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Effect of routine zinc supplementation on pneumonia in children aged 6 months to 3 years: randomised controlled trial in an urban slum

Nita Bhandari, Rajiv Bahl, Sunita Taneja, Tor Strand, Kåre Mølbaek, Rune Johan Ulvik, Halvor Sommerfelt, Maharaj K Bhan

Department of
Paediatrics, All
India Institute of
Medical Sciences,
Ansari Nagar,
New Delhi-110029,
India

Nita Bhandari
scientist

Rajiv Bahl
scientist

Sunita Taneja
scientist

Maharaj K Bhan
professor

Centre for
International
Health, University
of Bergen, 5021
Bergen, Norway

Tor Strand
research fellow

Halvor Sommerfelt
professor

Statens Serum
Institut, Artillerivej
5-2300

Copenhagen S,
Denmark

Kåre Mølbaek
senior researcher

Institute of Clinical
Biochemistry,
University of
Bergen, Bergen

Rune Johan Ulvik
professor

Correspondence to:
M K Bhan
community.research@cih.uib.no

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Abstract

Objectives To evaluate the effect of daily zinc supplementation in children on the incidence of acute lower respiratory tract infections and pneumonia.

Design Double masked, randomised placebo controlled trial.

Setting A slum community in New Delhi, India.

Participants 2482 children aged 6 to 30 months.

Interventions Daily elemental zinc, 10 mg to infants and 20 mg to older children or placebo for four months. Both groups received single massive dose of vitamin A (100 000 IU for infants and 200 000 IU for older children) at enrolment.

Main outcome measures All households were visited weekly. Any children with cough and lower chest indrawing or respiratory rate 5 breaths per minute less than the World Health Organization criteria for fast breathing were brought to study physicians.

Results At four months the mean plasma zinc concentration was higher in the zinc group (19.8 (SD 10.1) v 9.3 (2.1) $\mu\text{mol/l}$, $P < 0.001$). The proportion of children who had acute lower respiratory tract infection during follow up was no different in the two groups (absolute risk reduction -0.2%, 95% confidence interval -3.9% to 3.6%). Zinc supplementation resulted in a lower incidence of pneumonia than placebo (absolute risk reduction 2.5%, 95% confidence interval 0.4% to 4.6%). After correction for multiple episodes in the same child by generalised estimating equations analysis the odds ratio was 0.74, 95% confidence interval 0.56 to 0.99.

Conclusions Zinc supplementation substantially reduced the incidence of pneumonia in children who had received vitamin A.

Introduction

Zinc deficiency is common in children in developing countries because of low food intake, particularly from animal sources, limited zinc bioavailability from local diets, and losses of zinc during recurrent diarrhoeal illnesses.^{1 2} Zinc deficiency leads to impairment in immunological and other defences that increases rates of serious infections.³⁻⁹ Trials of zinc supplements are a reliable method of assessing the health consequences of zinc deficiency. In developing countries a significantly lower incidence and prevalence of diarrhoea has consistently been observed in children given zinc supplements.^{2 10 11}

Lower respiratory tract infections are a common cause of death in childhood. The effect of zinc supplementation on such infections is still unclear. Two of the published trials that found no significant effect were small.² Another relatively larger trial reported a 45% reduction in the incidence of pneumonia,¹² but the cri-

teria for its diagnosis included high fever, a sign that is not diagnostic for pneumonia nor an established indicator of its severity.

We evaluated the impact of daily zinc supplementation in preschool children who had received a large dose of vitamin A, a routine practice in this setting, on the incidence of acute lower respiratory tract infections and pneumonia.

Methods

Study setting

The trial took place in the urban slum of Dakshinpuri in New Delhi, India, comprising 15 000 dwellings and 75 000 inhabitants. Recent data from a neighbouring community indicated that childhood malnutrition, zinc deficiency, diarrhoea, and lower respiratory tract infections were common.^{3 11 12}

Randomisation and masking

We included children if their parents gave informed consent. Eligible children were individually randomised by a simple randomisation scheme in blocks of eight. Zinc or placebo syrups were prepared and packaged in unbreakable bottles. Six bottles, one for each month and two extra, for each child were produced and labelled before enrolment commenced. The zinc and placebo syrups were similar in appearance, taste, and packaging. Masking was maintained during analyses by coding the groups as A or B.

