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## Zinc supplementation for the treatment of measles in children (Review)

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[Intervention Review]

# Zinc supplementation for the treatment of measles in children

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## ABSTRACT

### Background

Measles is an important cause of childhood morbidity and mortality globally, despite increasing vaccine coverage. Zinc plays a significant role in the maintenance of normal immunological functions, therefore supplements given to zinc-deficient children will increase the availability of zinc and could reduce measles-related morbidity and mortality. This is an update of a review first published in 2015.

### Objectives

To assess the effects of zinc supplementation in reducing morbidity and mortality in children with measles.

### Search methods

We searched CENTRAL (03 February 2017, Issue 2), MEDLINE (1946 to 03 February 2017), Embase (1974 to 03 February 2017), CINAHL (1981 to 03 February 2017), LILACS (1982 to 03 February 2017), Web of Science (1985 to 03 February 2017), and BIOSIS Previews (1985 to 27 June 2014). We also searched ClinicalTrials.gov, the Australian New Zealand Clinical Trials Registry and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) on 03 February 2017 to identify unpublished and ongoing studies.

### Selection criteria

Randomised controlled trials (RCTs) and quasi-RCTs evaluating the effects of zinc in reducing morbidity and mortality in children with measles.

### Data collection and analysis

Two review authors independently assessed the studies for inclusion and extracted data on outcomes, details of the interventions, and other study characteristics using a standardised data extraction form. We used risk ratio (RR) and hazard ratio (HR) as measures of effect with 95% confidence intervals (CI). We included only one study, and did not conduct meta-analysis.

## **Main results**

We did not identify any new studies for inclusion in this update. One RCT met our inclusion criteria. The study was conducted in India and included 85 children diagnosed with measles and pneumonia. The trial showed no significant difference in mortality between children with measles and pneumonia who received zinc supplements and those who received placebo (RR 0.34, 95% CI 0.01 to 8.14). There was no significant difference in time to absence of fever between children who received zinc supplements and those who did not (HR 1.08, 95% CI 0.67 to 1.74). No treatment-related side effects were reported in either group. We assessed the overall quality of the evidence as very low.

## **Authors' conclusions**

We could not draw any definitive conclusions from this review about the effects of zinc supplementation on clinical outcomes of children with measles due to the very low quality of the evidence available. There is insufficient evidence to confirm or refute the effect of zinc supplementation in children with measles.

## **PLAIN LANGUAGE SUMMARY**

### **Zinc supplementation for the treatment of measles in children**

#### **Review question**

What is the effect of zinc supplementation in the treatment of children with measles?

#### **Background**

Measles infection has reduced globally over the last decade, but large outbreaks still occur, especially in low-income countries. Zinc is one of the essential micronutrients necessary for the optimal functioning of the immune system. Zinc deficiency is particularly common in children in low- and middle-income countries. It was therefore important to examine the potential role of zinc supplementation in controlling the symptoms of measles infection in children.

We aimed to critically assess the current evidence from published studies on the effect of zinc supplementation for the treatment of measles in children.

#### **Search date**

We searched for evidence up to 03 February 2017. This is an update of a review first published in 2015. We did not include any new studies for this update.

#### **Study characteristics**

We found one small randomised trial (involving 85 children) that compared zinc supplements versus placebo administered to children with measles and pneumonia. All 85 children received supportive care and vitamin A. The study was conducted in India and funded by the Child Health Foundation USA and the Nestlé Foundation.

#### **Key results**

The included study was small and did not provide enough data to determine whether zinc had an effect on mortality when compared with placebo. Although no adverse effects were reported, there was insufficient evidence to draw any conclusions about the use of zinc supplements to improve measles symptoms in children. More research is needed to clarify any benefits or harms.

#### **Quality of the evidence**

We assessed the quality of the evidence as very low.

## SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Zinc versus placebo for the treatment of measles in children						
<b>Patient or population:</b> children with measles and pneumonia <b>Settings:</b> tertiary care centre in a low-income country <b>Intervention:</b> zinc <b>Comparison:</b> placebo						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Zinc				
<b>Mortality</b> Follow-up: mean 6 days	<b>Study population</b>		<b>RR 0.34</b> (0.01 to 8.14)	85 (1 study)	⊕⊕○○ <b>very low</b> <sup>1,2</sup>	
	23 per 1000	8 per 1000 (0 to 189)				
<b>Time to fever abatement</b> Follow-up: mean 6 days	<b>Study population</b>		<b>HR 1.08</b> (0.67 to 1.74)	78 (1 study)	⊕⊕○○ <b>very low</b> <sup>1,2</sup>	
	Median time to absence of fever 96 hours IQR (74 to 116)	Median time to absence of fever 96 hours IQR (72 to 116)				

\*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** confidence interval; **HR:** hazard ratio; **IQR:** interquartile range; **RR:** risk ratio

GRADE Working Group grades of evidence

**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Very low quality:** We are very uncertain about the estimate.

<sup>1</sup>Serious imprecision: wide confidence intervals, small sample size, and few events.

<sup>2</sup>Indirectness: study population differed clinically from children with uncomplicated measles.

## BACKGROUND

### Description of the condition

Measles is an important cause of childhood morbidity and mortality globally. It is a highly contagious acute viral infection characterised by high fever, cough, rhinitis, conjunctivitis, a rash on the mucous membranes, and a red maculopapular rash (Mason 2016). According to the World Health Organization, 535,000 children died of measles in 2000 (WHO 2012). Between 2000 and 2010, there was a 74% reduction in measles deaths globally as a result of improved vaccine coverage efforts (Simons 2012). However, large outbreaks occurred in Bulgaria in 2009 to 2010 and France in 2011 as a result of suboptimal immunisation levels (Carrillo-Santistevé 2012). Measles outbreaks occurred in Sierra Leone (between 2009 and 2010) and South Africa (between 2003 and 2005; 2009 and 2011), likely due to HIV infection and poor vaccine coverage (Sartorius 2013). Case fatality rates for measles among young children in low-income countries still hover at around 5% to 6% (Wolfson 2009). Acute lower respiratory infection is a common complication of measles, and is associated with mortality. Other important complications of measles include otitis media, laryngotracheobronchitis (croup), diarrhoea, encephalitis, and cortical damage leading to blindness (Perry 2004).

