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Zinc supplementation as an adjunct to antibiotics in the treatment of pneumonia in children 2 to 59 months of age

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[Intervention Review]

Zinc supplementation as an adjunct to antibiotics in the treatment of pneumonia in children 2 to 59 months of age

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ABSTRACT

Background

Diarrhoeal disorders and acute respiratory infections (ARIs), especially pneumonia, are the most common causes of death in low-income countries. Studies evaluating the impact of zinc supplementation as an adjunct in the management of pneumonia are limited and have shown variable results.

Objectives

To evaluate zinc supplementation, as an adjunct to antibiotics, in the treatment (clinical recovery) of pneumonia in children aged two to 59 months.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2011, Issue 1), which contains the Cochrane Acute Respiratory Infections (ARI) Group's and the Cochrane Infectious Diseases Group's Specialised Registers, MEDLINE (1950 to March week 2, 2011), EMBASE (1974 to March 2011), CINAHL (1981 to March 2011), LILACS (1985 to March 2011), AMED (1985 to March 2011), CAB Abstracts (1910 to March 2011) and Web of Science (2000 to March 2011).

Selection criteria

Randomised control trials (RCTs) evaluating supplementation of zinc as an adjunct to antibiotics for pneumonia in children aged two to 59 months.

Data collection and analysis

Two review authors independently assessed trial eligibility and screened all available titles and abstracts for inclusion. If the relevance could not be ascertained by screening the title and abstract, we retrieved and reviewed the full text of the article.

Main results

We included four trials in which 3267 children aged two to 35 months participated. Analysis showed that zinc supplementation in addition to standard antibiotic therapy in children with severe and non-severe pneumonia failed to show a statistically significant effect on time-to-clinical recovery (hazard ratio 1.02; 95% confidence interval (CI) 0.93 to 1.11). Similary, zinc supplementation in children with severe pneumonia, as an adjunct to standard antibiotic therapy, did not show a statistically significant effect on time-to-recovery from tachypnoea (respiratory rate > 50 breaths per minute) (hazard ratio 1.13; 95% CI 0.82 to 1.57) and time-to-recovery from chest in-drawing (hazard ratio 1.08; 95% CI 0.88 to 1.31) as compared to the control group. Zinc supplementation in children with severe pneumonia also showed a non-significant effect on time-to-hospital discharge as compared to the control (hazard ratio 1.04; 95% CI 0.89 to 1.22).

Authors' conclusions

Evidence provided in this review is insufficient to recommend the use of zinc as an adjunct to standard antibiotic therapy for pneumonia in children aged two to 35 months.

PLAIN LANGUAGE SUMMARY

Zinc supplementation as an adjunct to antibiotics in the treatment of pneumonia in children two to 59 months of age

Gastroenteritis and respiratory infections (particularly pneumonia) are the two most common causes of death in low-income countries. Preventive zinc supplementation may correct any deficiency leading to immunodeficiency and indeed some evidence suggests that preventive zinc supplementation may reduce child mortality and morbidity from infectious diseases, particularly pneumonia. Pnumeonia is the inflammation of the lungs and is caused by viruses, bacteria or other microorganisms. Studies evaluating the impact of zinc supplementation as an adjunct in the management of pneumonia are limited and have shown variable results. The aim of this review is to evaluate the role of zinc supplementation, as an adjunct to antibiotics, in the treatment of pneumonia in children aged two months to 59 months.

The review authors found four randomised control trials of adequate quality evaluating the impact of zinc supplementation as an adjunct to antibiotics for pneumonia in children. These studies were conducted in Bangladesh, Nepal and India, in which 3267 children aged two to 35 months were randomly assigned to receive zinc or placebo. No serious adverse events were observed. Analysis did not show any significant effect on the clinical recovery of patients in terms of time-to-recovery from tachypnoea (respiratory rate > 50 breaths per minute) and time-to-recovery from chest indrawing. It also showed non-significant effects of the intervention on the time-to-hospital discharge. Evidence provided in this review is insufficient to recommend use of zinc as an adjunct to standard antibiotic therapy for pneumonia in children aged two to 35 months.

BACKGROUND

Description of the condition

Acute respiratory infections (ARIs), especially pneumonia and diarrhoeal disorders are the two most common causes of death in low-income countries (Bryce 2005; Rudan 2008). The annual estimated incidence of pneumonia is 151 million new cases per year (Rudan 2004), of which two million die annually. It is the largest killer, accounting for 19% of all child deaths in low-income countries (Bryce 2005; Rudan 2008), and with the inclusion of neonatal pneumonia, recent estimates indicate that it accounts for 28% to 34% of deaths globally in children below five years of age (Wardlaw 2006). Interventions that affect mortality due to pneumonia are thus of great importance in any effort to improve childhood survival.

Description of the intervention

Zinc is a trace element and an essential mineral which is present in all tissues, fluids and secretions in the body. It is critical to cellular metabolism, physical growth, immunocompetence, reproductive

functions, integrity of intestinal mucosa and neuro-behavioural development (Aggett 1995; Bhatangar 2004). Zinc deficiency is associated with decreased immunocompetence (Golden 1995; Sazawal 1997; Shankar 1998), high rates of serious infectious disease, such as skin infections, diarrhoea, respiratory infections, malaria (Black 2001; Lopez 1989; Murray 1996) and delayed wound healing (Bahl 1998; Black 1998; Prasad 1985). Zinc deficiency may be an underlying cause of increased infant mortality in malnourished children in low-income countries (Castillo-Duran 2001).

The daily requirement of zinc varies with age, with the recommended dietary allowance (RDA) for infants and children aged one to five years being 5 mg and 10 mg per day, respectively (RDA 1989). Manifestations of zinc deficiency also vary with age (Hambidge 1986). Diarrhoea, neuro-behavioural problems and learning impairment are prominent symptoms of zinc deficiency in infancy (Penland 2000) and skin problems, hair loss, growth retardation and recurrent infections are common findings in school-aged children (Van Wouwe 1989). Zinc deficiency has at least five general causes: inadequate intake from foods (particularly from animal sources), increased requirements, malabsorption, increased losses during recurrent diarrhoeal illnesses (Bhutta 1999; Black 1998) and impaired metabolic utilisation (Solomons 1984).

How the intervention might work

Zinc plays an important role in maintaining a normal immune function and participates in all major biochemical pathways. It plays multiple roles in the perpetuation of genetic material and cellular division. Studies have suggested that zinc deficiency impairs immunocompetence with reduced cell-mediated immune responses, decreased T-lymphocytes, abnormal T-helper and/or suppressor functions, impaired macrophage function, 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). Preventive zinc supplementation may correct any deficiency leading to immunodeficiency and indeed some evidence suggests that preventive zinc supplementation may reduce child mortality and morbidity from infectious diseases, particularly diarrhoea and pneumonia (Bhutta 1999; Lassi 2010). Zinc supplementation during respiratory infections could work through similar pathways to reduce morbidity and expedite recovery. Because zinc is not stored in the body, adequate zinc supplementation is required.

Why it is important to do this review

Current evidence on zinc supplementation as a preventative measure has shown beneficial effects by reducing the incidence of diarrhoea and pneumonia in children (Aggarwal 2007; Bhutta 1999; Bhutta 2008; Brooks 2005). The preventative aspect of zinc in reducing pneumonia has also been evaluated in another Cochrane review (Lassi 2010). Established evidence of the benefit of zinc supplementation in the management of children with diarrhoea, along with oral rehydration solution, is available and has formed the basis of the Joint WHO/UNICEF recommendation (WHO 2004). Studies evaluating the impact of zinc supplementation as an adjunct in the management of pneumonia are limited and have shown variable results. The Brooks 2004 trial shows a reduction in the duration of pneumonia in young children when zinc is administered along with an antimicrobial therapy. However, the Bose 2006 trial failed to show a benefit of zinc supplementation in the management of pneumonia. To reduce deaths due to pneumonia, it is important to evaluate the role of zinc supplementation as an adjunct to antibiotics, in the treatment of pneumonia in children aged two months to 59 months.

OBJECTIVES

To evaluate the role of zinc supplementation, as an adjunct to antibiotics, in the treatment (clinical recovery) of pneumonia in children aged two months to 59 months.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs), irrespective of publication status and language, evaluating supplementation of zinc as an adjunct to antibiotics for pneumonia in children aged two months to 59 months. We included both individual and cluster-RCTs. We excluded non-RCTs (quasi-RCTs).

Types of participants

We included children aged two months to 59 months suffering from pneumonia. We considered studies of children suffering from an episode of pneumonia and diagnosed in the following ways.

1. Reported cough or difficulty breathing with a respiratory rate above the WHO defined age-specific values (respiratory rate $\geq$ 50 breaths per minute for children aged two to 11 months, or

respiratory rate ≧ 40 breaths per minute for children aged 12 to 59 months) (WHO 1990); and either documented fever of > 101^{o}F or chest indrawing.