Enrolment and intervention delivery

Enrolment commenced on 15 February 1999. All children aged 6 to 30 months in the community were identified through a survey. We excluded children if consent was refused, if they were likely to move out of the study area within the next four months, and if they needed urgent admission to hospital on the enrolment day or had received massive dose of vitamin A (100 000 IU for infants and 200 000 for older children) within the two months before enrolment. The follow up of the last child was completed on 30 September 2000.

Doses of elemental zinc were 10 mg for infants and 20 mg for children (twice the recommended daily doses) as zinc gluconate. Zinc or placebo was taken daily for four months. An attendant administered the syrup daily for four months except on Sundays, when the mother administered it.

Measurement of outcomes

Field workers visited each child every seventh day during the entire study. At each visit, mothers were asked about fever, cough, other characteristics of illness, and whether they had sought treatment for the child in the previous seven days. Respiratory rates were counted twice for one minute each and the temperature

recorded. Children with cough and respiratory rates ≥ 35 /min at age ≥ 12 months and ≥ 45 /min at < 12 months or lower chest indrawing were brought to study physicians for assessment. We used the cut offs of 5 breaths/min below the WHO criteria for fast breathing to maximise detection of acute lower respiratory tract infections and pneumonia. Two study physicians examined and repeated measurements of respiratory rate, clinical indicators of hypoxaemia, and auscultation. In cases of disagreement, a senior paediatrician assessed the child. Mothers were encouraged to bring their children to the study clinic whenever they were ill and they were similarly assessed.

Acute lower respiratory tract infections were defined by cough and fast breathing or lower chest indrawing as assessed by the physician; other clinical signs were not taken into account.¹³ Fast breathing was defined as two counts of ≥ 50 breaths/min for infants and ≥ 40 breaths/min for older children. The day of onset of infection was the first day when this combination was detected. The day of recovery was the day after the last day when this combination was present. Pneumonia was diagnosed either by a combination of cough with crepitations or bronchial breathing by auscultation or as an episode of acute lower respiratory tract infection associated with at least one of lower chest indrawing, convulsions, not able to drink or feed, extreme lethargy, restlessness or irritability, nasal flaring, or abnormal sleepiness. For episodes to be counted as individual, there had to be at least 14 intervening days. At enrolment and at the end of the study we measured plasma zinc concentrations.

Results

We identified 3802 children and randomised 2482. The children in the two groups were comparable for age, anthropometry, child feeding practices, morbidity in the previous 24 hours, socioeconomic characteristics, and plasma zinc concentration.

Ninety per cent of intended intervention doses were administered to the trial children. There was a small but significant increase in the average number of days with vomiting in the zinc group (4.3 (SD 5.8) *v* 2.6 (SD 3.9); difference in means 1.7, 95% confidence interval 1.3 to 2.1). Only eight children in the zinc

group and none in the placebo group discontinued the intervention because of vomiting.

Intervention efficacy

The mean plasma zinc concentration was significantly higher at the end of the study in the children who received zinc supplementation (19.8 (SD 10.1) *v* 9.3 (SD 2.1) $\mu\text{mol/l}$, $P < 0.001$ non-parametric test). The change from enrolment was also substantially higher in the zinc group (10.4 (SD 10.0) $\mu\text{mol/l}$) compared with the placebo group (-0.3 (SD 2.2) $\mu\text{mol/l}$, $P < 0.0001$ non-parametric test).

Acute lower respiratory tract infections

In the child based analyses, 425 children in the zinc group and 423 in the placebo group experienced at least one episode of acute lower respiratory tract infection (absolute risk reduction -0.2% , 95% CI -3.9% to 3.6%).

In the person time analyses, the incidence of acute lower respiratory tract infections was 0.53 and 0.54 episodes per four month child period of actual follow up in zinc and placebo groups respectively (absolute risk reduction 1%, -2.9% to 5%). As multiple episodes of acute lower respiratory tract infections in a child may not be independent we performed a generalised estimating equations analysis to correct for this correlation. The results of this analysis were similar to those of the uncorrected analysis (odds ratio 0.98, 0.86 to 1.13, table).

Pneumonia

Eighty one children in the zinc group and 112 in the placebo group had at least one episode of pneumonia (absolute risk reduction 2.5%, 0.4% to 4.6%). The number needed to treat was therefore 40—that is, supplementation of 40 children would be expected to prevent one child from having from pneumonia.

In the person time analyses, the incidence of pneumonia for the four month child period was similarly lower in the zinc group (absolute risk reduction 2.4%, 0.2% to 4.6%). The findings were similar in the generalised estimating equations analysis (odds ratio 0.74, 0.56 to 0.99, table 1).