The global prevalence of zinc deficiency is estimated to be more than 20% (Wuehler 2005), and in many low-income countries, is extremely prevalent among children (World Bank 2016). Most zinc is excreted through the gastrointestinal tract, therefore children who are regularly exposed to gastrointestinal pathogens and who have poor nutrition, low in animal products and high in phytate, are most at risk of zinc deficiency (Lazzerini 2016). Zinc deficiency results in the dysfunction of both humoral and cell-mediated immunity and increases susceptibility to infectious diseases such as diarrhoea and respiratory infection (Tuerk 2009). Respiratory tract infections, such as acute lower respiratory tract infections, are common complications of measles infection (Aggarwal 2007; Roth 2008; Shakur 2009).

### Description of the intervention

Zinc is one of the most important trace elements in the human body. It is a component of over 1000 transcription factors and is required in more than 300 zinc-containing enzymes (Haase 2009; Stefanidou 2006). Zinc supplementation may reduce the duration of acute and persistent diarrhoea in children over six months of age (Lazzerini 2016), and frequency of diarrhoeal and respiratory illnesses in children (Aggarwal 2007). Zinc supplements can be given in the forms of zinc sulphate, zinc gluconate, zinc acetate, or zinc chloride. The recommended daily dose is 10 mg to 20 mg of zinc for children with diarrhoea (WHO/UNICEF 2004).

### How the intervention might work

Several studies have demonstrated the importance of zinc in the maintenance of normal immune functions (Bach 1989; Prasad 1998; Prasad 2000; Prasad 2009; Stefanidou 2006; Tapiero 2003). Zinc is said to be crucial for effective innate and acquired immunity, and insufficient zinc status could be the most common cause of secondary immunodeficiency in humans (Tapiero 2003). Zinc deficiency impairs phagocytosis of macrophages and neutrophils, oxidative burst activity, and complement natural killer cell activity (Prasad 2000). Zinc is also involved in T-cell differentiation and enhancement of T-cell and natural killer cell actions through its role in thymulin activity (Bach 1989). In the absence of zinc, lymphocyte proliferation is depressed, as well as delayed-type hypersensitivity skin responses and T-cell dependent antigen-antibody responses (Prasad 1998). Zinc has also been shown to have anti-inflammatory and antioxidant properties (Prasad 2009; Stefanidou 2006). Supplements increase the availability of zinc for these immunologic processes and may improve measles morbidity and mortality. In children, zinc supplementation is reported to reduce morbidity, mortality, and recovery time from acute infectious diseases (Cuevas 2005). Sazawal 2007 showed that zinc supplements given to children aged between 1 month and 48 months resulted in reduced mortality from acute infections including measles. Zinc supplementation has also been shown to significantly reduce respiratory morbidity in preschool children (Sazawal 1998), and may reduce the incidence of acute lower respiratory tract infections by improving measles morbidity.

### Why it is important to do this review

Several reviews have shown that zinc supplementation is associated with reduced incidence and prevalence of pneumonia in children (Aggarwal 2007; Bhutta 1999; Lassi 2016). Other Cochrane Reviews evaluating zinc supplementation in children have looked at otitis media and diarrhoea (Gulani 2014; Lazzerini 2016). This review aimed to identify, critically appraise, and synthesise data from studies evaluating the effects of zinc supplementation in children with measles.

## OBJECTIVES

To assess the effects of zinc supplementation in reducing morbidity and mortality in children with measles.

## METHODS

### Criteria for considering studies for this review

## Types of studies

Randomised controlled trials (RCTs) and quasi-RCTs evaluating the effects of zinc in reducing morbidity and mortality in children with measles.

## Types of participants

Children aged up to 18 years diagnosed with measles.

## Types of interventions

Zinc supplementation (irrespective of dosage, duration, and route of administration) combined with standard treatment compared with standard treatment alone or standard treatment with placebo. (Standard treatment was defined as relief of common symptoms such as fever, cough, blocked nose, conjunctivitis, and sore mouth; provision of nutritional support; and vitamin A (WHO 2004).)

## Types of outcome measures

### Primary outcomes

1. All-cause mortality.

### Secondary outcomes

1. Duration of fever, coryza, cough, and rash.
2. Duration of hospitalisation.
3. Incidence of complications such as pneumonia, otitis media, diarrhoea, and croup.
4. Effect on disability-adjusted life years.
5. Adverse events.

## Search methods for identification of studies

### Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (03 February 2017, Issue 2), which contains the Cochrane Acute Respiratory Infections Group Specialised Register, MEDLINE (1946 to 03 February 2017), Embase (1974 to 03 February 2017), CINAHL (Cumulative Index to Nursing and Allied Health Literature) (1981 to 03 February 2017), LILACS (Latin American and Caribbean Health Science Literature Database) (1982 to 03 February 2017), Web of Science (1985 to 03 February 2017), and BIOSIS Previews (1985 to 27 June 2014). We did not update the BIOSIS Previews search in February 2017 due to lack of institutional access to that database.

We used the search strategy described in [Appendix 1](#) to search CENTRAL and MEDLINE. We combined the MEDLINE search with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-

maximising version (2008 revision); Ovid format (Lefebvre 2011). We adapted the search strategy to search Embase ([Appendix 2](#)), CINAHL ([Appendix 3](#)), LILACS ([Appendix 4](#)), Web of Science ([Appendix 5](#)), and BIOSIS Previews ([Appendix 6](#)). We did not apply any language or publication restrictions.