2. A diagnosis of pneumonia based on chest examination by a physician.

3. A diagnosis of pneumonia based on a chest radiograph.

We excluded studies including children suffering from other debilitating diseases.

Types of interventions

Oral supplements containing zinc versus oral supplements without zinc or a placebo. All participants should receive standard antibiotic therapy. Supplementation of zinc should be the only difference between the intervention and control group.

Types of outcome measures

Primary outcomes

Time-to-clinical recovery* (clinical recovery defined as recovery from tachypnoea, fever and chest indrawing for at least 12 to 24 hours).

*Clinical recovery as a composite outcome i.e. resolution of all three symptoms. We also analysed data for the resolution of individual symptoms.

Secondary outcomes

1. Time-to-hospital discharge (from randomisation to discharge).
2. Re-admission/re-diagnosis with pneumonia within three months, starting from the last day of current episode.
3. Mortality within 10 days of randomisation.
4. Mortality within one month of randomisation.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2011, Issue 1) www.thecochranelibrary.com (accessed 24 March 2011), which contains the Cochrane Acute Respiratory Infections (ARI) Group's and the Cochrane Infectious Diseases Group's Specialised Registers, MEDLINE (1950 to March week 2, 2011), EMBASE (1974 to March 2011), CINAHL (1981 to March 2011), LILACS (1985 to March 2011), AMED (1985 to March 2011), CAB abstracts (1910 to March 2011) and Web of Science (2000 to March 2011).

See Appendix 1 for the MEDLINE search strategy. We did not use a filter to identify randomised trials as there were too few results. We adapted the search strategy to search CENTRAL (see Appendix 2), EMBASE (see Appendix 3), CINAHL (see Appendix 4), LILACS (see Appendix 5), AMED (see Appendix 6), CAB abstracts (see Appendix 7) and Web of Science (see Appendix 8).

Searching other resources

We imposed no language or publication restrictions. We also searched the related conference proceedings for relevant abstracts. We contacted organisations, 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 (BAH, ZSL) independently assessed trial eligibility and screened all available titles and abstracts for inclusion. We retrieved and reviewed the full text of the article if we could not ascertain the relevance of the article by screening the title and abstract. We independently assessed the eligibility by filling out eligibility forms designed in accordance with the specified inclusion criteria. We resolved any disagreements by discussion or, if required, we consulted a third review author (ZAB). We displayed studies excluded from the review in the Characteristics of excluded studies table along with the reason(s) for exclusion.

Data extraction and management

Two review authors (BAH, ZSL) piloted, tested and subsequently used a data extraction form to collect data. Both review authors then compared the extracted data to enable them to correct errors and resolve any disagreements through discussion. We used the Review Manager (RevMan) software (RevMan 2011) for data entry.

We attempted to contact the trial authors to provide further details when information regarding any of the above was unclear.

Assessment of risk of bias in included studies

Two review authors (BAH, ZSL) independently assessed the methodological quality of the selected trials by using methodological quality assessment forms. We undertook quality assessment of the trials using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Any disagreements between the two review authors were resolved by discussion.

1. Sequence generation (selection bias)

For each included study we described the methods 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:

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

2. Allocation concealment (selection bias)

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

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

3. Blinding (performance bias)

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

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel; and
- low, high or unclear risk of bias for outcome assessors.

4. Incomplete outcome data (attrition bias through withdrawals, dropouts, protocol deviations)

For each included study, and for each outcome or class of outcomes, we described 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:

- low risk of bias;
- high risk of bias; or
- unclear risk of bias.

5. Free of 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:

- low risk of bias (where it is clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review have been reported); or
- high risk of bias (where not all the study's prespecified outcomes have been reported; one or more reported primary outcomes were not prespecified; 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 risk of bias.

6. Free of other sources of bias

For each included study we described any important concerns we had about other possible sources of bias. We assessed whether each study had:

- low risk of bias;
- high risk of bias; or
- unclear risk of bias.

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 2011). With reference to (1) to (6) above, we assessed the likely magnitude and direction of the bias and whether we considered it 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 time-to-event data, we presented results as summary hazard ratios (HR) with 95% confidence intervals (CIs) such that a HR >1 reflected faster recovery times in the treatment group as compared to the control group. None of the included studies presented data for dichotomous outcomes of re-admission/re-diagnosis with pneumonia and mortality outcomes. However, for future updates, for these listed outcomes, we will present results as summary risk ratios (RR) with 95% CIs. We did not include any continuous outcome in the review.

Unit of analysis issues

All included studies were individual randomised trials with no issues of unit of analysis.

Dealing with missing data

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 and all participants were analysed in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial was the number randomised minus any participants whose outcomes are known to be missing

Assessment of heterogeneity

We measured heterogeneity among trials by calculating the I^2 statistic, Chi^2 statistics and by visual inspection of the forest plots. If I^2 statistic exceeded 50%, Chi^2 P value is less than 0.1, and visual inspection of the forest plots is indicative, we considered heterogeneity to be substantial. We did not find substantial heterogeneity in any of the outcomes; therefore, did not undertake any subgroup analyses. However, we evaluated the effect of intervention in subgroups defined on the basis of the severity of disease.

Assessment of reporting biases

For outcomes with 10 or more studies in the meta-analysis, we planned to investigate reporting biases (such as publication bias) by using funnel plots. We proposed assessment by evaluating funnel plot asymmetry visually and formal tests for funnel plot asymmetry; test by Egger 1997 for continuous outcomes and the test by Harbord 2006 for dichotomous outcomes measuring effects as odds ratios. However, we did not evaluate for these biases due to the small number of studies included in the review.

Data synthesis

We carried out statistical analysis using the Review Manager software (RevMan 2011). In the absence of significant heterogeneity, where trials were sufficiently similar, we used a fixed-effect meta-analysis model for combining data. If we found heterogeneity, we explored this by a subgroup analyses followed by a random-effects model, if required.

Subgroup analysis and investigation of heterogeneity

We planned to carry out following subgroup analyses for the investigation of heterogeneity.

- Different doses of zinc used.
- Different durations of zinc supplementation.
- Baseline zinc deficiency in the population.
- Severity of disease (defined by the presence of either chest in-drawing or at least one other critical sign, such as central cyanosis, excessive sleepiness, inability to drink, convulsions).
- Wheezing at the time of enrolment.
- Co-interventions.

Sensitivity analysis

We planned to carry out sensitivity analysis to explore the effect of trial quality by excluding high risk trials in which method of randomisation and allocation concealment or blinding was not achieved or trials with a large loss to follow up (> 20%). However, we did not do a sensitivity analysis as only Bansal 2011, which did not contribute any data to the analyses, had inadequate allocation concealment.

RESULTS

Description of studies

Results of the search

We retrieved 381 records from electronic searches up to March 2011. We only retrieved 12 records for full text appraisal and four met our eligibility criteria.

Included studies

We included four trials in this review with a total of 3267 participants.

The Brooks 2004 RCT included 270 children aged between two and 23 months, diagnosed with severe pneumonia. The trial was conducted in a rural hospital in Bangladesh. Children with concurrent diarrhoea or severe malnutrition were excluded. The participants were randomised to receive 20 mg elemental zinc per day (10 mg zinc acetate per 5 mL syrup) or placebo until they were discharged from the hospital. Both groups were similar at baseline in terms of demographic and social characteristics and baseline serum zinc levels. The mean serum zinc level at baseline in both groups was 10.1 µmol/L. The intervention group had a reduced duration of severe pneumonia and overall length of hospital stay.

The Bose 2006 study conducted in a large referral hospital in Vellore, India was a randomised trial of 300 children aged between two and 23 months with severe pneumonia. The children were randomised to receive either 20 mg of zinc sulphate daily or placebo until discharge or a maximum of 15 days (whichever came first). Both groups were similar in demographic and social

characteristics. The baseline mean serum zinc levels in the intervention and placebo groups were 11.0 µmol/L and 10.9 µmol/L, respectively. There were no clinically or statistically significant differences in the duration of tachypnoea, hypoxia, chest indrawing, inability to feed, lethargy, severe illness or hospitalisations. Zinc supplementation was associated with a significantly longer duration of pneumonia in the hot season (summer).

Another study was conducted in Bhaktapur, Nepal in children aged two to 35 months with cough or difficulty in breathing (Valentiner-Branth 2010). Children with severe or non-severe pneumonia (according to the WHO definition) were randomised to either zinc (10 mg for children aged between two and 11 months, 20 mg for children aged 12 months) or placebo daily for 14 days. There was no difference in time to recovery between the zinc and placebo groups for non-severe or severe pneumonia.

Bansal 2011 was a prospective, randomised, triple-blind, placebo-controlled trial, which included children aged two to 24 months, presenting in the paediatric emergency department of a teaching referral hospital in north India with severe LRTI (according to the WHO definition). These children were randomised to either zinc or a placebo group. The zinc group received 20 mg of elemental zinc per day (5 ml syrup per day) as a single daily dose after meals for five days. Zinc supplementation failed to reduce recovery time and duration of hospital stay in children with acute LRTI.

