Zinc Deficiency, Infectious Disease and Mortality in the Developing World[1,2]

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ABSTRACT Zinc deficiency places children in many low-income countries at increased risk of illness and death from infectious diseases. Randomized controlled trials of zinc supplementation provide the best estimate of this risk through demonstrated preventive benefits. In six of nine trials that evaluated prevention of diarrhea, significantly lower incidence of diarrhea occurred in the zinc group than in the controls; a pooled analysis demonstrated 18% (95% confidence interval, 7–28%) less diarrhea. In five trials, a lower rate of pneumonia infection was found in the zinc-supplemented groups, and there was some indication of a preventive effect in three trials with a clinical malaria outcome. Zinc was also found to have a therapeutic benefit in seven trials of acute diarrhea and five of persistent diarrhea. Studies to evaluate the effect of zinc supplementation on mortality are under way, but a recently published study from India identified a 68% reduction in mortality in small-for-gestational-age term infants that were supplemented with zinc from 1 to 9 mo of age. The important effects of zinc deficiency are now clear, and nutrition programs should address this prevalent problem. J. Nutr. 133: 1485S–1489S, 2003.

KEY WORDS: • *child nutrition* • *diarrhea* • *malaria* • *pneumonia* • *zinc*

Zinc deficiency, which appears to be widespread in developing countries, has long been recognized to impair growth and immune function (1,2). Although effects on the immune system are known to occur with even mild zinc deficiency (3), the importance of this with regard to the risk of childhood infectious diseases has only recently become better understood (4). Observational studies provide some evidence of a relationship between low plasma-zinc concentration in children and higher risk of infectious diseases (5), but inferences from these studies are limited owing to a lack of adequate zinc-deficiency indicators at the individual level.

Randomized, controlled trials of zinc supplementation provide the best evidence for the roles of zinc in infectious diseases, which are presumably mediated through alterations in host defenses including epithelial barriers and immune responses. Results of these trials are reviewed and summarized with regard to effects on diarrhea, pneumonia and malaria incidence as well as on total child mortality. In addition to these preventive trials in which zinc was given on a routine, usually daily, basis for an extended period of time, there are other trials in which zinc was provided as an adjunct to therapy for acute or persistent diarrhea. This review is limited to published trials.

Prevention of infectious disease morbidity

The effects of zinc supplements on rates of diarrhea and pneumonia incidence have been well studied, and there is also some information on malaria incidence. In total, 11 trials are available for inclusion in this review (6–17). Ten of these trials assess the effect of zinc supplementation on the incidence of diarrhea, five on the incidence of pneumonia and three on the incidence of malaria (**Table 1**). These trials were performed with preschool children who reside in typical developing country settings. Although the settings of these trials might be expected to include a substantial prevalence of zinc deficiency as would be expected in most developing countries, the populations of children were not preselected on the basis of zinc deficiency. Six of the trials were performed with all children in the targeted age group, whereas five of the trials had some enrollment restrictions (Table 1). Two of these trials employed children that were selected with at least a moderate degree of undernutrition, whereas one trial stratified the enrollment based on individuals who were or were not stunted.

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TABLE 1

Trials evaluating effects of zinc supplementation on preventing morbidity in children

Country	Ref.	Zinc supplement (mg) and type	Duration (wk)	No. of children in zinc/control group	Age (mo)	Enrollment restriction[1]
The Gambia	(6)	70, acetate	60	55/54	6–28	—
Vietnam	(7)	10, sulfate	22	73/73	4–36	W/A and H/A $< -2z$
India	(8,9)	10, gluconate	26	286/293	6–35	Recovered from acute diarrhea
Mexico	(10)	20, methionate	54	97/97	18–36	—
Guatemala	(11)	10, sulfate	28	45/44	6–9	—
Papua New Guinea	(12)	10, gluconate	46	136/138	6–60	—
Jamaica	(13)	5, sulfate	12	31/30	6–24	W/H $< -2z$
Peru	(14)	10, gluconate	26	80/79	6–35	Recovered from persistent diarrhea
Ethiopia	(15)	10, sulfate	26	92/92	6–12	Stratified on H/A $< -2z$
Burkina Faso	(16)	12.5, sulfate	26	356/353	6–31	—
India	(17)	10/20, gluconate	16	1,241/1,241	6–35	—

[1] W/A, weight for age; H/A, height for age; W/H, weight for height.

Two of the trials enrolled children after they had recovered from either acute or persistent diarrhea. Taken collectively, the studies were done in settings that represent a wide range of conditions with regard to nutritional status and risk of infectious diseases.