### Searching other resources

We searched ClinicalTrials.gov, the Australian New Zealand Clinical Trials Registry and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) for unpublished and ongoing studies (latest search 03 February 2017). We scrutinised the reference lists of the included studies and relevant review articles for additional references.

## Data collection and analysis

### Selection of studies

Two review authors (AA, OO) independently screened the titles and abstracts of articles identified by the searches for eligibility. We classified these studies as 'included' or 'excluded'. We retrieved full-text articles of studies that did not have an abstract or had a limited abstract and assessed them for inclusion. Two review authors (AA, OO) independently assessed full-text articles classified as 'include' for inclusion in the review using a standardised form with explicit inclusion and exclusion criteria. Any disagreements were resolved by the two review authors. Only one study met our inclusion criteria.

### Data extraction and management

Two review authors (AA, AS) independently extracted data from the included studies using a pre-designed data extraction form. We extracted the following information:

- general information (study ID, date of extraction, title, authors, and source of study if not published);
- study characteristics (study design, participants, and inclusion/exclusion criteria used in the study);
- details of the interventions (including zinc dosage, treatment duration, comparison details, duration of follow-up);
- outcomes as described in [Types of outcome measures](#) above; and
- details necessary for 'Risk of bias' assessment.

We resolved disagreements by discussion.

### Assessment of risk of bias in included studies

We identified no new studies in this update. For the 2015 version of this review, we used the 'Risk of bias' assessment tool and criteria set out in the *Cochrane Handbook for Systematic Reviews*



of *Interventions* to assess the risk of bias for the included study (Higgins 2011). Two review authors (AA, AS) independently assessed the risk of bias of the included study by assessing randomisation sequence generation; allocation concealment; blinding of participants, personnel, and outcome assessors; incomplete outcome data; selective outcome reporting; and other sources of bias. We resolved disagreements through discussion. We reported results in a 'Risk of bias' table.

### Measures of treatment effect

We presented results for dichotomous outcomes as risk ratio (RR) and hazard ratio (HR) with 95% confidence intervals (CI) (as reported in the included study). For continuous outcomes, we intended to express the measure of effect as a mean difference (MD) with 95% CI. However, data from the included study did not permit this analysis.

### Dealing with missing data

We found attrition rates of 9.52% in the zinc arm and 11.62% in the placebo arm of the included study. We did not impute missing data.

### Assessment of heterogeneity

We planned to assess statistical heterogeneity via visual inspection of forest plots of the included trials, using the  $\text{Chi}^2$  test and the  $I^2$  statistic, where data from included trials could be pooled. However, as there was only one included study, we could not conduct this assessment using the available data.

### Assessment of reporting biases

We compared the list of outcomes in the methods section of the included study to the outcomes reported. We could not create an inverted funnel plot to check for possible publication bias because there were too few included studies.

### Data synthesis

We entered data into Review Manager 5 software (RevMan 2014). As only one study was included in this review, data could not be combined for meta-analysis. We provided a narrative summary of findings for the included study.

### GRADE and 'Summary of findings' table

We created a [Summary of findings for the main comparison](#) using the following outcomes: mortality and time to fever abatement. We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of evidence as it related to the included study (Atkins 2004). We used methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), employing GRADEpro GDT software (GRADEpro GDT 2014). We justified decisions to downgrade study quality in footnotes, and made comments to aid readers understanding of the review where necessary.

### Subgroup analysis and investigation of heterogeneity

We planned to explore any observed significant heterogeneity by conducting subgroup analyses based on the characteristics of participants (inpatient and outpatient, age group), type of comparison (placebo and standard treatment), type of supplement, dose and duration of supplement, and immunisation status. Due to insufficient data we were unable to conduct these analyses.

### Sensitivity analysis

We planned to conduct sensitivity analyses to assess the impact of high risk of bias on meta-analysed outcomes by gradually adding studies with high risk of bias to pooled studies with low risk of bias. We did not perform these analyses due to insufficient data.

