day for 6 months. The child's parent or guardian was given 1 packet at the first 2 visits and two packets at each monthly follow-up visit thereafter, and was instructed on how to give the tablet

Bobat 2005 (*Continued*)

Outcomes	The primary outcome measure was plasma HIV-1 viral load
Notes	Outpatient management of children with HIV-1 infection is provided by a team of paediatricians, medical officers, and nurses who care for about 20 to 30 children per week. After starting zinc or placebo, children were assessed at Grey's Hospital every 2 weeks for the first month, monthly for 5 months, and a final visit 9 months after zinc or placebo supplementation started. Pneumonia was diagnosed by history and physical examination, including chest auscultation, and confirmed by chest radiograph

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Children were block-randomised in three age strata (6 to 23, 24 to 41, and 42 to 60 months)"; "Randomisation lists were computer generated at the WHO in a fixed block size of eight" Comment: adequately done
Allocation concealment (selection bias)	Unclear risk	Quote: "Tablets of zinc sulphate or placebo were produced by the same manufacturer (Nutriset, Bierne, France) and supplied in blister packets of 14 dispersible tablets"; "An investigator at Grey's Hospital assigned children to the treatment groups. The investigators were unaware of the treatment allocation until follow up was completed" Comment: insufficient information to permit judgement
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "double-blind"; tablets of zinc sulphate or placebo were produced by the same manufacturer (Nutriset, Bierne, France) and supplied in blister packets of 14 dispersible tablets." An investigator at Grey's Hospital assigned children to the treatment groups. The investigators were unaware of the treatment allocation until follow up was completed." Comment: participants and the care givers were blinded to the treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	9/105 (8.6%) were excluded. 2/46 (4.4%) and 9/50 (18%) did not complete trial in zinc and placebo groups, respectively. The reasons for lost to follow-up were given

Bobat 2005 (*Continued*)

Selective reporting (reporting bias)	Low risk	The study appears to be free of selective reporting

Brooks 2005

Methods	It is a randomised controlled trial in which random assignment to zinc or placebo was done with permuted blocks of variable length between 2 and 8. Placebo was designed to be identical to the zinc syrup in colour, odour, and taste
Participants	Children aged 60 days to 12 months at the time of enrolment and excluded those with known or suspected tuberculosis, chronic respiratory or congenital heart disease, or severe malnutrition requiring hospital admission. Pneumonia was diagnosed if crepitations were heard on inspiration with a respiratory rate greater than 50 breaths per minute; severe pneumonia was diagnosed if there was also chest indrawing, or at least one other danger sign. Children with wheezing or rhonchi with crepitations were also diagnosed with pneumonia. 809 children were randomly assigned to zinc and 812 to placebo. There were no significant differences between groups at baseline, except for a slightly higher proportion of boys in the zinc group. There was no difference between the groups in serum zinc values at baseline
Interventions	Zinc was given orally as a syrup (35 mg zinc acetate per 5 mL). The placebo was non-nutritious and vitamin-free. Compliance required intake of two teaspoons of syrup (10 mL). Children with pneumonia were treated with co-trimoxazole (10 mg/kg trimethoprim, twice daily for 5 days) for pneumonia. Children on antibiotics were assessed within 72 hours of starting treatment; those who did not improve (i.e., the respiratory rate did not change by more than 5 breaths/min from baseline) were switched to treatment with amoxicillin (40 mg/kg, three times daily for 5 days). If oral treatment failed, or if they had severe pneumonia, children were referred to hospital for parenteral treatment (ceftriaxone 75 mg/kg intramuscularly per day). Children with only expiratory wheezes or rhonchi were managed with salbutamol syrup (0·3 mg/kg, three times daily), or referred to hospital for danger signs
Outcomes	The main outcome was to find out the incidence of pneumonia in both groups. Other outcomes included frequency of other illnesses and mortality
Notes	The study was conducted at Kamalapur, southeastern Dhaka, Bangladesh. The medical officer diagnosed pneumonia if crepitations were heard on inspiration with a respiratory rate greater than 50 breaths per minute; severe pneumonia was diagnosed if there was also chest indrawing, or at least one other danger sign