These trials are consistent in showing that zinc-supplemented children have lower rates of diarrhea than control children (**Table 2**). Six of the nine studies had statistically significant differences between the zinc and control groups. A pooled analysis that includes most of these studies reveals the overall incidence of diarrhea in zinc-supplemented children to be 18% [95% confidence interval (CI), 7–28%] less than in children who did not receive zinc (18). This analysis shows trends (not statistically significant) that children with lower plasma zinc concentrations or wasting, or were female or in their second or later year of life (versus infants) have greater effects of zinc supplementation.

The five studies with available information are also consistent in showing that zinc-supplemented children have a lower incidence of pneumonia than control children (Table 2). In the pooled analysis, there was a 41% (95% CI, 17–59%) lower rate of pneumonia in zinc-supplemented children (18). A study that was more recently completed shows a statistically significant 26% reduction in the incidence of pneumonia as diagnosed by clinical examination by two physicians using specific predefined clinical criteria (17).

TABLE 2

Effects of zinc in prevention of diarrhea, pneumonia, malaria and mortality in children

Country	Ref.	Diarrhea incidence (% lower)	Pneumonia incidence (% lower)	Malaria incidence (% lower)	Mortality (% lower)
The Gambia	(6)	—	—	32	—
Vietnam	(7)	44[1]	44[1]	—	—
India	(8,9)	8	43[1]	—	68[1]
Mexico	(10)	37[1]	—	—	—
Guatemala	(11)	18[1]	—	—	—
Papua New Guinea	(12)	12	—	38[1]	—
Jamaica	(13)	8	88	—	—
Peru	(14)	12[1]	15	—	—
Ethiopia	(15)	55[1]	—	—	—
Burkina Faso	(16)	16[1]	—	2	58
India	(17)	N/A[2]	26[1]	—	—

[1] Statistically significant, i.e., $P < 0.05$.
[2] N/A, not available.

The information regarding the effects of zinc supplementation on malaria is more limited. Studies in the Gambia and Papua New Guinea reveal reductions of about one-third in the rate of visits to health facilities for a clinical syndrome consistent with malaria and confirmed by parasitologic examination of the blood. Given the extremely high rate of malaria parasitemia in some endemic populations, visits to health facilities with confirmed malaria are generally considered to be the most valid measure of malaria incidence and have been used by the World Health Organization (WHO) to estimate the malaria burden of disease (19). The third trial of zinc supplementation that examined an effect on malaria was done in Burkina Faso. This trial had only community-based surveillance of malaria and did not ascertain health-facility visits. The study found no effect of zinc supplementation on rates of fever as ascertained from household visits 6 d/wk. This may not be surprising in that the study in Papua New Guinea did not find an effect of zinc supplementation on "malaria" as ascertained from community-based surveillance but did find a significant benefit with regard to malaria visits to the health facilities (12).

Therapeutic effects for diarrhea

There are currently 12 published trials of zinc supplementation in the therapy of acute or persistent diarrhea that are available for review (20–30). Seven of these trials are for acute diarrhea (**Table 3**). The five trials on persistent diarrhea are likely the only ones that will be available, because WHO has recommended that zinc be used in the treatment of persistent diarrhea, which makes controlled trials no longer appropriate. Five additional trials of zinc supplementation for acute diarrhea have been conducted. Although these are as-yet unpublished, they were reviewed in a recently published meeting report (31). Most find beneficial effects of zinc supplementation as do the published trials.

The trials on persistent diarrhea, i.e., episodes lasting ≥14 d, demonstrate overall benefits of zinc supplementation (**Table 4**). Generally, the zinc-supplemented children have shorter-duration episodes, lower stool frequency or stool volume and importantly, in three of the four studies, a reduction in treatment failure or death. A meta-analysis of these five trials yields a statistically significant summary effect (32). Overall, in this analysis there is a 42% (95% CI, 10–63%) reduced rate of treatment failure or death. In a pooled analysis of these trials,