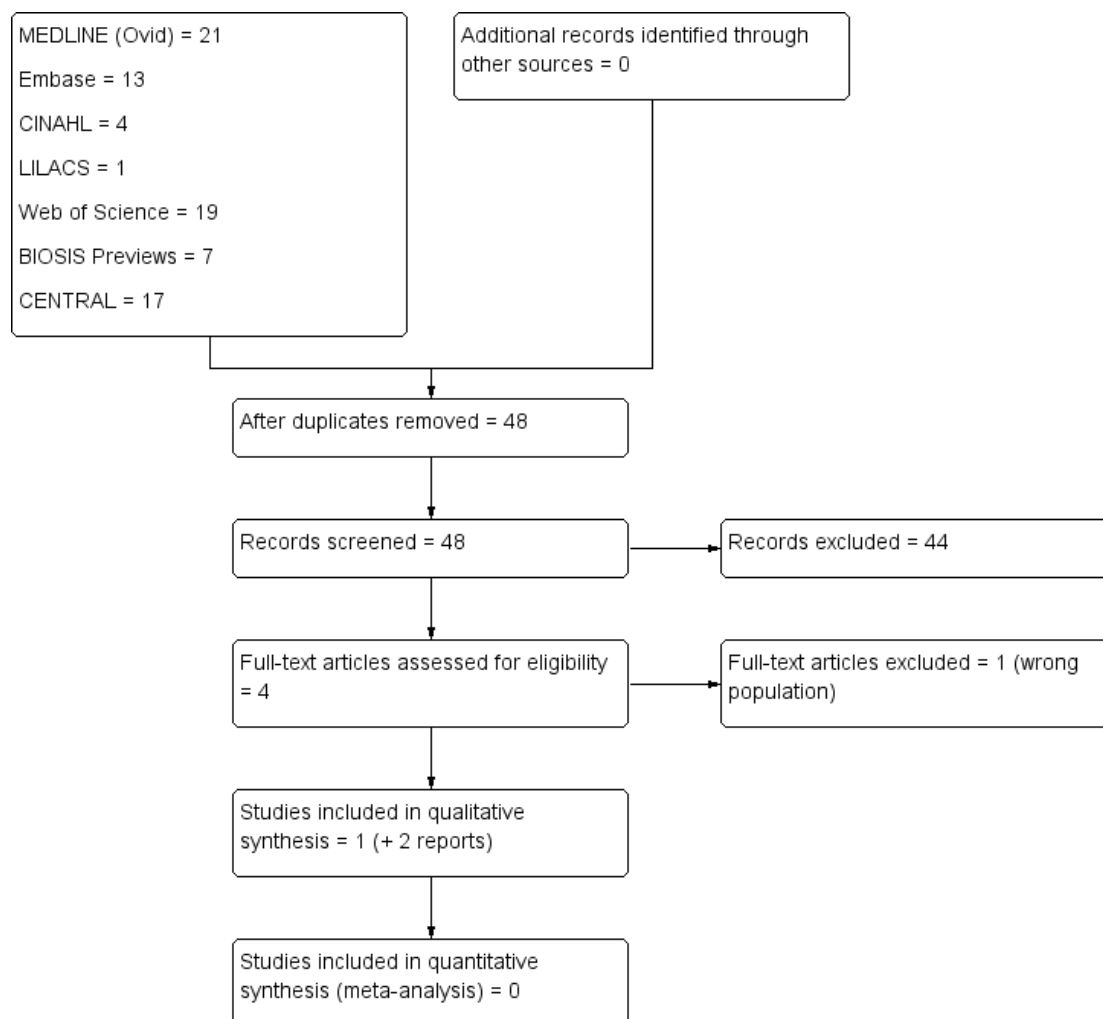
## RESULTS

### Description of studies

#### Results of the search

This is an update of a review first published in 2015. The most recent search (February 2017) did not identify any new studies for inclusion (Figure 1; [Characteristics of included studies](#)).

**Figure 1. Study flow diagram.**



We retrieved 48 records from the searches of electronic databases. We found no ongoing studies in the following trial registries: ClinicalTrials.gov, the Australian New Zealand Clinical Trials Registry, and the WHO ICTRP. Two review authors (AA, OO) independently scanned titles and abstracts using prespecified inclusion criteria. We identified four potentially eligible studies and obtained full-text articles. One study met our inclusion criteria and was included in the review. We provided reasons for excluding a potentially eligible study (see [Characteristics of excluded studies](#)).

### Included studies

We included one RCT (three reports) that compared zinc supplement with placebo ([Mahalanabis 2002](#)). This was a double-blind, randomised, placebo-controlled trial carried out in a tertiary care

hospital in India. There were 85 participants: 42 in the zinc group and 43 in the placebo group. Participants were children admitted to the hospital with an illness that was compatible with measles (generalised maculopapular rash with fever and at least one of the following: cough, coryza, or conjunctivitis and a clinical diagnosis of acute lower respiratory tract infection (pneumonia)). Children who had congenital anomalies, chronic diseases, or severe malnutrition were excluded from the study.

[Mahalanabis 2002](#) compared a zinc acetate mixture containing 20 mg elemental zinc with placebo, each given twice daily for six days. All trial participants also received a single dose of vitamin A and antibiotics. The duration of therapy and follow-up was six days. The study aimed to compare the clinical status (duration of significant illness, fever and tachypnoea) of participants in the

zinc and placebo groups. The study also assessed serum zinc and retinol concentrations. Mahalanabis 2002 used the Chi<sup>2</sup> test or Fisher's exact test as well as survival analysis (Cox proportional hazards model) to compare groups. P values were reported.

The baseline characteristics of children in the zinc and placebo groups were similar. These included age, gender, duration of measles rash, weight-for-age (z score), height-for-age (z score), and difficulty in eating or feeding (%). Five participants in the placebo arm and three in the zinc arm withdrew from the study; one child in the zinc arm dropped out on day one due to breakage of the bottle containing the supplement. One child in the control group, who was admitted in a coma and diagnosed clinically with septi-

caemia, died.