The outcome of clinical recovery was defined differently in the above included studies. See Characteristics of included studies Table 1 and Table 2 for detailed descriptions of study participants, interventions, outcome definitions and median recovery times.

There are four ongoing trials; the details of methods, participants, interventions and outcomes are available in the Characteristics of ongoing studies table.

Excluded studies

Five studies (Chang 2006; Khaled 2001; Mahalanabis 2002; Mahalanabis 2004; Shah 2011) were excluded as they did not satisfy the inclusion criteria of the review. The studies by Mahalanabis 2002 and Chang 2006 included participants up to 15 years of age and 11 years respectively, and did not report separate outcomes for children under five years of age. In addition, Mahalanabis 2002 evaluated the effect of zinc on measles-related pneumonia and all participants received vitamin A in addition to standard antimicrobial therapy. The trial conducted by Khaled 2001 was published only as an abstract and contained insufficient information. The study by Mahalanabis 2004 in India was a factorial design with vitamin A. The trial reported only sex-based estimates and was therefore excluded. The trial by Shah 2011 included children between six to 59 months of age who were assigned to the zinc or placebo group and the incidence of acute LRTIs was measured.

Risk of bias in included studies

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

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

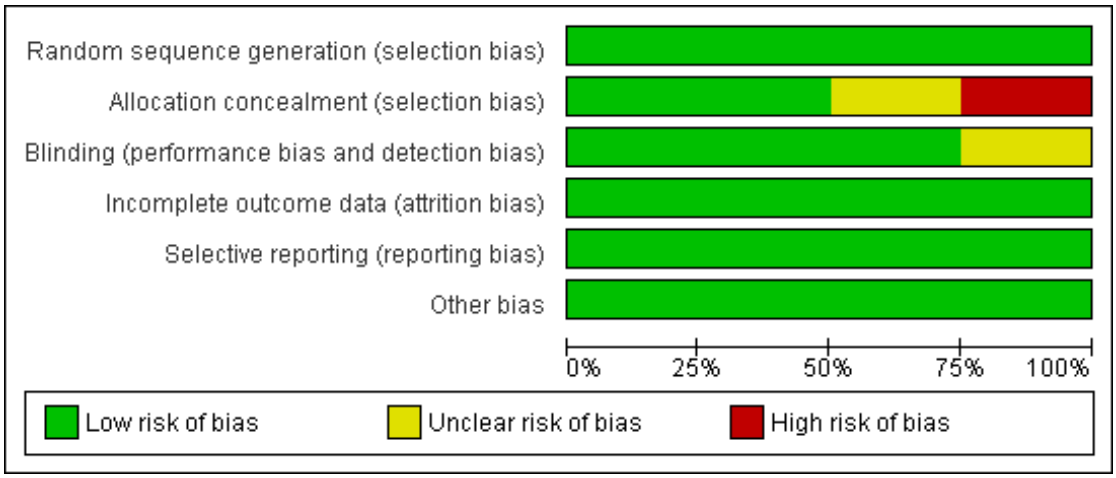
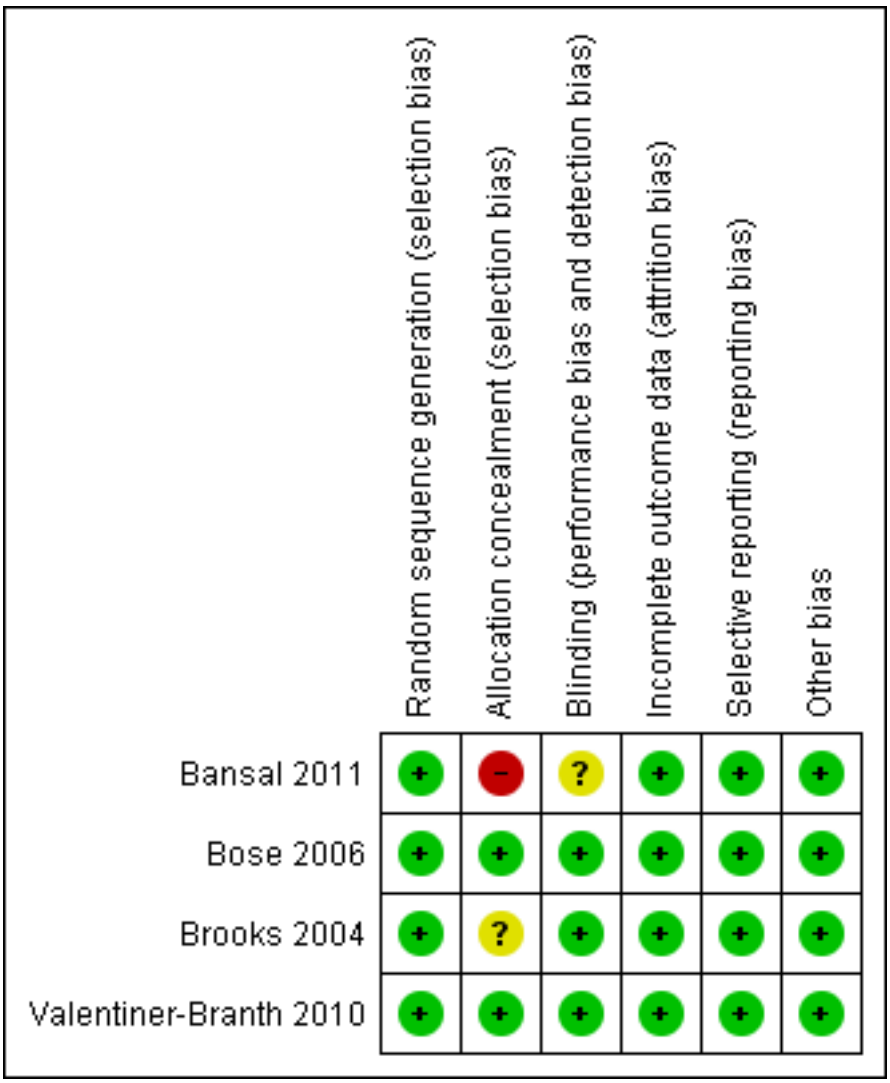


Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Allocation

The Bose 2006 and Valentiner-Branth 2010 trials had adequate sequence generation with adequate allocation concealment. However, Bansal 2011 used a random number table for sequence generation but allocation concealment was known to the hospital pharmacist who dispensed the drugs in identical looking serially numbered plastic bottles. The Brooks 2004 study does not clearly state any method for allocation concealment.

Blinding

Participants, study personnel and outcome assessors were blinded in two trials (Bose 2006; Valentiner-Branth 2010). Participants were blinded in Brooks 2004 but the blinding of study personnel and outcome assessors is unclear from the text. Details on blinding were not given in Bansal 2011. However, they did mention that the study was a triple-blind study.

Incomplete outcome data

Attritions and exclusions were 1.1%, 1.3%, 1.8% and 2.6% in Valentiner-Branth 2010, Bose 2006, Bansal 2011 and Brooks

2004, respectively.

Selective reporting

All outcomes in the included studies have been measured and reported as predefined in the methodology of the study.

Other potential sources of bias

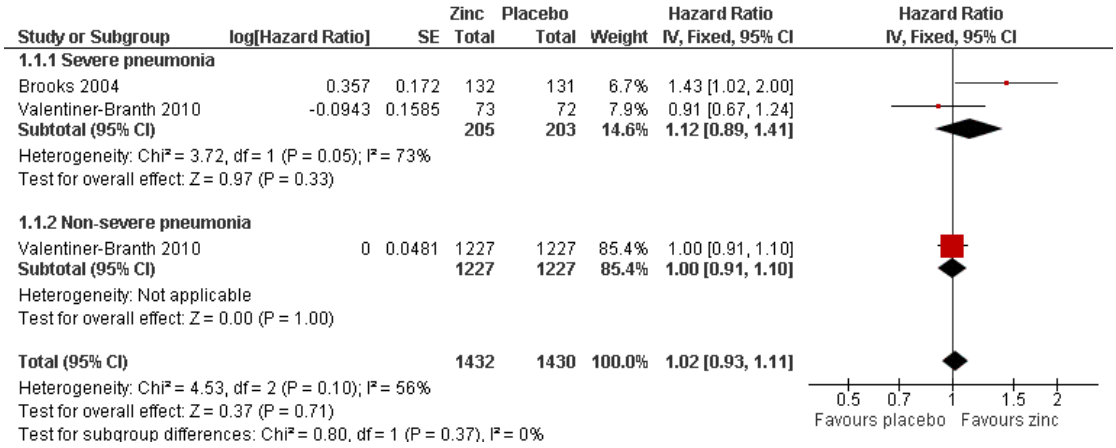
All included studies appears to be free of other sources of bias.