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Random assignment to zinc or placebo was done with permuted blocks of variable length between two and eight" Comment: adequately done

Brooks 2005 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "ACME Laboratories (Dhaka) prepared, labelled and masked the identity of both preparations. Both placebo and treatment were designed to be identical in colour, odour, and taste"; "identity of both the preparations were masked" Comment: participants and care givers were blinded to the treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	The loss to follow up was 9.1% for the whole study
Selective reporting (reporting bias)	Low risk	The study appears to be free of selective reporting

Luabeya 2007

Methods	The study was conducted in northern KwaZulu-Natal Province, South Africa. Children were enrolled into the study by nurses at five government primary health care clinics	
Participants	Children eligible for study were 4 to 6 months old. Children were excluded from the study if they were: less than 60% of median weight-for-age using United States National Center for Health Statistics standards; had nutritional oedema; had received vitamin or micronutrient supplements in the previous month; had diarrhoea for more than seven days at the time of study enrolment; or were enrolled in another study of a clinical intervention. Confirmed pneumonia was defined as an elevated respiratory rate at rest measured by the fieldworker using WHO/UNICEF Integrated Management of Childhood Illness guidelines	
Interventions	The 3 treatment arms were: vitamin A alone; vitamin A plus zinc; and vitamin A, zinc and multiple micronutrients. All supplements were given daily at home from entry into the study until 24 months of age	
Outcomes	Diarrhoea, pneumonia	
Notes	Pneumonia by maternal report was considered to have occurred if there was a history of either fast breathing or chest in-drawing. Confirmed pneumonia was defined as an elevated respiratory rate at rest measured by the fieldworker using WHO/UNICEF Integrated Management of Childhood Illness guidelines	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Random sequence generation (selection bias)	Low risk	Quote: "An allocation list was prepared using computer-generated random numbers and a block size of six"; assignment to the three treatment arms was done separately for three cohorts of children stratified by HIV status of child and mother: HIV-infected children and mothers; HIV-uninfected children of HIV-infected mothers; and HIV-uninfected children of HIV-uninfected mothers Comment: adequately done
Allocation concealment (selection bias)	Low risk	Quote: "The manufacturer prepared numbered packs of tablets corresponding to the allocation list. Children enrolled in the study were assigned by a study physician to one of the three study cohorts after results of the HIV tests became available. The physician then allocated the next pack of tablets from the blocks assigned to that cohort to the participant" Comment: adequately done
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Investigators, study staff and participants were blind to the treatment assignments" Comment: participants, care givers and outcome assessors were blinded to the treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Exclusion (12.7%) and attrition (8.1% in vitamin A + zinc and 8.9% in vitamin A group) data were reported along with their reasons
Selective reporting (reporting bias)	Low risk	The study appears to be free of selective reporting

Penny 2004

Methods	This randomised, double-masked, placebo-controlled, community-based trial was carried out in Canto Grande, a shanty town on the outskirts of Lima, Peru. The study was carried out in 2 phases. During the first phase they evaluated the effect of zinc or multiple micronutrient supplementation on the recovery from persistent diarrhoea. During the second phase they assessed the effect of continued supplementation on morbidity from new infections during the following 6 months
Participants	412 children aged 6 to 36 months with diarrhoea for 14 days were randomly assigned, after being stratified for breastfeeding status, to receive 2 weeks of daily supplementation with 1 of 3 indistinguishable supplements: placebo; 20 mg Zn/d as zinc gluconate (Zn group); or 20 mg Zn/d as zinc gluconate plus a mixture of other micronutrients, i.e., vitamins and minerals (ZnVM group). A subset of children consisting of the first 246 children enrolled who intended to remain in the study area subsequently received the same assigned supplement at one-half the initial daily dose (10 mgZn/d) and continued under observation for a total of 6 months
Interventions	The supplements were supplied as individual doses of a dry micronutrient mixture with added sugar, colorings, and flavouring agents, which were dissolved in clean water in the participants' homes and provided as a liquid beverage under the supervision of study personnel on Monday through Friday and by parents or other caregivers during the weekends. There were two intervention arms, zinc plus vitamins and minerals who were given 10 mg of zinc supplementation along with different combinations of mineral and vitamins. Another interventional arm was given zinc 10 mg and the control group was not given any supplementation
Outcomes	Changes in plasma zinc, hematocrit, hemoglobin, plasma ferritin. Children with dysentery, diarrhoea and pneumonia
Notes	In this review, groups with zinc and placebo are included for analysis. Examination always included assessment of hydration status, measurement of rectal temperature and monitoring of respiratory rate, which was counted for 1 min and repeated if the rate was greater than age-specific upper limits (50/min for children aged 6 to 11 mo and 40/min for children aged 11 mo). Children were referred to the study physician for diagnosis and treatment when the fieldworker or caregiver was concerned about the child's health status or if the child had any one of several predefined signs of illness, including fever, presentation or worsening of cough with elevated respiratory rate (i.e., fieldworker-defined acute lower respiratory infection), persistent diarrhoea, diarrhoea with signs of dehydration, or vomiting or skin conditions requiring diagnosis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement

Penny 2004 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "double-masked" Comment: participants and treatment assigners were blinded to the treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	14/81 (17.3%) in zinc and 13/83 (15.7%) placebo groups lost to follow-up with reasons reported
Selective reporting (reporting bias)	Low risk	The study appears to be free of selective reporting

Sazawal 1998a

Methods	It is a double-blind RCT in which the loss of follow up was less than 2%
Participants	Children, 6 to 35 months of age, presenting to a community based clinic for acute diarrhoea and before enrolment, a parent of the child was given an explanation of the study and written informed consent was obtained. The baseline characteristics for the child-periods included in the analysis were similar between the two groups. The zinc group had 298 participants and the placebo one had 311
Interventions	Children were randomised to receive either zinc or placebo in a liquid preparation containing vitamins A (800 units), B1 (0.6 mg), B2 (0.5 mg), B6 (0.5 mg), D3 (100 IU) , and E (3 mg) and niacinamide (10 mg); the zinc preparation contained zinc gluconate (10 mg elemental zinc). The liquid preparation 5 ml was given daily for 6 months to all enrolled children; during diarrhoeal illness this was increased to 10 mL to provide for excess zinc losses
Outcomes	Incidence and prevalence of ALRI. ALRI was diagnosed as using WHO criteria for respiratory disease episodes based on fast breathing alone
Notes	The study was conducted in a low socioeconomic population of urban India

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation schedules with permuted blocks of 10 were used for children" Comment: adequately done
Allocation concealment (selection bias)	Low risk	Quote: "Supplements were prepared and coded by Sandoz India Ltd (Mumbai). Both formulation were liquid preparations, similar in colour and taste"

Sazawal 1998a (*Continued*)

		Comment: adequately done
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "double-blind"; "The Code, which was kept by WHO personnel, was not available to the investigator until the end of the study; "both formulation were liquid preparations, similar in colour and taste" Comment: participants, care givers and outcome assessors were blinded to the treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Exclusion and attrition rates with their reasons were not described in the study
Selective reporting (reporting bias)	Low risk	The study appears to be free of selective reporting

Sazawal 1998b

Methods	Same as Sazawal 1998a
Participants	Same as Sazawal 1998a
Interventions	Same as Sazawal 1998a
Outcomes	ALRI defined as child having cough and at least one assessment documenting: a) an elevated respiratory rate more than the age-specific value on both 1-minute estimations; and b) a recorded temperature of more than 101°F or lower chest indrawing (LCI)
Notes	Same as Sazawal 1998a

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Randomisations schedules with permuted blocks of 10 were used for children" Comment: adequately done
Allocation concealment (selection bias)	Low risk	Quote: "Supplements were prepared and coded by Sandoz India Ltd (Mumbai). Both formulation were liquid preparations, similar in colour and taste" Comment: adequately done
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "double-blind"; "The Code, which was kept by WHO personnel, was not available to the investigator until the end of the study" Comment: participants, care givers and outcome assessors

