Role of Zinc in Child Health and Survival

Robert E. Black · Christa Fischer Walker

Department of International Health, Johns Hopkins University, Bloomberg School of Public Health, Baltimore, MD, USA

Abstract

Zinc deficiency has been estimated to result in more than 450,000 child deaths annually by increasing the risk of diarrhea and pneumonia mortality. Trials of daily supplemental zinc have shown preventive benefits in childhood diarrhea with a 20% reduction in incidence. Use of zinc in treatment of diarrhea has also been successful in shortening the duration of the episode by 10% and reducing the number of prolonged episodes. The World Health Organization recommends that zinc supplements be used for 10–14 days for every episode of childhood diarrhea along with oral hydration and feeding. Large-scale effectiveness trials of these recommendations in Bangladesh and India have found a reduction in hospitalizations due to diarrhea and pneumonia and in child mortality. Trials have also demonstrated a reduction in the incidence childhood pneumonia with zinc supplements and some, but not all, studies have found a therapeutic benefit of zinc as adjunctive treatment along with antibiotics as well. Preventive zinc also improves the growth of children in developing countries and reduces total deaths in 1- to 4-year-old children by 18%. Zinc supplementation is an intervention with proven effectiveness and broad application to address pneumonia and diarrhea, the two most important childhood infectious diseases globally.

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A large proportion of the world's population is at risk of zinc deficiency which has serious consequences for health and survival, especially in children under 5 years of age [1]. The initial descriptions of severe human zinc deficiency in adolescent boys included stunting of growth, immune compromise, high rates of infectious diseases and substantially reduced survival [2]. More recently, it has been demonstrated, largely through controlled trials of zinc supplementation, that even less severe zinc deficiency in preschool children is associated...
with growth faltering, increased risk for serious infectious diseases and excess mortality.

**Childhood Growth and Development**

Stunting of linear growth in early childhood, a good overall measure of child health, occurs in a third of children worldwide [1]. Zinc deficiency is one contributor to stunting. Most meta-analyses of trials demonstrate that zinc supplementation enhances growth [3], and subgroup analyses suggest that the effect is greatest in growth-retarded children in less developed countries [4]. A number of trials of zinc supplementation also find benefits on child activity and developmental measures, although the evidence is more limited and less clear than for the effects on growth [4].

**Childhood Diarrhea**

Diarrheal diseases remain one of the top two causes of child death globally in spite of reductions over several decades associated with improved nutritional status and increased implementation of preventive and therapeutic interventions [5]. Children with zinc deficiency are more susceptible to infections causing diarrhea, and the loss of zinc during diarrhea exacerbates dietary inadequacy of zinc, contributing to a vicious cycle of infection and nutritional deficiency.

Numerous trials comparing oral zinc supplements, usually given daily, with placebo have been done and summarized in meta-analyses. The most recently published of these included 33 comparisons and more than 16,000 child participants [3]. This analysis found an overall effect of zinc supplementation of a 20% lower incidence of diarrhea. One of the initial trials of zinc supplementation reported 27% lower rate of diarrhea in children 12 months of age or more but no effect in infants [6]. The meta-analysis likewise found a 27% (95% confidence interval, CI: 13–39%) lower diarrheal incidence in children with an initial age greater than 12 months and no effect in infants [3]. The effect of zinc was also found to be significantly greater in children who were stunted at enrollment.

Diarrhea treatment with oral rehydration solution has become a mainstay for controlling diarrhea mortality, but this has no effect on diarrheal duration. In contrast, zinc supplementation has been found to reduce the duration and severity of the episode. Since the first definitive trial of zinc for treatment of diarrhea [7], there have been numerous trials in low- and middle-income countries. There have been several meta-analyses of these trials, demonstrating benefits with regard to episode duration, proportion of episodes persisting beyond 7 days and stool frequency. The most recently published systematic review found that zinc in treatment of diarrhea reduced the mean duration by 19.7%
There is heterogeneity in the trial results, and the benefits have been found in some but not all studies in infants 1–5 months of age.

Several early trials of treatment of diarrhea provided zinc for 2 weeks during and following the episode. These trials were summarized in a pooled analysis to show that there was a 34% (95% CI: 17–48%) reduction in the prevalence of diarrhea and a 26% non-statistically significant reduction in the incidence of pneumonia in the 2–3 months following the diarrheal episode [9].

