# Should zinc be used in the prevention and management of acute respiratory infections?

Primary Reviewer: **Philip Ayieko**[1], **Mike English**[1] Secondary Reviewer: **W Abdullah Brooks**[2]

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*1 Kenya Medical Research Institute/ Wellcome Trust Collaboration, Nairobi, Kenya*
*2 Department of International Health, Bloomberg School of Public Health, Johns Hopkins University*

The World Health Organization has produced guidelines for the management of common illnesses in hospitals with limited resources. This series reviews the scientific evidence behind WHO's recommendations. The WHO guidelines, and more reviews are available at:
http://www.who.int/child-adolescent-health/publications/CHILD_HEALTH/PB.htm

**This review addresses the question:** *Should zinc be used in the prevention and management of acute respiratory infections?*

The WHO Pocketbook of Hospital Care for Children currently has no recommendation for the use of zinc in ARI.

## INTRODUCTION

The central objective of the WHO's programme for the Control of Acute Respiratory Infections is to reduce the severity of and the mortality from pneumonia in young children. Case management intervention studies have demonstrated the substantial impact which can be achieved by treating children with inexpensive oral antibiotics.[1] Preventive strategies can supplement case management efforts by reducing the incidence of pneumonia or severity of disease when it occurs.[2]Vaccination against pneumococci and Haemophilus influenzae type B have recently been shown to be effective though these may not be readily available in countries where they are most needed due to financial constraints.[3][4][5] Zinc is reported to prevent pneumonia and the 20mg tablet now in production would cost a modest US $ 0.15 for a treatment course.[6] Zinc efficacy trials conducted in children with mild to moderate zinc deficiency have shown significant efficacy in the prevention of pneumonia and improved outcomes during episodes of severe disease. Data from randomized trials are now available on the impact of zinc on incidence and outcomes of respiratory illness.

The purpose of this review is to determine if zinc should be used in the prevention of pneumonia and managing disease episodes when they occur.

## METHODS

The Medline database was searched using Pub Med clinical queries. The clinical search strategy employed was follows: zinc AND pneumonia. Using the clinical filters for both "therapy" and "specific", 7 articles were found; using the same filter but restricting the search to systematic reviews only, 3 further articles were found. All abstracts were read, if there was any doubt as to the relevance of the article, the complete article was sourced. 5 RCTs were found; one was excluded since it was done in children with measles accompanied with pneumonia. All included articles were type 1b. Investigators coordinating ongoing studies on zinc and pneumonia in developing countries were also contacted for information concerning the studies.

## RESULTS

### Effects of zinc on the incidence of pneumonia

Mild to moderate zinc deficiency is common in children in developing countries and increases the risk of respiratory morbidity. Three controlled trials have assessed the effect of zinc supplementation on incidence of pneumonia. Among Indian children from low socioeconomic classes aged 6 to 30 months, daily zinc supplementation substantially reduced the incidence of pneumonia (Absolute risk reduction, 2.5%; 95% CI 0.4% to 4.6%).[7] A study of effects of weekly zinc supplements on incidence of pneumonia and diarrhoea in children younger 2 than years in an urban, low-income population in Bangladesh found that there were significantly fewer incidents of pneumonia in the zinc group than the control group (199/809 vs. 286/812; relative risk 0.83, 95%CI 0.73 to 0.95), and a small but significant effect on the incidence of diarrhea (1881 vs. 2406; 0.94, 0.88-.099).[8]The third study conducted among children with HIV infection in South Africa demonstrated that the proportion of scheduled and illness visits at which children were diagnosed with pneumonia were lower in the zinc than placebo group, but the difference was not significant [57(14%) vs. 83 (18.6%); p=0.07]. [9]

### Effect of zinc on disease in controlled trials

One controlled trial has assessed the effect of zinc administered during a severe episode of pneumonia on the course of the illness.[6] The study showed clinically and statistically significant reductions in recovery time from severe pneumonia and overall hospital stay in children aged less than 2 years old given zinc with standard antimicrobial therapy. Children were included if they had severe pneumonia (raised respiration and either chest indrawing or presence of cyanosis or lethargy or inability to feed). After age was controlled for, each severe pneumonia indicator improved in zinc-supplemented children compared to those receiving placebo. There were shorter durations of chest indrawing [Median duration; 40 h vs. 48 h, Relative hazard; 95% CI 0.80 (0.61-1.05)], respiratory rate more than 50 per minute [48 h vs. 56 h, RH 0.74 (0.57-0.98)], and hypoxia [80 h vs. 88 h, RH 0.79 (0.61-1.04)], leading to shorter

durations of severe pneumonia [72 h vs. 96 h; RH 0.70 (0.51-0.98)] and hospitalization [RH 0.75; 0.57-0.99)].