Effects of interventions

Primary outcome measure

Zinc supplementation in addition to standard antibiotic therapy in children with severe and non-severe pneumonia did not show any statistically significant effect on time-to-clinical recovery as compared to the control (hazard ratio 1.02; 95% CI 0.93 to 1.11, fixed-effect model (two studies, N = 2862)) (Analysis 1.1; Figure 3). Overall results were not heterogenous (I^2 = 56%, P value = 0.10). Zinc supplementation as an adjunct to standard antibiotic therapy failed to show a statistically significant effect on the outcome among children with severe pneumonia (hazard ratio 1.12; 95% CI 0.89 to 1.41, fixed-effect model (two studies, N = 408)) (Analysis 1.1; Figure 3) and non-severe pneumonia (hazard ratio 1.00; 95% CI 0.91 to 1.10 (one study, N = 2454)) (Analysis 1.1; Figure 3).

Figure 3. Forest plot of comparison: 1 Zinc supplementation versus placebo, outcome: 1.1 Time-to-clinical recovery.



In children with severe pneumonia, zinc supplementation as an adjunct to standard antibiotic therapy failed to show a statistically significant effect on time-to-recovery from tachypnoea (respiratory rate > 50 breaths per minute) as compared to the control group (hazard ratio 1.13; 95% CI 0.82 to 1.57, random-effect model (two studies, N = 562)) (Analysis 1.2; Figure 4). Overall, the results were heterogeneous (I^2 statistic = 69%, P value = 0.07). The effect of adjuvant zinc supplementation on time-to-recovery from chest indrawing was not statistically significant as compared to control (hazard ratio 1.08; 95% CI 0.88 to 1.31, fixed-effect (two studies, N = 562)) (I^2 = 57%, P value = 0.13). (Analysis 1.3; Figure 5).

Figure 4. Forest plot of comparison: 1 Zinc supplementation versus placebo, outcome: 1.2 Time-to-recovery from tachypnoea (respiratory rate > 50 breaths per min).

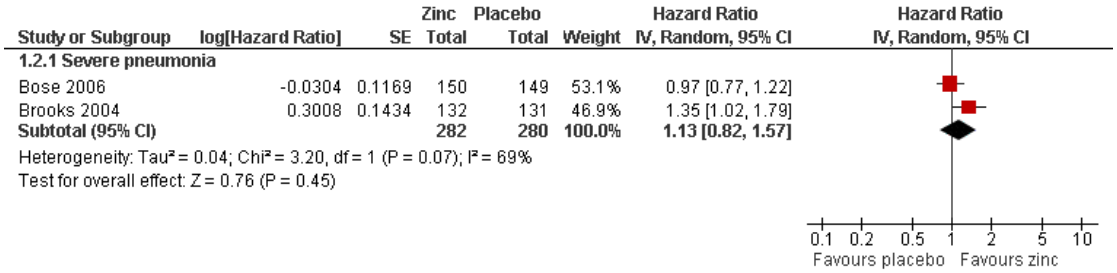
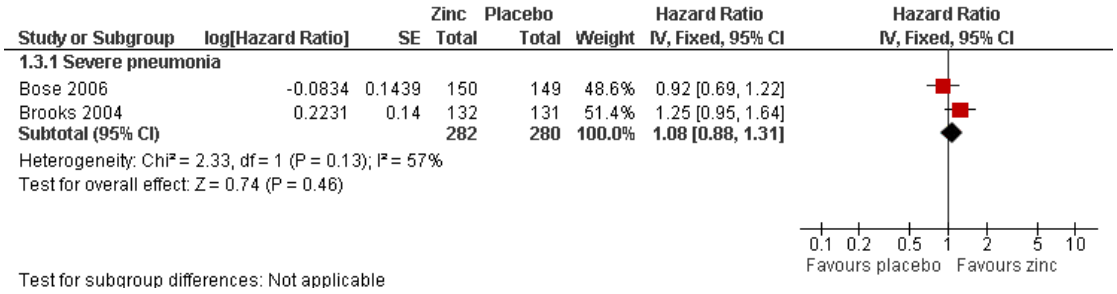


Figure 5. Forest plot of comparison: 1 Zinc supplementation versus placebo, outcome: 1.3 TIme-to-recovery from chest in-drawing.

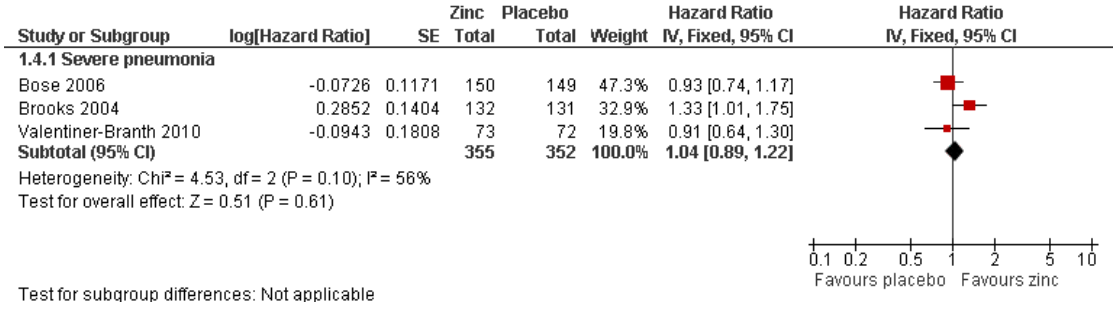


Results from Bansal 2011 were reported only as median (interquartile ranges (IQR)) and could not be pooled with the other trials. The trial displayed no effect of zinc as an adjunct to antibiotic on the time to clinical recovery (zinc group, median 60 h; IQR: 24 to 78 versus control, median 54 h; IQR: 30 to 72 h, P value = 0.98); resolution of tachypnoea (zinc group, median 60 h; IQR: 24 to 72 versus control, median 48 h; IQR: 24 to 72 h, P value = 0.89); and respiratory distress (zinc group, median 30.5 h; IQR: 16 to 48 versus control, median 24 h; IQR: 13 to 48 h, P value = 0.57).

Secondary outcome measure

Zinc supplementation in children with severe pneumonia showed a non-significant effect on time-to- hospital discharge as compared to the control group (hazard ratio 1.04; 95% CI 0.89 to 1.22, fixed-effect (three studies, N = 707) I^2 statistic = 56%, P value = 0.1 (Analysis 1.4; Figure 6). The duration of hospital stay in Bansal 2011 was shorter by nine hours in the zinc group. However, the difference was not significant (P value = 0.53) (zinc group: median 5 days; IQR: 4 to 5.5 versus control: median 5 days; IQR: 3 to 6.5).

Figure 6. Forest plot of comparison: 1 Zinc supplementation versus placebo, outcome: 1.4 Time-to-hospital discharge.



The included studies did not measure any effect on the outcomes of readmission/rediagnosis with pneumonia within three months, mortality within 10 days of randomisation and mortality within one month of randomisation. We did not perform any subgroup analyses because of the small number of studies included in the review.

DISCUSSION

Summary of main results

Zinc supplementation as an adjunct to antibiotics failed to show any significant effect on time-to-clinical recovery from pneumonia in children. We found four trials which compared the effect of zinc supplementation in children (two to 35 months of age) with severe pneumonia. Data from five trials could not be used in the analysis (Chang 2006; Khaled 2001; Mahalanabis 2002; Mahalanabis 2004; Shah 2011). Three studies included children up to 15 years of age, one reported sex-based estimates and the other was a published abstract with insufficient information (Chang 2006; Mahalanabis 2002; Mahalanabis 2004). Another trial compared zinc versus no zinc and prescribed antibiotics only when pneumonia developed (Shah 2011), whereas Khaled 2001 had insufficient information and the outcomes reported by the trial were not of interest to the review.

Brooks 2004 evaluated the effect of 20 mg of daily zinc supplementation on clinical recovery in children treated for severe pneumonia with intravenous antibiotic therapy (ampicillin and gentamicin). They did not find any impact of zinc on recovery from severe pneumonia. The Bose 2006 trial also evaluated the effect of daily 20 mg zinc supplementation in children with severe pneumonia treated with intravenous benzyl penicillin and gentamicin and found no overall effect of zinc supplementation on clinical recovery or duration of hospitalisation. Similarly, Bansal 2011 did not find any significant effect of zinc on clinical recovery and duration of hospital stay in children presenting with severe LRTI. The trial from Nepal by Valentiner-Branth 2010 evaluated 10 mg of zinc for children less than 12 months of age and 20 mg of zinc for children older than 12 months of age with severe and non-severe pneumonia. Children with non-severe pneumonia were given oral cotrimoxazole whereas those with severe pneumonia were treated with intravenous benzyl/penicillin. Analysis of data from the included studies did not show a significant impact of the intervention on time-to-hospital discharge and time-to-clinical recovery in terms of resolution of tachypnoea and chest indrawing.