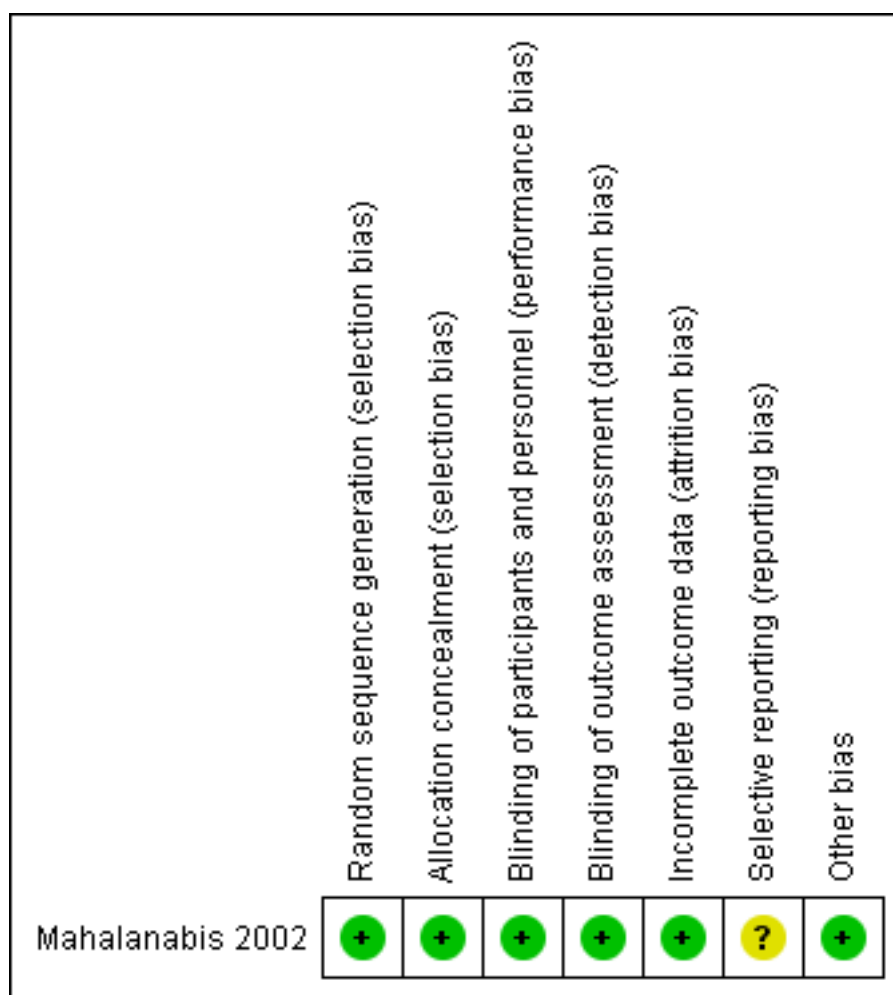
### Excluded studies

We excluded one study: Tielsch 2007 included children who did not have measles (see Characteristics of excluded studies).

### Risk of bias in included studies

We assessed risk of bias in the included study using the Cochrane 'Risk of bias' tool for RCTs (Figure 2). We assessed risk of bias as low for most domains, and unclear for selective reporting.

**Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.**



## Allocation

Allocation of participants to receive either the zinc supplement or placebo was done using permuted blocks of random numbers to create a master randomisation schedule. The allocation sequence was concealed using serially numbered, identical bottles. We assessed Mahalanabis 2002 as at low risk of bias for this domain.

## Blinding

Participants received serially numbered bottles, which contained mixtures that were identical in colour, consistency, and taste, ensuring adequate blinding. We assessed Mahalanabis 2002 as at low risk of bias for this domain.

## Incomplete outcome data

Losses to follow-up were similar in both the intervention and control groups. The attrition rates were 9.52% in the zinc group and 11.62% in the placebo group. We assessed Mahalanabis 2002 as at low risk of bias for this domain.

## Selective reporting

We could not locate a registered trial protocol to compare the pre-specified outcomes with the outcomes reported in the manuscript. We assessed Mahalanabis 2002 as at unclear risk of bias for this domain.

## Other potential sources of bias

We did not identify any other potential sources of bias.

## Effects of interventions

See: [Summary of findings for the main comparison Zinc versus placebo for the treatment of measles in children](#)

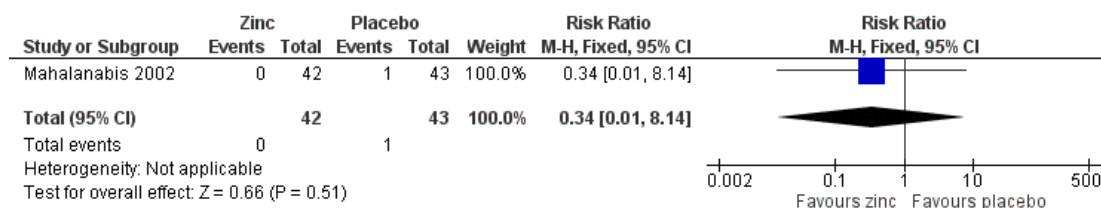
Mahalanabis 2002 reported the following outcomes: median (quartiles) time required for resolution of fever and tachypnoea, return of appetite, and achievement of a much improved or cured status. This review proposed assessment of a number of other outcomes that were not reported by Mahalanabis 2002: duration of coryza, cough, and rash; incidence of complications such as pneumonia, otitis media, diarrhoea, and croup; and effect on disability-adjusted life years.

## Primary outcome

### I. All-cause mortality

There was no statistically significant difference in all-cause mortality between children in the zinc supplementation plus standard treatment group and children in the placebo plus standard treatment group (RR 0.34, 95% CI 0.01 to 8.14;  $P = 0.51$ ; [Analysis 1.1](#); [Figure 3](#)).

**Figure 3. Forest plot of comparison: I Zinc versus placebo, outcome: I.I Mortality.**

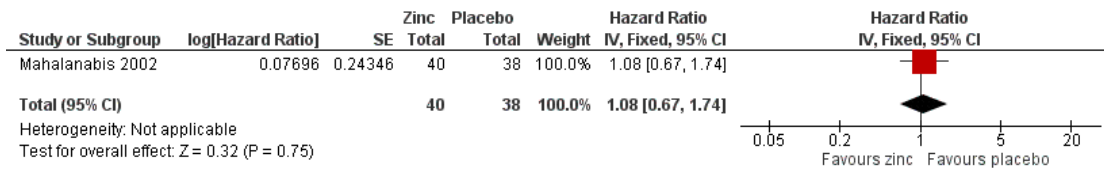


## Secondary outcomes

### I. Duration of fever, coryza, cough, and exanthema (rash)

Zinc supplementation in children with measles showed a non-significant effect on time to absence of fever compared to the placebo group (HR 1.08, 95% CI 0.67 to 1.74, fixed-effect model;  $P = 0.75$ ; [Analysis 1.2](#); [Figure 4](#)).

**Figure 4. Forest plot of comparison: I Zinc versus placebo, outcome: I.2 Time to fever abatement.**



## 2. Duration of hospitalisation

All children enrolled were hospitalised for the study duration (Mahalanabis 2002).

## 3. Incidence of complications such as pneumonia, otitis media, diarrhoea, and croup

Mahalanabis 2002 did not report the incidence of complications.