Sazawal 1998b (*Continued*)

		were blinded to the treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Exclusion and attrition rates with their reasons were not described in the study
Selective reporting (reporting bias)	Low risk	The study appears to be free of selective reporting

ALRI: acute lower respiratory infection
LCI: lower chest indrawing

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

Study	Reason for exclusion
Baqui 2002	Zinc supplementation was given for 2 weeks
Baqui 2003	ALRI was diagnosed if the child had reported symptoms of cough or difficulty in breathing with rapid breathing with or without chest indrawing
Bates 1993	Zinc supplement was delivered in a fortified drink form
Castillo-Duran 1987	Zinc supplementation period too short (60 d); did not study effects on diarrhoea or respiratory illnesses
Lind 2004	Considered 'cough and fever' as ALRI outcome
Lira 1998	Infants were recruited and supplemented from birth; short-course supplementation was provided; only cough was reported
Long 2006	Respiratory tract infection outcomes were defined as the occurrence of cough alone, cough and fever, or cough and rapid respiratory rate as reported by the mother
Ninh 1996	Respiratory outcome was cough and fever
Osendarp 2002	Infants were recruited and supplemented from 4 weeks of age
Rahman 2001	Supplementation was given for 2 weeks only
Reul 1997	Respiratory infections were defined as the presence of at least two of the following symptoms: runny nose, cough, wheezing, difficulty breathing, or fever
Richard 2006	An ALRI was parent defined by the presence of cough and rapid respiration
Rosado 1997	Their respiratory illness was presence of runny nose, common cold, sore throat or cough

(*Continued)*

Roy 1999	Zinc supplementation period was 2 weeks
Sempértegui 1996	Zinc supplementation period was 60 days
Sur 2003	Infants were recruited and supplemented from within 7 days of birth
Taneja 2009	Zinc supplementation was given to infants between 2 to 4 wk and 12 mo of age
Tielsch 2007	Trial was on children aged 1 to 35 months
Umeta 2000	Cough was only reported respiratory outcome

ALRI: acute lower respiratory infection
d: days
mo: months
wk: week

DATA AND ANALYSES

Comparison 1. Zinc supplementation vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pneumonia incidence	8	7850	Risk Ratio (Fixed, 95% CI)	0.87 [0.81, 0.94]
1.1 Diagnosis based on age-specific fast breathing with or without lower chest indrawing	4	3259	Risk Ratio (Fixed, 95% CI)	0.95 [0.86, 1.06]
1.2 Diagnosis based age-specific fast breathing AND confirmed by chest examination or chest radiograph	4	4591	Risk Ratio (Fixed, 95% CI)	0.79 [0.71, 0.88]
2 Pneumonia prevalence	1	3296	Risk Ratio (Fixed, 95% CI)	0.59 [0.35, 0.99]

Analysis 1.1. Comparison 1 Zinc supplementation vs placebo, Outcome 1 Pneumonia incidence.

Review: Zinc supplementation for the prevention of pneumonia in children aged 2 months to 59 months

Comparison: 1 Zinc supplementation vs placebo

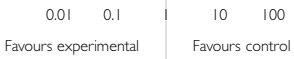
Outcome: 1 Pneumonia incidence

Study or subgroup	Zinc N	Placebo N	log [Risk Ratio] (SE)	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
1 Diagnosis based on age-specific fast breathing with or without lower chest indrawing						
Bhandari 2002a	621	621	-0.0202 (0.067)		32.7 %	0.98 [0.86, 1.12]
Luabeya 2007	113	113	0.191 (0.358)		1.1 %	1.21 [0.60, 2.44]
Penny 2004	80	79	-0.128 (0.131)		8.6 %	0.88 [0.68, 1.14]
Sazawal 1998a	816	816	-0.117 (0.137)		7.8 %	0.89 [0.68, 1.16]
Subtotal (95% CI)					**50.3 %**	**0.95 [0.86, 1.06]**
Heterogeneity: Chi² = 1.24, df = 3 (P = 0.74); I² =0.0%						
Test for overall effect: Z = 0.90 (P = 0.37)						
2 Diagnosis based age-specific fast breathing AND confirmed by chest examination or chest radiograph						
Bhandari 2002b	620	620	-0.301 (0.142)		7.3 %	0.74 [0.56, 0.98]
Bobat 2005	46	50	-0.288 (0.158)		5.9 %	0.75 [0.55, 1.02]