Baseline serum zinc levels in children with pneumonia were measured at the time of recruitment in trials. Since serum zinc levels fall during an acute infection, the baseline values noted at the time of recruitment may not reflect the true underlying zinc status (in the absence of an acute infection) of these study populations. Differences in the prevalence of zinc deficiency in the study populations may have implications on the role of adjuvant zinc therapy in the treatment of pneumonia. Additionally, Bose 2006 and Valentiner-Branth 2010 used benzyl penicillin which is effective against *Streptococcus pneumoniae* (*S. pneumoniae*) but is not effective against *Haemophilus influenzae (H. influenzae)*. Both trials used third-generation cephalosporins as second-line drugs if the patients failed to respond to the first-line treatment. Cephalosporins have high efficacy which may have lead to similar recovery rates in the groups masking any potential benefit of zinc in these patients.

Overall completeness and applicability of evidence

The four included studies were conducted in Bangladesh, Nepal and India and the study participants were recruited from hospitals in these low-income countries. Children included two to 35 months old and admitted with severe pneumonia (Bansal 2011; Bose 2006; Brooks 2004; Valentiner-Branth 2010) and non-severe pneumonia (Valentiner-Branth 2010). Pneumonia was de-

fined clinically in all studies using more or less similar criteria. Though baseline zinc levels in children suffering from pneumonia were measured, prevalences of zinc deficiency in the study populations were not available. Considering these findings, the results of the review can be applied to similar populations as those included in the studies.

Quality of the evidence

Comparability of study methodology and outcome assessment are of prime importance in compiling evidence. Of note, almost all trials included in the analysis reported pneumonia to the closest possible WHO definition. Therefore, there is little risk of bias due to selective reporting in these trials. Adequate allocation concealment 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 and sequence generation were adequately described in all except Brooks 2004 and Bansal 2011, which suggests that results should be interpreted with caution. However, all included studies were adequately blinded for treatment assignment. Completion rates were greater than 95%.

Potential biases in the review process

In this review we used clearly specified inclusion and exclusion criteria and a systematic, comprehensive search strategy for the identification of relevant studies. Two review authors (BAH, ZSL) independently undertook study selection and data extraction and in case of any discrepancy, they reached consensus by discussion with the third review author (ZAB). We published a protocol for this review with methods specified a priori.

Agreements and disagreements with other studies or reviews

We drew consistent findings with previous reviews that also studied the role of adjuvant zinc therapy in children with pneumonia (Haider 2009; Natchu 2008). Haider 2009 did not find a beneficial effect of adjunct zinc therapy in children with pneumonia. However, significant reductions were observed in the mean duration of acute diarrhoea and persistent diarrhoea in the zinc supplemented group compared to the control group. Natchu 2008 concluded that the benefit from zinc supplementation during acute LRTI is not universal and explained that the variations in the results were due to the difference in aetiologies, definitions of pneumonia and recovery, and the timing of zinc supplementation in the course of the illness.

AUTHORS' CONCLUSIONS

Implications for practice

This review does not provide any evidence for the beneficial effect of zinc supplementation as an adjunct in the treatment of children with pneumonia. Results from four ongoing trials will be available in the near future and contribute to the evidence base for this intervention.

Implications for research

Well-designed, large scale RCTs are needed to evaluate the effect of zinc supplementation in the treatment of pneumonia in low-income countries where zinc deficiency and pneumonia are common. Future studies may consider evaluating the underlying zinc deficient status of the populations in a sample of non-diseased children.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Bansal 2011

Methods	This prospective, randomised, triple-blind, placebo-controlled trial was conducted from April 2007 to June 2008 in a teaching referral hospital in north India
Participants	Children in the age group of 2 to 24 months presenting to a paediatric emergency department with severe acute LRTI were eligible for enrolment. Acute LRTI was defined as presence of tachypnoea (respiratory rate more than 50 breaths per min for children aged 2 to 12 months and more than 40 breaths per min for children aged > 12 months) and either chest indrawing (any subcostal recession) or one of the following danger signs: cyanosis, inability to feed/drink, lethargy and convulsions. Children with concurrent diarrhoea, severe malnutrition (weight for age < 50% of reference value), congenital heart disease and those already on zinc supplements were excluded
Interventions	Eligible children were randomly allocated to zinc or control groups. Zinc group received 20 mg of elemental zinc per day (5 ml syrup per day) as a single daily dose after meals for 5 days. Control group received an equal amount of placebo which was appropriately modified to give the taste, smell, colour and consistency similar to zinc mixture
Outcomes	Time to be asymptomatic, time to disappearance of danger signs, time to resolution of respiratory distress, time to resolution of tachypnoea, duration of stay (days)
Notes	The study protocol was approved by Research and Ethics Committees of the hospital and written informed consent was obtained from parents before enrolment of the subjects

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Simple randomisation sequence was generated using a random number table" Comment: probably done
Allocation concealment (selection bias)	High risk	Quote: "Allocation sequence was known only to hospital pharmacist who dispensed the study drugs in identical looking, serially numbered, sealed 30 ml plastic bottles" Comment: probably not done
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "A Triple-Blind Randomized Placebo Controlled Trial"; "Allocation sequence was known only to hospital pharmacist who dispensed the study drugs in identical looking, serially numbered, sealed

Bansal 2011 (*Continued*)

		30 ml plastic bottles" Comment: did not mention if participants and outcome analyser was blinded, while dispenser was not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	52/53 and 52/53 completed the study
Selective reporting (reporting bias)	Low risk	Study appears to be free of selective reporting
Other bias	Low risk	The study appears to be free of other sources of bias

Bose 2006

Methods	A randomised, double-blinded, placebo controlled clinical trial conducted in a tertiary referral hospital in India for a duration of 1 year (September 2003 to August 2004) to evaluate the effect of adjuvant zinc therapy on recovery from severe pneumonia in hospitalised children receiving standard antibiotic therapy
Participants	Children aged between 2 and 23 months of age who consented to enrol in the study and were clinically diagnosed by a study physician as having severe pneumonia (having RR > 50/min accompanied by crepitations on auscultation and presence of at least one or more of the following danger signs: chest indrawing, lethargy, inability to feed or central cyanosis) were included. Participants were excluded if they had chronic cardiac or renal disease, illness severe enough to require ventilation, severe malnutrition requiring immediate rehabilitation therapy, hospitalisation in the previous 21 days or current zinc supplementation. 300 participants were enrolled, with 150 participants in each group. The participant population lived in economically poor conditions and possibly suffered from malnutrition
Interventions	20 mg of elemental zinc, in the form of zinc sulphate tablets, was administered orally to the participants in two divided doses. Zinc or placebo were given daily until discharge from the hospital. Tablets were dissolved in water for younger infants
Outcomes	Reported outcomes were: time taken for resolution of severe pneumonia, duration of hospital stay, time taken for resolution of clinical symptoms as tachypnoea (RR > 50/min), chest indrawing, inability to feed orally, hypoxaemia (arterial oxygen saturation < 93%), fever (axillary temperature > 37.5 °C) and cough
Notes	Children were treated parenterally with a combination of benzyl penicillin and gentamicin

Risk of bias

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

Bose 2006 (*Continued*)

Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was conducted at the individual level and in blocks of 8 and 10." "randomly assigned to each of the treatment groups" Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote: "codes were generated by a scientist at the headquarters of WHO, which was not associated with the study." "Treatment codes were kept in an envelope in a locked cabinet at WHO headquarters in Geneva" Comment: probably done
Blinding (performance bias and detection bias) All outcomes	Low risk	"double-blind". "The zinc and placebo tablets were indistinguishable in appearance, consistency, and taste." "locked cabinets that could be accessed only by study physicians who were responsible for dosing the participants" Comment: blinding of participants, study personnel and outcome assessors probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Exclusions and attrition was 1.3%. Reasons for attrition and exclusions for all major outcomes in each intervention group were reported
Selective reporting (reporting bias)	Low risk	All outcomes have been measured and reported as predefined in the methodology of the study
Other bias	Low risk	The study appears to be free of other sources of bias

Brooks 2004

Methods	Randomised, double-blinded, placebo controlled trial conducted in a rural hospital in Matlab, Bangladesh for 2 years (August 1999 to August 2001) on the effect of zinc supplementation in addition to standard therapy in children suffering from severe pneumonia on time taken to recover and discharge from hospital
Participants	Infants (2 to 23 months of age) hospitalised for severe pneumonia i.e. presence of cough, RR > 50/min, crepitations on chest auscultation and either chest indrawing or lethargy or inability to feed or cyanosis. Children with concurrent diarrhoea, were receiving zinc supplements, or who had severe malnutrition were excluded. The participants had low baseline serum zinc levels. 270 children participated in the trial. The participant population lived in economically poor conditions and possibly suffered from malnutrition

Brooks 2004 (*Continued*)

Interventions	Zinc acetate syrup (10 mg zinc per 5 ml of syrup), 20 mg of elemental zinc was given daily by mouth in 2 divided doses to the participants until discharge. The control group received placebo
Outcomes	The outcomes reported were mean duration of chest indrawing, RR > 50/min, hypoxia (oxygen saturation < 95% on air), to cessation of severe pneumonia and discharge from hospital
Notes	Children were treated with intravenous ampicillin + gentamicin