The WHO is currently supporting three large clinical trials in Nepal [10][11]and Tanzania[12] to assess whether routine zinc supplementation reduces mortality in childhood pneumonia. A fourth study in Bangladesh [13] aims to determine if zinc supplementation in the early stages of outpatient non-severe pneumonia can reduce both the duration of illness and the likelihood of treatment failure.

## DISCUSSION

Daily zinc supplementation of infants and children in socio-economically disadvantaged groups prevents one quarter of the episodes of pneumonia in children.[7] However, daily zinc supplementation might be impractical especially in low resource settings. Large dose weekly zinc supplementation has been shown to effectively reduce the incidence of pneumonia in children. Additional studies have demonstrated that zinc when administered with antibiotics during an episode of severe pneumonia significantly reduces recovery time and overall hospital stay in children. Although these studies of treatment and prevention efficacy have been done in regions with documented Zn deficiency, none of the children in the Bangladesh study had evidence of clinical deficiency and the exact mechanism of action remains unknown at this time. Thus, documentation of deficiency should not be a requirement prior to administration of adjuvant or preventive therapy. Moreover, in none of the randomized controlled prevention trials on healthy children, or treatment trials on children with severe pneumonia have these standard Zn doses shown any harmful effects. Some very young children experience a vomiting tendency with the initial doses, but this appears to resolve. The current dispersible Zn sulphate tablet appears to be particularly well-tolerated.

## SUMMARY

Although the mechanism is still unclear, zinc is effective as an adjunct treatment for pneumonia and prevents disease episodes. (Grade A evidence) If the results of ongoing trials show a reduction in primary outcome measures (mortality, duration of illness, treatment failure) routine zinc supplementation may be promoted for prevention and management of pneumonia.

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**TABLE 1** Clinical trials investigating the impact of zinc on incidence and outcome of pneumonia in children

| Study, Design | Country, Setting | Sample size | Inclusion criteria | Intervention | Outcomes | Level of evidence |
|---|---|---|---|---|---|---|
| Bobat [9], RCT | South Africa, Urban tertiary care hospital OPD | 96 | Children between 6 and 60 months of age with HIV infection being cared for at the hospital and not on antiretroviral therapy. | 10 mg of elemental zinc as sulphate or placebo every day for 6 months. | Pneumonia diagnosis during scheduled and illness visits in zinc and placebo groups: 57(14%) v 83(18.6%); p=0.07 | 1b |
| Brooks [8], RCT | Bangladesh, Poor urban population | 1665 | Children aged 60 days to 12 months at the time of enrollment without underlying respiratory disease, congenital heart disease or severe malnutrition. | 70 mg zinc given orally as syrup (35 mg zinc acetate per 5 mls) or placebo once a week. | Incidents of pneumonia in zinc group compared to placebo group: 199/809 v 286/812; Relative risk 0.83, 95%CI 0.73-0.95 | 1b |
| Bhandari [7], RCT | India, Urban slum community | 2482 | All children aged 6 to 30 months in the community not requiring urgent admission to hospital on the enrollment day or not received massive dose of vitamin A recently. | Elemental zinc (10 mg for infants, 20 mg for children) as gluconate or placebo taken daily for four months. | Mean plasma zinc concentration at 4 months: 19.8 (SD 10.1) in zinc group v 9.3 (2.1) µmol/l in placebo group; p<0.001. Incidence of pneumonia in zinc v placebo group (Absolute risk reduction 2.5%; 95% CI 0.4% to 4.6%) | 1b |
| Brooks [6], RCT | Bangladesh, Hospital (rural facility) | 270 | Children between 2 to 23 months admitted to hospital with severe pneumonia. | 20 mg elemental zinc per day (10 mg zinc per 5 mls syrup) as acetate or placebo until discharge from hospital | Duration of severe pneumonia in zinc compared to placebo groups: Relative hazard 0.70; 95% CI 0.51- 0.98 | 1b |