## 4. Effect on disability-adjusted life years

Mahalanabis 2002 did not report the effect on disability-adjusted life years.

## 5. Adverse events

Mahalanabis 2002 did not report any treatment-related side effects in either group.

# DISCUSSION

## Summary of main results

This is an update of a review first published in 2015 and included no new studies. Previous conclusions are unchanged.

The included study involved 85 children: 42 received a zinc acetate mixture containing 20 mg elemental zinc, and 43 received placebo (Mahalanabis 2002). All children were diagnosed with measles and pneumonia and all received vitamin A and antibiotics. One child in the placebo group died during the trial.

Mahalanabis 2002 demonstrated no significant difference in duration of fever between groups. All enrolled children were hospitalised for the entire duration of the study. No treatment-related side effects were reported in either group.

## Overall completeness and applicability of evidence

We conducted a comprehensive search to identify all relevant studies that met our inclusion criteria. We found only one study that met the inclusion criteria. There was no significant difference in outcomes reported between groups in the included study (Mahalanabis 2002).

The evidence for this review was drawn from a single small study that was not adequately powered. Mahalanabis 2002 was conducted in a tertiary healthcare setting in India. We are not confident about the observed effect estimates because of imprecision of the results. It is therefore difficult to comment on the applicability of the available evidence.

## Quality of the evidence

We used the GRADE approach to assess the quality of the evidence in this review (GRADEpro GDT 2014; Higgins 2011; Schünemann 2011). We carried out one comparison: zinc acetate versus placebo for children with measles for two outcomes (mortality and reduction of fever duration). We downgraded the quality of the evidence based on imprecision of the effect estimates (small sample size and few events) and indirectness. We assessed the quality of the evidence as very low. We are therefore very uncertain about the estimate.

## Potential biases in the review process

We identified one RCT for inclusion using the comprehensive search strategy developed by the Cochrane Acute Respiratory Infections Group. We applied no language or publication limitations. We also searched three clinical trial registries and did not find any ongoing trials. Other potential biases were limited by ensuring that two review authors independently conducted the study selection, quality assessment, and data extraction.

## Agreements and disagreements with other studies or reviews

A previous Cochrane Review did not find sufficient evidence to support use of zinc as an adjunct to standard antibiotic therapy for pneumonia in children aged 2 months to 35 months (Haider 2011). Another Cochrane Review concluded that zinc supplementation in children is associated with a reduction in the incidence and prevalence of pneumonia (Lassi 2016).

## AUTHORS' CONCLUSIONS

### Implications for practice

We could draw no definitive conclusions from this review about the effects of zinc supplementation on clinical outcomes for children with measles due to the very low quality of the available evidence. The current evidence is not conclusive and neither supports nor refutes the use of zinc supplementation in children with measles.

### Implications for research

Adequately powered studies addressing clinically relevant outcomes such as age-specific mortality, incidence of complications (such as pneumonia, otitis media, diarrhoea, and croup), and the effect on disability-adjusted life years are required for better assessment of the impact of zinc supplementation in children with measles.

## ACKNOWLEDGEMENTS

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We thank Sarah Thorning for her help with the search strategy. We also thank the following people for commenting on the draft of this review: Derek Ansel, Theresa Wrangham, Robert Black, Elaine Beller, and Taixiang Wu.

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\* Mahalanabis D, Chowdhury A, Jana S, Bhattacharya MK, Chakrabarti MK, Wahed MA, et al. Zinc supplementation as adjunct therapy in children with measles accompanied by pneumonia: a double-blind, randomized controlled trial. *American Journal of Clinical Nutrition* 2002;**76**(3):604–7. [PUBMED: 12198006]

Mahalanabis D, Chowdhury A, Jana S, Bhattacharya MK, Chakrabarty MK, Wahed MA, et al. Zinc supplementation of children suffering from measles with pneumonia: effect on diseases severity. *FASEB Journal* 2001;**15**(5):A1094.

### References to studies excluded from this review

#### Tielsch 2007 {published data only}

Tielsch JM, Khatry SK, Stoltzfus RJ, Katz J, LeClerq SC, Adhikari R, et al. Effect of daily zinc supplementation on child mortality in southern Nepal: a community-based, cluster randomised, placebo-controlled trial. *Lancet* 2007; **370**(9594):1230–9. [PUBMED: 17920918]

### Additional references

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\* Indicates the major publication for the study



## CHARACTERISTICS OF STUDIES

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

#### Mahalanabis 2002

Methods	Study design: randomised, placebo-controlled trial Study duration: 6 days (dates not reported)
Participants	<p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Setting: tertiary care hospital</li> <li>• Country: India</li> <li>• Health status: children admitted to the hospital with an illness that was compatible with measles and a clinical diagnosis of acute lower respiratory infection (pneumonia)</li> <li>• Number: zinc + supportive care (N = 42); placebo + supportive care (N = 43)</li> <li>• Age: 9 months to 15 years</li> <li>• Sex (M/F): zinc group (18/24); placebo (25/18)</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Congenital anomalies</li> <li>• Chronic diseases</li> <li>• Severe malnutrition</li> </ul>
Interventions	<p><b>Zinc group</b></p> <ul style="list-style-type: none"> <li>• Zinc acetate mixture containing 20 mg elemental zinc given twice daily for 6 days</li> <li>• Vitamin A and antibiotics</li> </ul> <p><b>Placebo group</b></p> <ul style="list-style-type: none"> <li>• Syrup-based mixture given twice daily for 6 days</li> <li>• Vitamin A and antibiotics</li> </ul>
Outcomes	The main outcome of the study was the clinical status of the participants. Serum zinc and retinol concentrations were also assessed
Notes	The study protocol was approved by the hospital's ethics committee Funding: The study was funded by the Child Health Foundation (USA) and the Nestlé Foundation