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "We pre allocated group assignments by fixed randomisation using permuted blocks of variable length" Comment: probably done
Allocation concealment (selection bias)	Unclear risk	Quote: "A health worker not involved with the patients care gave all doses" Comment: no clear method of allocation concealment stated
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "zinc and placebo syrups were identical in appearance, colour, odour, and taste." "A health worker not involved with the patients care gave all doses" Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition and exclusion was 2.59%. Reasons for attrition were stated
Selective reporting (reporting bias)	Low risk	All outcomes have been measured and reported as predefined in the methodology of the study
Other bias	Low risk	The study appears to be free of other sources of bias

Valentiner-Branth 2010

Methods	This study was a double-blind, randomised, placebo-controlled trial in children to measure the efficacy of daily zinc administration for 14 days on the recovery from severe or non-severe pneumonia. Trial was conducted in Bhaktapur, Nepal
Participants	Children aged 2 to 35 months with severe or non-severe pneumonia according to WHO definitions and if 6 months had lapsed from a previous enrolment. Non-severe pneumonia was defined as fast breathing without LCI. A child had fast breathing if the lower of 2 counts of RR was 50 breaths/min in children aged 2 to 11 months and 40 breaths/min in children aged 12 months. Severe pneumonia was defined as LCI but without general danger signs (i.e. inability to drink/breast feed, persistent vomiting, convulsions, lethargy or unconsciousness). In a child with wheezing, two 2.5 mg doses of nebulised salbutamol were given 15 minutes apart, and the child was reassessed after 30 minutes to establish whether he or she still fulfilled the inclusion criteria. Exclusion criteria were as follows: non consent, not planning to live in the area for the next 6 months, requiring special care for very severe disease (i.e. with any general danger sign), severe malnutrition (defined as being 70% of the median weight for height according to National Center for Health Statistics standards), presence of congenital heart disease, documented tuberculosis, documentation of any oral antibiotic treatment in the past 48 h, cough for 14 d, severe anaemia (defined as haemoglobin, 7 G/dL) or dysentery
Interventions	Zinc 10 mg for children aged 2 to 11 mo and 20 mg for children aged 12 mo
Outcomes	For the severe pneumonia stratum, the median time to recovery from severe pneumonia (i.e. the beginning of a 24 h period without LCI) was 2 d for infants and 1 d for toddlers, treatment failure, length of hospital stay
Notes	The children received antibiotic treatment according to WHO standard case management guidelines for pneumonia with oral co-trimoxazole in a dose of 4 mg trimethoprim /kg bodyweight and 20 mg sulphamethoxazole/kg bodyweight twice daily for 5 d

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "randomisation was stratified on age < 1 year and > 1 year as well as on severe and non-severe pneumonia. Children were allocated to either of the intervention groups by being randomly assigned to blocks of 16" Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote: "For each enrolment, the child was given a unique serial number and a package with the intervention or placebo with the corresponding number" Comment: probably done

Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "The randomisation list that linked the serial numbers to the treatment groups was generated offsite by using Stata (Stata Corporation, College Station, TX) by a scientist who was otherwise not involved in the study. The scientist sent this list to the manufacturer of the placebo and zinc tablets that labelled the packages. The list was not available for any of those involved in the study until all participants had been enrolled and completed follow-up, data cleaning and management were finished, and the plan of analysis had been prepared." "Tablets of both groups were similar in packaging, appearance, taste, and inactive ingredients" Comment: blinding of participants, study personnel and outcome assessors probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	1300/1314 in the zinc group and 1299/1314 from the control group
Selective reporting (reporting bias)	Low risk	Study seems to be free from selective reporting
Other bias	Low risk	Study seems free from other biases

LCI = lower chest indrawing
RR = respiratory rate
h = hours
d = days
mo = months

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

Study	Reason for exclusion
Chang 2006	The trial included children up to 11 years of age. They did not report disaggregated data on children of 2 to 59 months of age
Khaled 2001	Published abstract with insufficient information was only available. Also, the outcomes reported by the trial were not of interest to the review

(*Continued*)

Mahalanabis 2002	Trial included children up to 15 years of age with measles accompanied by pneumonia. Both groups received standard antibiotics along with vitamin A
Mahalanabis 2004	The trial reported sex-based estimates only
Shah 2011	Children were first assigned to zinc and no zinc group and antibiotics were given when they developed acute ALRI

ALRI = acute lower respiratory infection

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

NCT00142285

Trial name or title	Zinc pneumonia outpatient trial in children < 2 years
Methods	It is a randomised, placebo controlled, double-blind trial to determine whether zinc can be used in combination with standard antibiotics to reduce the duration of illness and the likelihood of treatment failure among children less than two years old who have non-severe, outpatient pneumonia in an urban slum among children less than 2 years old
Participants	Children up to 23 months with clinical diagnosis of pneumonia. Exclusion will be those with wheezing at presentation, history of chronic lung, heart or other system disease, suspected tuberculosis, active measles, severe malnutrition requiring hospitalisation, signs of systemic illness (sepsis, meningitis), those who have already received zinc/placebo supplements during this study, those known to be pretreated with antibiotics prior to presenting to clinic
Interventions	Oral antibiotics will be given for a standard 5-day course, while zinc (20 mg) or placebo will be administered once daily for 10 days Patients will be followed up on a daily basis at home to monitor their progress and document compliance
Outcomes	Primary outcome measures: duration of illness, treatment failure Secondary outcome measures: incidence of subsequent illness episodes (pneumonia and any other)
Starting date	November 2004
Contact information	Abdullah Brooks, ICDRR, B Centre for health and population research
Notes	

NCT00347386

Trial name or title	Zinc as an immunomodulator in the treatment of possible serious bacterial infections in infants 7 days and up to 4 months of age
Methods	This is a double-blind, RCT
Participants	Evidence of possible serious bacterial infection, defined as a CRP > 20 mg/L and any one of the following clinical features • Fever (axillary temperature > 38 ^{o}C) or hypothermia (axillary temperature < 35.5 ^{o}C), lethargic or unconscious, no attachment to the breast in breast fed infants, no suckling in breast fed infants, convulsions in the present episode, bulging fontanel • History of acute refusal of feed in the present episode • Acute history of excessive cry or irritability in the present episode • Fast breathing defined as > 60 breaths/minute (on second count) • Grunting in the absence of any non-infective cause • Cyanosis in the absence of any non-infective cause • Severe chest indrawing • Unexplained shock Exclusion criteria: • Congenital malformations, e.g. hydrocephalus, structural CNS malformation • Severe birth asphyxia defined as: One minute APGAR (if available) of < 4/10 CT scan or MRI or EEG abnormalities if available suggestive of hypoxic ischaemic encephalopathy • Known structural defects, which interfere with feeding, e.g. cleft palate oesophageal abnormalities, intestinal atresia and stenosis malrotation of the gut, anorectal malformation • Subjects requiring ventilation or inotropic support • History of diarrhea in the present episode • Known inborn error of metabolism • Chronic disorders of other organs e.g. neonatal cholestasis, chronic renal failure, pre-existing seizure disorder • Infants born of known HIV mothers • Clinical suspicion of necrotising enterocolitis • Congenital heart disease
Interventions	Drug: zinc (zinc sulphate) Drug: placebo
Outcomes	Primary outcome: proportion with treatment failures Secondary outcome measures: the effect of zinc administration on plasma zinc and copper the efficacy of zinc on the duration of severe bacterial illness the efficacy of zinc given during severe bacterial illness on markers of inflammation
Starting date	March 2005
Contact information	Shinjini Bhatnagar, All India Institute of Medical Sciences, New Delhi
Notes	

NCT00373100

Trial name or title	Efficacy of zinc as an adjunct therapy in the management of severe pneumonia among Gambian children
Methods	RCT from Gambia
Participants	Inclusion criteria: children aged 2 to 59 months presenting with severe or very severe pneumonia to the MRC Hospital or the Royal Victoria Teaching Hospital, Banjul Exclusion criteria: children with severe malnutrition or signs of systemic infection other than pneumonia
Interventions	Zinc sulphate or placebo. Zinc will be given once daily orally at a dose of 10 mg in those aged 2 to 11 months and 20 mg in those 12 to 59 months. All participants will receive zinc or placebo for 7 days, while a randomly selected subgroup will receive 6 months supplementation Please note that this amendment reflects an error in the information provided at time of registration and not a change in protocol; zinc sulphate has been used throughout the trial Interventions provided at time of registration: zinc acetate or placebo. Zinc will be given once daily orally at a dose of 10 mg in those aged 2 to 11 months and 20 mg in those 12 to 59 months. All participants will receive zinc or placebo for 7 days, while a randomly selected subgroup will receive 6 months supplementation
Outcomes	Primary outcome: treatment failure at 5 days Secondary outcome: the following will be assessed after 6 months supplementation of zinc or placebo in a subgroup: 1. time to resolution of signs of severe and very severe pneumonia 2. length of admission 3. height 4. multi-antigen skin testing
Starting date	24/10/2005
Contact information	showie@mrc.gm MRC Laboratories, P.O. Box 273, Gambia
Notes	