(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	Zinc N	Placebo N	log [Risk Ratio] (SE)	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
Brooks 2005	809	812	-0.1863 (0.0655)		34.3 %	0.83 [0.73, 0.94]
Sazawal 1998b	817	817	-0.5798 (0.2546)		2.3 %	0.56 [0.34, 0.92]
Subtotal (95% CI)					**49.7 %**	**0.79 [0.71, 0.88]**
Heterogeneity: Chi^2 = 2.71, df = 3 (P = 0.44); I^2 =0.0%						
Test for overall effect: Z = 4.29 (P = 0.000018)						
Total (95% CI)					**100.0 %**	**0.87 [0.81, 0.94]**
Heterogeneity: Chi^2 = 9.74, df = 7 (P = 0.20); I^2 =28%						
Test for overall effect: Z = 3.66 (P = 0.00025)						
Test for subgroup differences: Chi^2 = 5.78, df = 1 (P = 0.02), I^2 =83%						



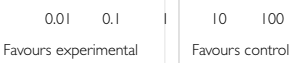
Analysis 1.2. Comparison 1 Zinc supplementation vs placebo, Outcome 2 Pneumonia prevalence.

Review: Zinc supplementation for the prevention of pneumonia in children aged 2 months to 59 months

Comparison: 1 Zinc supplementation vs placebo

Outcome: 2 Pneumonia prevalence

Study or subgroup	Zinc N	Placebo N	log [Risk Ratio] (SE)	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
Sazawal 1998a	1633	1663	-0.528 (0.266)		100.0 %	0.59 [0.35, 0.99]
Total (95% CI)					**100.0 %**	**0.59 [0.35, 0.99]**
Heterogeneity: not applicable						
Test for overall effect: Z = 1.98 (P = 0.047)						
Test for subgroup differences: Not applicable						



ADDITIONAL TABLES

Table 1. Zinc supplement schedule and duration

Study	Supplement		Schedule	Duration	Surveillance
	Zinc	Control			
Bhandari 2002a Bhandari 2002b	**Zinc gluconate** 10 mg	Both groups vitamin A	Daily	4 months	Once weekly
Bobat 2005	**Zinc sulphate** 10 mg	Placebo	Daily	6 months	Every 2 weeks
Brooks 2005	**Zinc acetate** 35 mg to infants 70 mg to children > 12 months	Placebo	Weekly	12 months	Once weekly
Luabeya 2007	**Zinc gluconate** 10 mg	Both groups vitamin A	Daily	(Continued until 24 months of age)	Once weekly
Penny 2004	**Zinc gluconate** 10 mg	Placebo	Daily	6 months	Once weekly
Sazawal 1998a Sazawal 1998b	**Zinc gluconate** 10 mg	Placebo	Daily	4 months	Every 5th day

APPENDICES

Appendix 1. Embase.com search strategy

14. #5 AND #9 AND #13
13. #10 OR #11 OR #12
12. child*:ab,ti OR schoolchild*:ab,ti OR preschool*:ab,ti OR kid:ab,ti OR kids:ab,ti OR toddler*:ab,ti OR pediatric*:ab,ti OR paediatric*:ab,ti OR kindergar*:ab,ti OR (school* NEAR/2 (nursery OR primary OR elementary OR age*)):ab,ti
11. infant*:ab,ti OR infancy:ab,ti OR newborn*:ab,ti OR baby*:ab,ti OR babies:ab,ti OR neonat*:ab,ti OR preterm*:ab,ti OR prematur*:ab,ti
10. 'infant'/exp OR 'child'/exp OR 'pediatrics'/exp OR 'school'/exp
9. #6 OR #7 OR #8
8. zinc:ab,ti OR zn:ab,ti
7. 'gluconate zinc'/exp
6. 'zinc'/exp
5. #1 OR #2 OR #3 OR #4
4. 'lower respiratory tract infection':ab,ti OR 'lower respiratory tract infections':ab,ti OR 'lower respiratory infection':ab,ti OR 'lower respiratory infections':ab,ti OR lrti:ab,ti
3. 'lower respiratory tract infection'/de