#### *Risk of bias*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Permuted blocks of random numbers to create a master randomisation schedule
Allocation concealment (selection bias)	Low risk	Serially numbered, identical bottles
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Serially numbered bottles that contained mixtures that were identical in colour, consistency, and taste, ensuring adequate blinding

**Mahalanabis 2002** (Continued)

		An independent pharmaceutical chemist ensured adequate blinding of the primary investigators
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The evaluating physician had no knowledge of the treatment group to which any of the children belonged
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates were 9.52% in the zinc group and 11.62% in the placebo group
Selective reporting (reporting bias)	Unclear risk	No protocol with prespecified outcomes identified.
Other bias	Low risk	None

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

Study	Reason for exclusion
<a href="#">Tielsch 2007</a>	This was a community-based, cluster-randomised, double-masked, placebo-controlled 2 x 2 factorial trial in children aged 1 to 35 months. The study participants did not have measles

## DATA AND ANALYSES

### Comparison 1. Zinc versus placebo

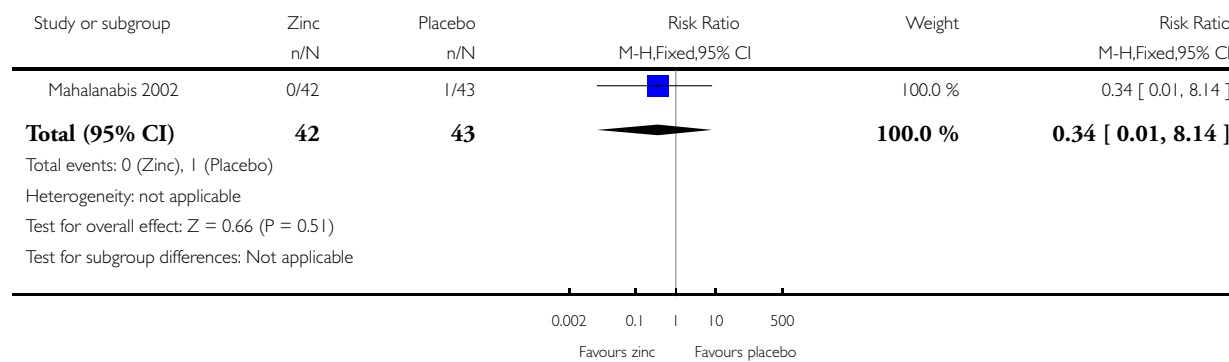
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	1	85	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.01, 8.14]
2 Time to fever abatement	1	78	Hazard Ratio (Fixed, 95% CI)	1.08 [0.67, 1.74]

#### Analysis 1.1. Comparison 1 Zinc versus placebo, Outcome 1 Mortality.

Review: Zinc supplementation for the treatment of measles in children

Comparison: 1 Zinc versus placebo

Outcome: 1 Mortality

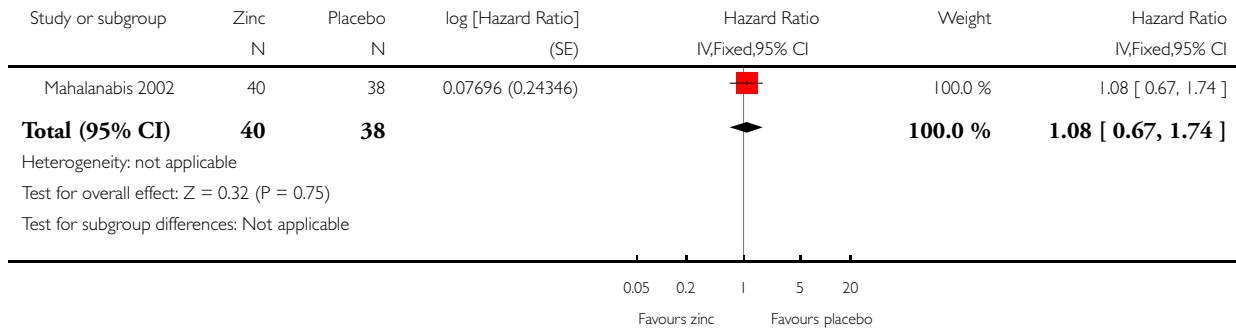


## Analysis 1.2. Comparison 1 Zinc versus placebo, Outcome 2 Time to fever abatement.

Review: Zinc supplementation for the treatment of measles in children

Comparison: 1 Zinc versus placebo

Outcome: 2 Time to fever abatement



## APPENDICES

### Appendix I. MEDLINE (Ovid) search strategy

- 1 exp Measles/
- 2 exp Measles virus/
- 3 Morbillivirus Infections/
- 4 Morbillivirus/
- 5 (measles\* or rubeola\*).tw.
- 6 or/1-5
- 7 exp Zinc/
- 8 exp Zinc Acetate/
- 9 Zinc Sulfate/
- 10 exp Zinc Compounds/
- 11 (zinc or zn).tw,nm.
- 12 Trace Elements/
- 13 Dietary Supplements/
- 14 or/7-13
- 15 6 and 14