NCT00513929

Trial name or title	Zinc as adjunct to treatment of pneumonia (EcuaPAZ)
Methods	It is a RCT, double-blind
Participants	Inclusion criteria: children from 2 to 59 months of age with severe pneumonia admitted to the Children's Hospital, whose parents are willing to provide written informed consent will be eligible for participation Exclusion criteria: children suffering from marasmus or kwashiorkor, measles, pneumonia due to aspiration of a foreign body, hepatic or renal disease, sepsis, congenital abnormalities (cardiac, renal or genetic), complicated pneumonia (lung abscess, pleural effusion, pneumatocoele, atelectasis) or severe anaemia (haemoglobin less than 8 g/dL) children whose parents refuse to provide written informed consent

NCT00513929 (*Continued*)

Interventions	Dietary supplement: zinc sulphate Arm X : zinc sulphate 10 mg will be given orally twice a day since admission to resolution of pneumonia episode in addition to standard antibiotic treatment
Outcomes	Primary outcome measures: time (hours) to resolution of clinical signs of pneumonia Secondary outcome measures: time (hours) to resolution of clinical signs of pneumonia by type of associated pathogens
Starting date	August 2007
Contact information	Contact: Fernando E Sempertegui, MD fersempert@andinanet.net
Notes	

CRP = C-reactive protein
CNS = central nervous system
APGAR = appearance pulse grimace activity respiration
CT scan = computed axial tomography scan
MRI = magnetic resonance imaging
EEG = electroencephalography

DATA AND ANALYSES

Comparison 1. Zinc supplementation versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Time-to-clinical recovery	2	2862	Hazard Ratio (Fixed, 95% CI)	1.02 [0.93, 1.11]
1.1 Severe pneumonia	2	408	Hazard Ratio (Fixed, 95% CI)	1.12 [0.89, 1.41]
1.2 Non-severe pneumonia	1	2454	Hazard Ratio (Fixed, 95% CI)	1.0 [0.91, 1.10]
2 Time-to-recovery from tachypnoea (respiratory rate > 50 breaths per min)	2		Hazard Ratio (Random, 95% CI)	Subtotals only
2.1 Severe pneumonia	2	562	Hazard Ratio (Random, 95% CI)	1.13 [0.82, 1.57]
3 TIme-to-recovery from chest in-drawing	2		Hazard Ratio (Fixed, 95% CI)	Subtotals only
3.1 Severe pneumonia	2	562	Hazard Ratio (Fixed, 95% CI)	1.08 [0.88, 1.31]
4 Time-to-hospital discharge	3		Hazard Ratio (Fixed, 95% CI)	Subtotals only
4.1 Severe pneumonia	3	707	Hazard Ratio (Fixed, 95% CI)	1.04 [0.89, 1.22]

Analysis 1.1. Comparison 1 Zinc supplementation versus placebo, Outcome 1 Time-to-clinical recovery.

Review: Zinc supplementation as an adjunct to antibiotics in the treatment of pneumonia in children 2 to 59 months of age

Comparison: 1 Zinc supplementation versus placebo

Outcome: 1 Time-to-clinical recovery

Study or subgroup	Zinc N	Placebo N	log [Hazard Ratio] (SE)	Hazard Ratio IV,Fixed,95% CI	Weight	Hazard Ratio IV,Fixed,95% CI
1 Severe pneumonia						
Brooks 2004	132	131	0.357 (0.172)		6.7 %	1.43 [1.02, 2.00]
Valentiner-Branth 2010	73	72	-0.0943 (0.1585)		7.9 %	0.91 [0.67, 1.24]
Subtotal (95% CI)	**205**	**203**			**14.6 %**	**1.12 [0.89, 1.41]**
Heterogeneity: Chi^2 = 3.72, df = 1 (P = 0.05); I^2 =73%						
Test for overall effect: Z = 0.97 (P = 0.33)						
2 Non-severe pneumonia						
Valentiner-Branth 2010	1227	1227	0 (0.0481)		85.4 %	1.00 [0.91, 1.10]
Subtotal (95% CI)	**1227**	**1227**			**85.4 %**	**1.00 [0.91, 1.10]**
Heterogeneity: not applicable						
Test for overall effect: Z = 0.0 (P = 1.0)						

(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	Zinc N	Placebo N	log [Hazard Ratio] (SE)	Hazard Ratio IV,Fixed,95% CI	Weight	Hazard Ratio IV,Fixed,95% CI
Total (95% CI)	**1432**	**1430**			**100.0 %**	**1.02 [0.93, 1.11]**

Heterogeneity: Chi^2 = 4.53, df = 2 (P = 0.10); I^2 =56%

Test for overall effect: Z = 0.37 (P = 0.71)

Test for subgroup differences: Chi^2 = 0.80, df = 1 (P = 0.37), I^2 =0.0%

Analysis 1.2. Comparison 1 Zinc supplementation versus placebo, Outcome 2 Time-to-recovery from tachypnoea (respiratory rate > 50 breaths per min).

Review: Zinc supplementation as an adjunct to antibiotics in the treatment of pneumonia in children 2 to 59 months of age

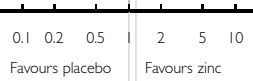
Comparison: 1 Zinc supplementation versus placebo

Outcome: 2 Time-to-recovery from tachypnoea (respiratory rate > 50 breaths per min)

Study or subgroup	Zinc N	Placebo N	log [Hazard Ratio] (SE)	Hazard Ratio IV,Random,95% CI	Weight	Hazard Ratio IV,Random,95% CI
1 Severe pneumonia						
Bose 2006	150	149	-0.0304 (0.1169)		53.1 %	0.97 [0.77, 1.22]
Brooks 2004	132	131	0.3008 (0.1434)		46.9 %	1.35 [1.02, 1.79]
Subtotal (95% CI)	**282**	**280**			**100.0 %**	**1.13 [0.82, 1.57]**

Heterogeneity: Tau^2 = 0.04; Chi^2 = 3.20, df = 1 (P = 0.07); I^2 =69%

Test for overall effect: Z = 0.76 (P = 0.45)



Analysis 1.3. Comparison 1 Zinc supplementation versus placebo, Outcome 3 TIme-to-recovery from chest in-drawing.

Review: Zinc supplementation as an adjunct to antibiotics in the treatment of pneumonia in children 2 to 59 months of age

Comparison: 1 Zinc supplementation versus placebo

Outcome: 3 TIme-to-recovery from chest in-drawing

Study or subgroup	Zinc N	Placebo N	log [Hazard Ratio] (SE)	Hazard Ratio IV,Fixed,95% CI	Weight	Hazard Ratio IV,Fixed,95% CI
1 Severe pneumonia						
Bose 2006	150	149	-0.0834 (0.1439)		48.6 %	0.92 [0.69, 1.22]
Brooks 2004	132	131	0.2231 (0.14)		51.4 %	1.25 [0.95, 1.64]
Subtotal (95% CI)	**282**	**280**			**100.0 %**	**1.08 [0.88, 1.31]**

Heterogeneity: Chi^2 = 2.33, df = 1 (P = 0.13); I^2 =57%

Test for overall effect: Z = 0.74 (P = 0.46)

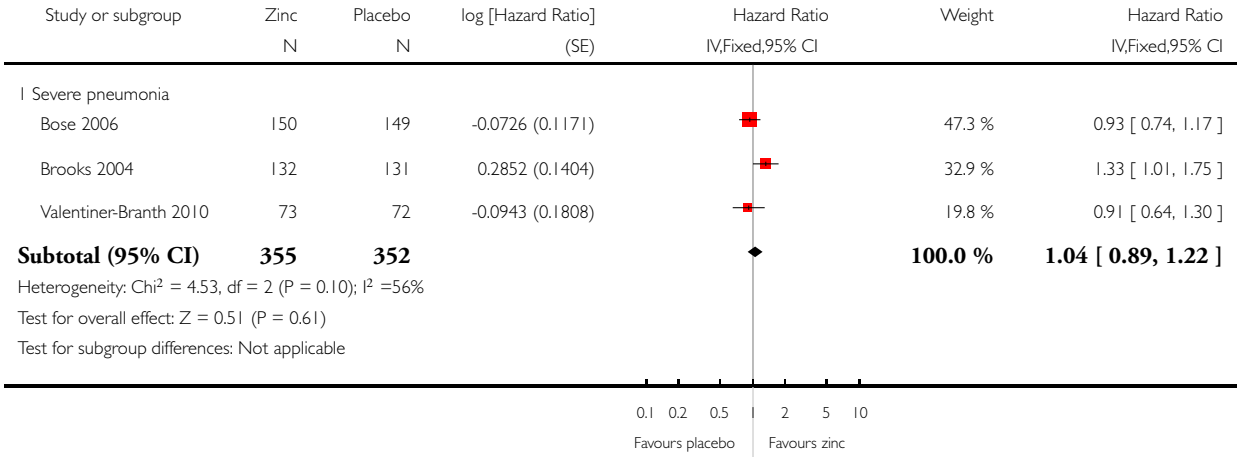
Test for subgroup differences: Not applicable

Analysis 1.4. Comparison 1 Zinc supplementation versus placebo, Outcome 4 Time-to-hospital discharge.

