Prevention of diarrhea and pneumonia by zinc supplementation in children in developing countries: pooled analysis of randomized controlled trials


Authors' objectives
To assess the effects of zinc supplementation in the prevention of diarrhea and pneumonia in children in developing countries.

Searching
MEDLINE, SCI-SCIMATE and Current Contents were searched. References from papers were screened. Contact was made with possible funding agencies and with investigators in micronutrition.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were included.

Specific interventions included in the review
Dietary supplementation of at least one half of the United States Recommended Daily Allowance (RDA) of zinc in children given for at least 2 weeks was studied. This Recommended Daily Allowance was 5 mg elemental zinc/d for infants and 10 mg/d for children aged 1 to 4 years. Actual supplements of zinc were given in the following forms: gluconate (10 mg); methionate (20 mg); sulphate (5 to 20 mg); and acetate (20 mg). Supplements were given either as "continuous" supplementation with supplements (1 to 2 RDA given 5 to 7 times per week) given for the entire period of morbidity surveillance or as "short-course" trials in which supplements (2 to 4 RDA daily) were given for a short period (2 weeks) and morbidity surveillance was done subsequently. Other minerals and vitamins were acceptable if provided to both experimental and control groups. Concurrent supplements included Vitamins A, B, D, E and iron and some control groups received a placebo. Duration of interventions ranged from 2 weeks to 54 weeks.

Participants included in the review
Children under 5 years of age in developing countries were studied. Participating children ranged in age from 3 to 60 months and included apparently healthy children, those recovering from acute or persistent diarrhea and those with weight/height and/or height/age less than 2 standard deviations compared with the National Center for Health Statistics. The study populations varied substantially in background characteristics, including nutritional status with children in the short-course trials being less well nourished than those in the continuous trials.

Outcomes assessed in the review
Rates of diarrhea and pneumonia were assessed with surveillance undertaken by household visits for at least 4 weeks. Definitions of diarrheal outcomes were as follows: a day of diarrhea defined as a 24-hour period with 3 or 4 unformed stools; episode of diarrhea defined as at least 1 day of diarrhea with the final day of the episode being the last day meeting the diarrhea definition followed by 48 hours without diarrhea; episode of dysentery defined as an illness meeting the definition of diarrhea with blood observed in the stools; and an episode of persistent diarrhea defined as a diarrheal illness lasting 14 or more days. Pneumonia was defined as: reported cough of difficult breathing, respiratory rate above WHO defined age specific values and either documented fever > 101 degrees F or chest indrawing; or diagnosis based on chest examination by a physician or chest radiograph.

How were decisions on the relevance of primary studies made?
Two researchers identified relevant studies. Investigators of all identified trials and two external advisors selected by the World Health Organization Program on Child Health and Development contributed to consensus on inclusion criteria.

Assessment of study quality
A methodological assessment and scoring system with a maximum of 100 points was developed. No details were given of criteria used. Studies were independently scored by two researchers with any disagreements being resolved by a further review of methods and consensus.

**Data extraction**
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction. The following data appears to have been extracted: country; sample size per intervention group; characteristics of children (age and enrolment criteria); intervention details; illiteracy rates in mothers; rates of growth retardation in sample; and plasma zinc concentrations. For trials meeting the inclusion criteria, all but one investigator provided the necessary data and descriptive information. Odds ratios (OR) and 95% confidence intervals were calculated for persistent diarrhea, dysentery and pneumonia.

**Methods of synthesis**
How were the studies combined?
A random-effects model was used to calculate summary ORs and 95% CI separately for continuous supplementation trials and short-course trials.

How were differences between studies investigated?
ORs of individual trials were presented graphically though no formal evaluation of statistical heterogeneity was undertaken. Analyses were defined a priori for the following subgroups: age (< 12 months vs >= 12 months); plasma zinc concentration (< 60 micrograms/dL vs >= 60 micrograms/dL); weight for height (< -2z vs >= -2z) compared with the National Center for Health Statistics reference; and sex.

**Results of the review**
Ten RCTs were included (1800 children) comprising 7 RCTs of continuous supplementation (1502 children) and 3 RCTs of short-course supplementation (298 children).