The number of children admitted to hospital for any cause was lower in the zinc group (absolute risk

Impact of zinc supplementation on acute lower respiratory infections, pneumonia, and admissions to hospital for all causes in children aged 6-35 months during four months of follow up

| | Zinc | Placebo | Absolute risk reduction (95% CI) | Odds ratio* (95% CI) |
|---|------------|------------|----------------------------------|----------------------|
| Child based analysis | | | | |
| No of children | 1241 | 1241 | — | — |
| No (%) with ≥ 1 episodes of acute lower respiratory tract infections | 425 (34.2) | 423 (34.1) | -0.2% (-3.9% to 3.6%) | — |
| No (%) with ≥ 1 episodes of pneumonia | 81 (6.5) | 112 (9.0) | 2.5% (0.4% to 4.6%) | — |
| No (%) admitted to hospital for any cause | 21 (1.8) | 30 (2.4) | 0.6% (-0.5% to 1.8%) | — |
| Person time based analysis† | | | | |
| No of four month child periods | 1100 | 1120 | — | — |
| Acute lower respiratory tract infections: | | | | |
| Total episodes | 581 | 594 | — | — |
| Episodes per four month period | 0.53 | 0.54 | 1% (-2.9% to 5%) | 0.98 (0.86 to 1.13) |
| Pneumonia: | | | | |
| Total episodes | 88 | 118 | — | — |
| Episodes per four month period | 0.08 | 0.105 | 2.4% (0.2% to 4.6%) | 0.74 (0.56 to 0.99) |

*After correction for correlation of data by generalised estimating equations.

†Person time for each child was calculated as total follow up days when reliable informant was available.

reduction 0.6%, -0.5% to 1.8%). Three children, all in the placebo group, died.

Discussion

Daily zinc supplementation of infants and young children in a relatively deprived population prevented one quarter of the episodes of pneumonia in children, all of whom had received the recommended dose of vitamin A. Zinc supplementation had no effect on acute lower respiratory tract infections defined by cough and fast breathing or lower chest indrawing. Routine administration of zinc may therefore be effective in preventing severe rather than mild illness. Previous trials have shown that zinc supplementation has a large effect on the incidence of severe but not mild diarrhoeal illness.^{2 10 11}

The WHO definition of acute lower respiratory tract infections that is commonly used in primary care programmes aims at high sensitivity for detection of true pneumonia at the expense of some loss in specificity. In our study, acute lower respiratory tract infections by WHO criteria had 80% sensitivity but only 69% specificity using physician diagnosis by auscultation as gold standard. Lack of specificity in the diagnostic criteria for measuring study outcomes biases the risk or rate ratio towards null values.¹⁴ This may be an alternate explanation for the observed impact on pneumonia but not on acute lower respiratory tract infections. We defined pneumonia by findings on auscultation or as acute lower respiratory tract infections associated with one or more previously validated indicators of severity.¹⁵⁻¹⁸ Radiology, the ideal method for diagnosis of pneumonia, was impractical to use under field conditions.

In a recent study in Bangladesh there was a significant reduction in the incidence and prevalence of acute lower respiratory tract infections in children supplemented with both zinc and vitamin A. In children who received zinc alone, however, incidence and prevalence increased.¹⁹ We did not examine this issue because vitamin A was given to all the children for ethical reasons. However, in a pooled analysis two of the four studies used zinc without vitamin A but did not report any increased respiratory morbidity.²

Prevention of pneumonia by optimising zinc intakes is biologically plausible. The low mean plasma zinc concentrations at enrolment show that deficiency was common in these children. Supplementation improves immune functions, including delayed cutaneous hypersensitivity, and increases the number of CD4 (helper) lymphocytes.^{20 21} In experimental models zinc deficiency has been shown to impair cellular and humoral immune function.^{21 22}

Conclusions

The findings of current and previous studies show that improving zinc status in deficient populations should substantially reduce serious morbidity. Prompt measures to improve zinc status are therefore warranted, given the substantial and consistent reduction in severe diarrhoea and pneumonia in supplementation trials. The possible approaches include food fortification, dietary diversification, cultivation of plants that are zinc-dense or have a decreased concentration of zinc

What is already known on this topic

Mild to moderate zinc deficiency is common in children in developing countries and increases the risk of respiratory morbidity

What this study adds

A third of children from low socioeconomic classes in India have low plasma concentrations of zinc

Routine zinc supplementation of such children aged 6 months to 3 years substantially reduced the incidence of pneumonia

absorption inhibitors or supplementation of selected subgroups.