Review: Zinc supplementation as an adjunct to antibiotics in the treatment of pneumonia in children 2 to 59 months of age

Comparison: 1 Zinc supplementation versus placebo

Outcome: 4 Time-to-hospital discharge



ADDITIONAL TABLES

Table 1. Zinc supplementation versus placebo

Study	Supplementation		Schedule	Antibiotic	Definition of clinical recovery	Discharge criteria
	Zinc	Placebo				
Bansal 2011	**Zinc gluconate** 20 mg	Placebo	Daily	Parenteral antibiotic	Time to be asymptomatic was defined as resolution of all four of the following symptoms: 1) danger signs; 2) respiratory distress; 3) tachypnoea and 4) hypoxia in room air, for at least 24 h	Children were discharged from hospital when they were asymptomatic for at least 24 h
Bose 2006	**Zinc sulphate** 20 mg	Placebo	Daily	Inj. benzyl penicillin + gentamicin	Resolution of the following: 1) respiratory rate 50 breaths/min and oxygen saturation 93%; 2) inabil-	Children were discharged when they were being fed entirely with oral feeds, the respiratory rate

Table 1. Zinc supplementation versus placebo (*Continued*)

					ity to drink, respiratory rate 50 breaths/min, and oxygen saturation 93%; and 3) chest indrawing, respiratory rate 50 breaths/min and oxygen saturation 93% for at least 16 h	was 50 breaths/min, oxygen saturation was 93%, and the attending paediatrician decided that the patient's clinical condition had resolved and did not require further hospital care
Brooks 2004	**Zinc acetate** 20 mg	Placebo	Daily	Inj. ampicillin + gentamicin	Resolution of the following: 1) chest indrawing; 2) respiratory rate more than 50 per min; and 3) hypoxia (oxygen saturation <95%) for at least 24 h	Children were discharged from hospital once respiratory rate fell to less than or equal to 40 breaths per min for 24 consecutive h, with no recurrence of respiratory distress, other danger signs, or fever (temperature > 37·9°C)
Valentiner-Branth 2010	**Zinc sulphate** 10 mg for < 12 months and 20 mg for > 12 months	Placebo	Twice daily	Oral co-trimoxazole for non-severe pneumonia benzyl penicillin for severe pneumonia	Recovery was defined as the beginning of the first 24 h period without LCI, without grunting and with no nasal flaring for at least 24 h	The child was considered for discharge when he/she recovered from severe pneumonia

LCI = lower chest indrawing; h= hour

Table 2. Median recovery time

Study	Outcome	Zinc group	Placebo group
Bansal 2011 Median (IQR)	Time to be asymptomatic (h)	60 (24, 78)	54 (30, 72)
	Time to resolution of respiratory distress (h)	30.5 (16, 48)	24 (13, 48)
	Time to resolution of tachypnoea (h)	60 (24, 72)	48 (24, 72)

Table 2. Median recovery time (*Continued*)

	Time to disappearance of danger signs (h)	20 (8, 36)	16 (8, 30)
Valentiner-Branth 2010 Median (IQR)	Time to recovery from severe pneumonia (d)	2 (1, 3)	2 (1, 3)
	Time to recovery (d)	4 (2, 7)	3 (2, 6)
	Time to discharge from hospital (d)	3 (3, 4)	3 (3, 4)
Bose 2006 Median (95% CI)	Time to be asymptomatic (h) (Inability to feed, O^2 saturation < 93%, RR > 50) (Chest indrawing, O^2 saturation <93%, RR > 50) (O^2 saturation <93%, RR > 50)	87.2 (70.7, 95.2) 111.3 (88.5, 138.0) 82.2 (70.3, 92.2)	76.2 (72.3, 88.1) 96.7 (78.2, 112.9) 75.9 (71.2, 88.0)
	Time to resolution of tachypnoea (RR > 50) (h)	72.0 (68.5, 88.0)	73.0 (64.5, 82.8)
	Hospitalisation (h)	71.1 (68.1, 87.3)	72.3 (67.7, 79.6)
Brooks 2004 Median (95% CI)	Time to recovery from severe pneumonia (h)	72 (72, 96)	96 (72, 96)
	Chest indrawing	40 (39, 48)	48 (40, 56)
	Hospital stay (d)	112 (104, 112)	112 (111, 129)

IQR= interquartile range; h = hour; d = day; CI = confidence interval; RR = respiratory rate

APPENDICES

Appendix 1. MEDLINE search strategy

MEDLINE (Ovid)

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.tw.
9 or/7-8
10 exp Child/
11 child*.tw.
12 exp Infant/
13 infant*.tw.
14 (paediatric* or pediatric* or toddler* or preschool*).tw.
15 or/10-14
16 6 and 9 and 15

Appendix 2. CENTRAL search strategy

#1MeSH descriptor Pneumonia explode all trees
#2(pneumon*):ti,ab,kw
#3(lower respiratory tract infection*):ti,ab,kw
#4(lower respiratory infection*):ti,ab,kw
#5(lrti):ti,ab,kw
#6(#1 OR #2 OR #3 OR #4 OR #5)
#7MeSH descriptor Zinc explode all trees
#8(zinc):ti,ab,kw
#9(#7 OR #8)
#10(#6 AND #9)

Appendix 3. EMBASE search strategy

Embase.com

#14. #5 AND #8 AND #13
#13. #9 OR #10 OR #11 OR #12
#12. pediatric*:ab,ti OR paediatric*:ab,ti OR toddler*:ab,ti OR preschool*:ab,ti
#11. 'pediatrics'/exp
#10. child*:ab,ti OR infant*:ab,ti OR infancy:ab,ti
#9. 'child'/exp
#8. #6 OR #7
#7. zinc:ab,ti
#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 4. CINAHL search strategy

CINAHL (Ebsco)

S10 S6 and S9
S9 S7 or S8
S8 TI zinc or AB zinc
S7 (MH "Zinc")
S6 S1 or S2 or S3 or S4 or S5
S5 TI lrti or AB lrti
S4 TI lower respiratory tract infection* or AB lower respiratory tract infection*
S3 TI lower respiratory infection* or AB lower respiratory infection*
S2 TI pneumon* or AB pneumon*
S1 (MH "Pneumonia+")

Appendix 5. LILACS search strategy

Database :	LILACS
Search on :	Mh Pneumonia OR Tw pneumon$ OR Tw neumon$ [Words] and Mh Zinc OR Tw zinc$ [Words]

Appendix 6. AMED search strategy

AMED (Ovid)

1 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.tw.
9 7 or 8
10 6 and 9

Appendix 7. CAB Abstracts search strategy

CAB Abstracts (Thomson Reuters)

Topic=(pneumon* or lower respiratory tract infect* or lower respiratory infect*) AND Topic=(zinc)
Timespan=2010. Databases=CAB Abstracts.

Appendix 8. Web of Science search strategy

Web of Science (Thomson Reuters)

Topic=(pneumon* or lower respiratory tract infect* or lower respiratory infect*) AND Topic=(zinc)
Refined by: Topic=(child* or infant* or toddler* or preschool* or pediatric* or paediatric*)
Timespan=2010. Databases=SCI-EXPANDED, CPCI-S.

WHAT'S NEW

Date	Event	Description
17 January 2013	Amended	Measurement of treatment effect section: Methods for the analysis of time-to-event outcome added. Types of outcome measures: clearly listed as time-to-event outcomes

CONTRIBUTIONS OF AUTHORS

Batool A Haider (BAH) and Zohra S Lassi (ZSL) extracted, entered and analysed the data and wrote the text of the review. Amina Ahmed also contributed to data extraction. Zulfiqar A Bhutta (ZAB) provided support and guidance for the review.

DECLARATIONS OF INTEREST

ZAB has been involved in a study of zinc supplementation for the treatment of diarrhoea in children. BAH and ZAB have also coauthored an earlier meta-analysis of the therapeutic benefits of zinc in infections in children.

SOURCES OF SUPPORT

Internal sources

- Aga Khan University, Pakistan.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

*Dietary Supplements; Anti-Bacterial Agents [*therapeutic use]; Length of Stay; Pneumonia [*drug therapy; physiopathology]; Randomized Controlled Trials as Topic; Recovery of Function; Respiratory Rate [drug effects; physiology]; Zinc [*administration & dosage; physiology]; Zinc Sulfate [administration & dosage]

MeSH check words

Child, Preschool; Humans; Infant