2. pneumon*:ab,ti
1. 'pneumonia'/exp

Appendix 2. LILACS search strategy

pneumon$ or namonia or pulmonia or neumonia [Words] and zinc$ or cinc [Words]
"PNEUMONIA" [Subject descriptor] and "ZINC" [Subject descriptor]

F E E D B A C K

Feedback comment by Joseph L. Mathew, 10 February 2011

Summary

Please note the following feedback.
1. The forest plot in Analysis 1.1 shows that participants in the trial by Bhandari et al, have been split to present two different outcomes. Half the participants in each arm are included for the outcome "Diagnosis based on age-specific fast breathing with or without lower chest indrawing" and half for the outcome "Diagnosis based age-specific fast breathing AND confirmed by chest examination or chest radiograph". Both outcomes have been presented as subgroup analysis in the same forest plot; although the trial report mentions that both outcomes were evaluated in all participants. Please confirm whether the procedure adopted in this review is standard practice; and the purpose of doing this.
2. A similar adjustment seems to have been made with the participants in the trial by Sazawal et al.
3. The reference section mentions three citations under Sazawal 1998a; and one under Sazawal 1998b. The third citation in Sazawal 1998a is the same as Sazawal 1998b. Further, none of the citations reports 3300 participants in the trial; whereas this is the number included in the meta-analysis. Sazawal's 1995 publication in the New England Journal of Medicine mention s937 participants; while the 1998 publication in Pediatrics reported 609 participants. Please confirm the basis for using the numbers in the meta-analysis.
4. The meta-analysis has pooled data from children with HIV infection, along with otherwise healthy children. While it seems reasonable to pool children with unknown HIV status with otherwise healthy children, it would be better to analyse HIV infected children separately since pneumonia in immuno-compromised children could be quite different from otherwise healthy children.
Submitter agrees with default conflict of interest statement:
I certify that I have no affiliations with or involvement in any organization or entity with a financial interest in the subject matter of my feedback.

Reply

We thank Dr Mathew for these comments and will take them into account in our update planned for this year i.e. 2012.

Contributors

Joseph L. Mathew

WHAT'S NEW

Last assessed as up-to-date: 26 January 2010.

Date	Event	Description
10 February 2012	Amended	Authors replied to Feedback comment

HISTORY

Protocol first published: Issue 2, 2006

Review first published: Issue 12, 2010

Date	Event	Description
8 August 2011	Feedback has been incorporated	Feedback added to review.

CONTRIBUTIONS OF AUTHORS

Zohra S Lassi (ZSL) entered the data, created the comparisons, did the analysis and wrote the text of the review under the guidance of Dr Zulfiqar A Bhutta (ZAB).

The draft protocol was written by Dr Batool A Haider (BAH) who also designed the eligibility and the data extraction forms.

BAH also took part in the initial stages of the review and assisted in data extraction.

DECLARATIONS OF INTEREST

Dr Bhutta has been involved in previous studies of zinc supplementation in diarrhoea and was part of the Zinc Investigators Collaborative Group that produced the initial meta-analysis of the preventive and therapeutic benefits of zinc. However, Dr Bhutta has not been involved in any studies of zinc supplementation in acute respiratory infections.

SOURCES OF SUPPORT

Internal sources

- The Aga Khan University, Pakistan.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Gluconates [administration & dosage]; Pneumonia [epidemiology; *prevention & control]; Randomized Controlled Trials as Topic; Zinc Acetate [administration & dosage]; Zinc Compounds [*administration & dosage]; Zinc Sulfate [administration & dosage]

MeSH check words

Child, Preschool; Humans; Infant