Methodological scores ranged from 76 to 95 (maximum 100).

Continuous supplementation:

Diarrheal incidence (7 RCTs): zinc supplementation was associated with significantly lower incidence. OR = 0.82 (95% CI: 0.72, 0.93).

Diarrheal prevalence (7 RCTs): zinc supplementation was associated with significantly lower incidence. OR = 0.75 (95% CI: 0.63, 0.88).

Persistent diarrhea (5 RCTs): no significant effect of zinc supplementation was found. OR = 0.67 (95% CI: 0.42, 1.06).

Dysentery (3 RCTs): no significant effect of zinc supplementation was found. OR = 0.87 (95% CI: 0.64, 1.19).

Pneumonia (4 RCTs): zinc supplementation was associated with significantly lower incidence. OR = 0.59 (95% CI: 0.41, 0.83).

Incidence of diarrheal illness or pneumonia did not vary significantly between any of the subgroups analyses (age, zinc concentration, nutritional status, and sex). Results displayed in graphical format only.

Overall there was no statistically significant interaction between methodological quality and any of the outcomes apart from diarrheal prevalence for which a negative correlation was found (Pearson r = -0.768, P = 0.04).

No significant effect was seen between dose and effect size for diarrheal incidence (Pearson r = 0.655, P = 0.11), diarrheal prevalence (Pearson r = 0.298, P = 0.52); or pneumonia incidence (Pearson r = -0.340, P = 0.66).
Short-course trials:

Diarrheal incidence (3 RCTs): no significant effect of zinc supplementation was found. OR = 0.89 (95% CI: 0.62, 1.28).

Diarrheal prevalence (3 RCTs): zinc supplementation was associated with significantly lower incidence. OR = 0.66 (95% CI: 0.52, 0.83).

Pneumonia (2 RCTs): no significant effect of zinc supplementation zinc was found. OR = 0.74 (95% CI: 0.40, 1.37).

Authors' conclusions

Zinc supplementation in children in developing countries is associated with substantial reductions in the rates of diarrhea and pneumonia, the two leading causes of deaths in these settings.

CRD commentary

The aims of the review were stated and inclusion criteria defined in terms of study design, participants, setting and outcomes. Several sources were searched for relevant studies and methods used to select primary studies and score validity were described. Primary studies were limited to RCTs and a validity assessment undertaken. Some relevant details of included studies were presented in tabular format. Sensitivity analyses were undertaken with subgroups determined a priori.

Full details of the search strategy such as keywords used, language restrictions and dates searched were omitted. Limiting retrieval to published studies may have resulted in publication bias. No details were given of validity criteria and assessment of statistical heterogeneity was limited to graphical presentation of OR from individual studies. It was not clear whether data were extracted on an intention-to-treat basis. Without more details of the literature search, it is not possible to assess the comprehensiveness of the search and without specification of validity criteria it is not possible to assess the quality of the studies on which conclusions are based. Hence, caution is advised when considering the authors' conclusions.

Implications of the review for practice and research

Practice: The authors state that the benefits of zinc supplementation are not limited to selected groups, and that interventions should include all economically disadvantaged children in developing countries with likely zinc deficiency and high rates of infectious morbidity.

Research: The authors state that assessment of the effect of zinc supplementation on child mortality is a priority, and that development of effective and feasible interventions to improve zinc status in developing country populations is essential. Dietary diversification, enhancement of bioavailable zinc in foods by genetic engineering and plant breeding, and periodic supplementation are possible interventions that should be evaluated. They consider that definitive answers will come from RCTs with stratification to assess effects in particular subgroups. They also state that it would be helpful to have simple dietary assessment methods to decide which populations would benefit from interventions to improve zinc nutrition.

Bibliographic details


PubMedID

10586170
Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
Child; Developing Countries; Diarrhea /prevention & control; Dietary Supplements; Humans; Pneumonia /prevention & control; Randomized Controlled Trials as Topic; Zinc /therapeutic use

AccessionNumber
12000000151

Date bibliographic record published
30/04/2001

Date abstract record published
30/04/2001

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.