## Appendix 2. Embase (Elsevier) search strategy

#1	<p>#1.14 #1.5 AND #1.13 87  #1.13 #1.6 OR #1.7 OR #1.8 OR #1.9 OR #1.10 OR #1.11 OR #1.12  #1.12 zinc:ab,ti OR zn:ab,ti AND [embase]/lim  #1.11 'zinc derivative'/de AND [embase]/lim  #1.10 'zinc chloride'/de AND [embase]/lim  #1.9 'gluconate zinc'/de AND [embase]/lim  #1.8 'zinc sulfate'/de AND [embase]/lim  #1.7 'zinc acetate'/de AND [embase]/lim  #1.6 'zinc'/de AND [embase]/lim  #1.5 #1.1 OR #1.2 OR #1.3 OR #1.4  #1.4 measles:ab,ti OR rubeola:ab,ti AND [embase]/lim  #1.3 'morbillivirus infection'/de AND [embase]/lim  #1.2 'measles virus'/de AND [embase]/lim  #1.1 'measles'/de AND [embase]/lim</p>
#2	<p>#2.8 #2.3 NOT #2.7 881901  #2.7 #2.4 NOT #2.6  #2.6 #2.4 AND #2.5  #2.5 'human'/de AND [embase]/lim  #2.4 'animal'/de OR 'nonhuman'/de OR 'animal experiment'/de AND [embase]/lim  #2.3 #2.1 OR #2.2  #2.2 random*:ab,ti OR placebo*:ab,ti OR crossover*:ab,ti OR 'cross over':ab,ti OR allocat*:ab,ti OR trial:ti OR (doubl* NEXT/1 blind*):ab,ti AND [embase]/lim  #2.1 'randomized controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp AND [embase]/lim</p>
#3	#1 AND #2

## Appendix 3. CINAHL (Ebsco) search strategy

S1 (MH "Measles+")  
S2 TI (measles or rubeola) OR AB (measles or rubeola)  
S3 S1 OR S2  
S4 (MH "Zinc")  
S5 (MH "Zinc Compounds+")  
S6 (MH "Trace Elements")  
S7 (MH "Dietary Supplements")  
S8 TI (zinc or zn) OR AB (zinc or zn)  
S9 S4 OR S5 OR S6 OR S7 OR S8  
S10 S3 AND S9

#### Appendix 4. LILACS (BIREME) search strategy

w:(mh:measles OR measles OR sarampión OR sarampo OR rubeola OR mh:c02.782.580.600.500.500\* OR mh:“Measles virus” OR mh:b04.820.455.600.650.500.500\* OR mh:b04.909.777.455.600.650.500.500\* OR mh:“Morbillivirus Infections” OR mh:morbillivirus) AND (mh:zinc OR zinc OR zinco OR mh:“Zinc Compounds” OR mh:d01.975\* OR mh:“Zinc Acetate” OR zn OR mh:“Trace Elements” OR mh:“Dietary Supplements”)) AND (instance:“regional”) AND ( type of study:(“clinical trials”))

#### Appendix 5. Web of Science (Thomas Reuters) search strategy

#1	<b>TOPIC:</b> (measles or rubeola) <i>Indexes=SCI-EXPANDED, SSCI, A&amp;HCI, CPCI-S, CPCI-SSH, CCR-EXPANDED, IC Timespan=All years</i>
#2	<b>TOPIC:</b> (zinc or zn) <i>Indexes=SCI-EXPANDED, SSCI, A&amp;HCI, CPCI-S, CPCI-SSH, CCR-EXPANDED, IC Timespan=All years</i>
#3	#2 AND #1 <i>Indexes=SCI-EXPANDED, SSCI, A&amp;HCI, CPCI-S, CPCI-SSH, CCR-EXPANDED, IC Timespan=All years</i>
#4	<b>TOPIC:</b> (random* or placebo* or crossover* or “cross over” or allocat* or ((singl* or doubl*) NEAR/1 blind*)) OR <b>TITLE:</b> (trial) <i>Indexes=SCI-EXPANDED, SSCI, A&amp;HCI, CPCI-S, CPCI-SSH, CCR-EXPANDED, IC Timespan=All years</i>
#5	#4 AND #3 <i>Indexes=SCI-EXPANDED, SSCI, A&amp;HCI, CPCI-S, CPCI-SSH, CCR-EXPANDED, IC Timespan=All years</i>

#### Appendix 6. BIOSIS Previews (Thomson Reuters) search strategy

#1	<b>TOPIC:</b> (measles or rubeola) <i>Indexes=BIOSIS Previews Timespan=All years</i>
#2	<b>TOPIC:</b> (zinc or zn) <i>Indexes=BIOSIS Previews Timespan=All years</i>
#3	#2 AND #1 <i>Indexes=BIOSIS Previews Timespan=All years</i>
#4	<b>TOPIC:</b> (random* or placebo* or crossover* or “cross over” or allocat* or ((singl* or doubl*) NEAR/1 blind*)) OR <b>TITLE:</b> (trial) <i>Indexes=BIOSIS Previews Timespan=All years</i>
#5	#4 AND #3 <i>Indexes=BIOSIS Previews Timespan=All years</i>

## WHAT'S NEW

Last assessed as up-to-date: 3 February 2017.

Date	Event	Description
3 February 2017	New citation required but conclusions have not changed	Our conclusions remain unchanged.
3 February 2017	New search has been performed	We did not identify any new trials for inclusion.

## CONTRIBUTIONS OF AUTHORS

Ajibola Awotiwon wrote the protocol, with insightful comments from Olabisi Oduwole, Anju Sinha, and Charles Okwundu.

Ajibola Awotiwon and Olabisi Oduwole reviewed the search outputs, selected studies for inclusion, and located copies of relevant studies.

Ajibola Awotiwon and Anju Sinha extracted data.

Ajibola Awotiwon wrote the review under the supervision of Charles Okwundu.

Ajibola Awotiwon, Olabisi Oduwole, and Anju Sinha reviewed the updated search results.

Ajibola Awotiwon updated the review.

## DECLARATIONS OF INTEREST

Ajibola Awotiwon: none known.

Olabisi Oduwole: none known.

Anju Sinha: none known.

Charles Okwundu: none known.

## SOURCES OF SUPPORT

### Internal sources

- Center for Evidence-based Health Care, Stellenbosch University, South Africa.

**External sources**

- No sources of support supplied

**INDEX TERMS****Medical Subject Headings (MeSH)**

Fever [therapy]; Measles [complications; mortality; \*therapy]; Pneumonia [therapy]; Randomized Controlled Trials as Topic; Zinc [\*administration & dosage; deficiency]

**MeSH check words**

Child; Humans