In addition, there have been two large trials in which health service areas were randomly assigned to provide for children with diarrhea ORS or ORS plus daily zinc supplements for 14 days during and after diarrhea. In Bangladesh, children in the zinc intervention service clusters had a 24% (95% CI: 10–35) shorter duration and 15% (95% CI: 4–24) lower incidence of diarrhea than children in the comparison group [10]. Admission to hospital for diarrhea was 24% (95% CI: 2–41%) lower in the intervention group and admission for pneumonia was 19% lower, but this was not statistically significant. The rate of non-injury child deaths in intervention clusters was 51% (95% CI: 6–75%) lower. In India, children in the zinc intervention clusters had lower 24-hour prevalences of diarrhea and acute respiratory infections than children in the comparison group [11]. All-cause, diarrhea and pneumonia hospitalizations were reduced in the intervention areas by 59, 31 and 71%, respectively (all statistically significantly different from comparison areas).

Pneumonia is the leading cause of child mortality, and zinc deficiency is a risk factor contributing to the incidence and severity of the disease [5]. As with diarrhea, the strongest evidence for the role of zinc deficiency comes from zinc supplementation trials. Because of the lower incidence of pneumonia than of diarrhea, the data are more limited. Furthermore, the use of a range of illness definitions for acute respiratory infections (ALRI)/pneumonia makes summarizing these results more complicated than for diarrhea. The ten available trials of zinc supplementation were analyzed with regard to the outcome definitions used [12]. Zinc supplementation provided daily or weekly reduced the incidence of ALRI defined using specific clinical criteria by 35% (95% CI: 18–48%). There was no effect found using less-specific outcome case definitions based on caregiver report. A separate meta-analysis found an overall reduction of ALRI of 15% (95% CI: 3–25%), but a larger effect in children who had lower initial height-for-age (stunted) and in studies using more specific clinical criteria for the outcome [3].

Zinc has also been used in trials as an adjunctive treatment along with antibiotics for pneumonia. An initial trial in Bangladesh of zinc for treatment of severe pneumonia found a reduction in the episode duration of one day (hazard
However, subsequent trials have not confirmed this result [14, 15], and the conclusion concerning a therapeutic effect in pneumonia will need to await several ongoing trials.

**Childhood Malaria**

Malaria is an important cause of child mortality, especially in sub-Saharan Africa [5], and zinc deficiency may be a risk factor for malaria infection or illness. Several randomized controlled trials have investigated the role of zinc supplementation for prevention of clinical malaria. Trials in The Gambia and Papua New Guinea found 32 and 38%, respectively, reductions in clinic visits for malaria, but a trial in Burkina Faso found no effect on the incidence of malaria diagnosed by home visits [3]. It is possible that the effect is on the severity of illness rather than the incidence, but the data are insufficient to determine if there is an important preventive effect. A multi-site trial of zinc for adjunctive treatment of malaria did not find any benefit [16].

**Child Mortality**

Two very large trials of daily zinc supplementation were done in Zanzibar and Nepal. These trials were designed to examine the effects on child mortality [17, 18]. In Zanzibar, children 1–36 months old were randomized to receive 10 mg of zinc (5 mg for infants) daily and followed for a total of 56,507 child-years [17]. Overall, there was a non-significant reduction of 7% in all-cause mortality in the zinc-supplemented group. The effect seemed to differ by age with a reduction of 18% (95% CI: 0–32%) in children 12–48 months and no effect in infants. There were non-significant trends for lower mortality due to malaria, diarrhea and other infections in the zinc group. In Nepal, children 1–35 months old were randomized using the same doses as Zanzibar and followed for total of 60,636 child-years [18]. Overall, there was a non-significant reduction of 8% in all-cause mortality. There was a non-significant reduction of 18% in mortality in children 12 months or older, but no effect in infants. There were non-significant trends for reductions in mortality due to diarrhea and ALRI in the zinc group.

In a meta-analysis of the effects of zinc supplementation on mortality, the study results were stratified by age and whether the zinc was given with iron and folic acid [3]. There was no effect of zinc supplementation in infants, but children 12 months old or more had an 18% reduction in all-cause mortality (95% CI: 4–30). When iron and folic acid were given with zinc, there was no benefit in either age group on mortality. Another meta-analysis of the effects of zinc supplementation on cause-specific mortality suggested effects on diarrhea and pneumonia of 15–18%, but these effects were non-significant [19].
Conclusions

Zinc deficiency is a prevalent condition that has important effects on childhood infectious diseases and mortality. It has been estimated that this deficiency results in more than 450,000 child deaths annually and nearly 4% of the disability-adjusted life years lost in children worldwide [1]. The preventive use of zinc supplements or fortified foods would be expected to reduce stunting and mortality, especially that due to diarrhea and pneumonia [20]. The benefits of zinc as adjunctive treatment for diarrhea are well demonstrated, and the World Health Organization and UNICEF since 2004 have recommended that zinc be used for treatment of all childhood diarrhea [21]. The usefulness of zinc for preventing malaria and treating pneumonia is unclear until the results of additional trials are available.

References