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Probiotics in prevention of antibiotic associated diarrhoea: meta-analysis

Aloysius L D'Souza, Chakravarthi Rajkumar, Jonathan Cooke, Christopher J Bulpitt



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Abstract

Objective To evaluate efficacy of probiotics in prevention and treatment of diarrhoea associated with the use of antibiotics.

Design Meta-analysis; outcome data (proportion of patients not getting diarrhoea) were analysed, pooled, and compared to determine odds ratios in treated and control groups.

Identification Studies identified by searching Medline between 1966 and 2000 and the Cochrane Library.

Studies reviewed Nine randomised, double blind, placebo controlled trials of probiotics.

Results Two of the nine studies investigated the effects of probiotics in children. Four trials used a yeast (*Saccharomyces boulardii*), four used lactobacilli, and one used a strain of enterococcus that produced lactic acid. Three trials used a combination of probiotic strains of bacteria. In all nine trials, the probiotics were given in combination with antibiotics and the control groups received placebo and antibiotics. The odds ratio in favour of active treatment over placebo in preventing diarrhoea associated with antibiotics was 0.39 (95% confidence interval 0.25 to 0.62; $P < 0.001$) for the yeast and 0.34 (0.19 to 0.61; $P < 0.01$) for lactobacilli. The combined odds ratio was 0.37 (0.26 to 0.53; $P < 0.001$) in favour of active treatment over placebo.

Conclusions The meta-analysis suggests that probiotics can be used to prevent antibiotic associated diarrhoea and that *S boulardii* and lactobacilli have the potential to be used in this situation. The efficacy of probiotics in treating antibiotic associated diarrhoea remains to be proved. A further large trial in which probiotics are used as preventive agents should look at the costs of and need for routine use of these agents.

Introduction

The term "probiotic" was first used to describe "a live microbial supplement, which beneficially affects the host by improving its microbial balance."¹ Since then, research has looked at possible clinical uses for these agents. In 1995, when a greater understanding of their properties had developed, the term "biotherapeutic agents" was proposed to describe micro-organisms with specific therapeutic properties that also inhibit the growth of pathogenic bacteria.²

Probiotics and their uses

- Probiotics are live organisms that improve the microbial balance of the host
- Probiotics have special properties that make them useful in fighting infections of mucosal surfaces such as the gut and vagina
- Different species of lactobacilli and the yeast *Saccharomyces boulardii* have the potential for use in clinical practice
- Probiotics are becoming increasingly available as capsules and dairy based food supplements sold in health food stores and some supermarkets
- The relative lack of side effects makes probiotics a possible way of preventing antibiotic associated diarrhoea

A number of agents have been isolated and studied with a view to clinical use. *Streptococcus thermophilus* and *Lactobacillus bulgaricus*, commonly used in the dairy food industry, were among the first to be studied. Other strains that have been used are *Bifidobacterium bifidum*, *B longum*, *Enterococcus faecium*, *Saccharomyces boulardii*, *L acidophilus*, *L casei*, and *Lactobacillus GG*. However, doctors are still reluctant to use these agents in clinical practice.

In this paper, we review the results from various trials carried out to study their benefits. We also look at the properties of biotherapeutic agents and options for further research.

Materials and methods

Literature search

We searched Medline between 1966 to 2000 with the terms "probiotics," "biotherapeutic agents," "lactobacilli," "antibiotic associated diarrhoea," and "*Clostridium difficile*." We also searched the Cochrane Controlled Trials Register and the Cochrane Database of Systematic Reviews. We included all randomised double blind trials that compared the effects of probiotic therapy and placebo (both given in combination with antibiotics).

Ten double blind placebo controlled trials were relevant to our area of interest (nine published in English and one in French).³⁻¹² Our meta-analysis included nine that looked at prevention of diarrhoea. We excluded the other trial, which looked at treatment of diarrhoea.¹²

Editorial by Barbut and Meynard

Care of the Elderly Section, Faculty of Medicine, Imperial College School of Medicine, Hammersmith Hospital, London W12 0NN

Aloysius L D'Souza
research fellow

Chakravarthi Rajkumar
senior lecturer and
honorary consultant
Jonathan Cooke
statistician

Christopher J Bulpitt
professor of geriatric
medicine

Correspondence to:
A L D'Souza
alouisius.dsouza@
ic.ac.uk

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