TABLE 3

Trials evaluating therapeutic effects of zinc in diarrhea

Country	Ref.	Zinc supplement and type	No. of children in zinc/control group	Age (mo)	Enrollment restriction[1]	Type of diarrhea
India	(20)	20 mg, sulfate	25/25	6–18	Exclude moderate-severe malnutrition	Acute
India	(21)	20 mg, sulfate	20/20	6–18	Exclude moderate-severe malnutrition	Persistent
India	(22)	20 mg, gluconate	456/481	6–35	Exclude severe malnutrition	Acute
Bangladesh	(23)	20 mg, acetate	57/54	3–24	Include W/A $<$ 76th percentile	Acute
Bangladesh	(24)	20 mg, acetate	95/95	3–24	—	Persistent
Indonesia	(25)	4–5 mg/kg, acetate	739/659	3–25	—	Acute
Peru	(14)	20 mg, gluconate	139/136	6–35	—	Persistent
Pakistan	(26)	3 mg/kg, sulfate	43/44	6–36	Include W/A $< -2z$	Persistent
Bangladesh	(27)	14/40 mg, acetate	343/341	6–23	Exclude severe malnutrition	Acute
India	(28)	40 mg, sulfate	44/36	3–24	Include W/A $<$ 80%	Acute
Bangladesh	(29)	20 mg, acetate	44/44	6–24	Include W/A $< -2z$	Persistent
Nepal	(30)	15/30 mg, gluconate	445/449	6–35	—	Acute

[1] W/A, weight for age.

the subgroups of children who are $<$ 12 mo of age, wasted or male have statistically significant effects of zinc supplementation. The corresponding alternative groups have smaller beneficial effects that are not statistically significant (Table 4).

Of the seven trials on acute diarrhea, all find that the episode duration is shorter in zinc-supplemented children, and four of these trials are individually statistically significant. Likewise, all of the five trials that measure an effect on diarrhea severity find that zinc-supplemented children have less diarrheal stool output than controls; three of these trials find statistically significant benefits. In a pooled analysis with original data from three of these trials, within subgroups by age ($<$ 12 mo versus $\geq$ 12 mo), wasting ($< -2z$ versus $\geq -2z$ weight per height) and sex, each subgroup has significant benefits of zinc supplementation. In subgroups of children with lower or higher initial plasma zinc concentrations, there are significant pooled effects in both groups, although the effects tend to be greater in the subgroup with lower plasma zinc concentration.

Effects on child mortality

Diarrhea, pneumonia and malaria are the most common causes of death among children in developing countries. The consistent and sizeable effects of zinc supplementation on the incidence and severity of these infectious diseases logically leads to the hypothesis that there will be a reduction in child mortality with zinc supplementation. One recent study in India provides preliminary evidence that this is correct (33). A randomized, double-blind, controlled trial enrolled 1,154 full-term small-for-gestational-age infants to receive one of the following supplements: riboflavin; riboflavin and zinc (5 mg as sulfate); riboflavin, calcium, phosphorus, folate and iron; or riboflavin, zinc, calcium, phosphorus, folate and iron. Children were supplemented between 30 and 284 d of age and visited 6 d/wk to provide the supplement and conduct surveillance for illness and death. When the main effects of the zinc or the other micronutrients are examined by survival analysis, it is found that zinc supplementation is associated with a significantly lower mortality with a ratio of 0.32 (95 CI, 0.12–0.89). Calcium, phosphorus, folate and iron supplementation are not associated with a reduction in mortality.

The widespread demonstration that zinc supplements reduce the incidence of diarrhea and the two-thirds reduction in mortality that was found in the Indian study have led to the initiation of three large trials of zinc supplementation in India, Nepal and Zanzibar. All trials will evaluate the effect of zinc on child mortality, and the studies in India and Zanzibar will also assess the effects on hospitalizations from infectious diseases (diarrhea and pneumonia in both and malaria also in Zanzibar). Results are expected by 2004.

TABLE 4

Effects of zinc in therapy of acute and persistent diarrhea

Country	Ref.	Episode duration	Severity	Treatment failure/death
India	(20)	9% Shorter duration	18% Less stool frequency	—
India	(21)	19% Shorter duration	21% Less stool frequency	—
India	(22)	21% Reduced probability of continuing diarrhea[1]	39% Less stool frequency[1]	—
Bangladesh	(23)	14% Reduced probability of continuing diarrhea	28% Lower stool output	—
Bangladesh	(24)	15% Reduced probability of continuing diarrhea	—	63% Less[1]
Indonesia	(25)	11% Reduced probability of continuing diarrhea[1]	—	—
Peru	(14)	18% Reduced probability of continuing diarrhea[1]	—	19% Less
Pakistan	(26)	2% Reduced probability of continuing diarrhea[1]	No effect	58% More
Bangladesh	(27)	20% Reduced probability of continuing diarrhea	—	—
India	(28)	32% Shorter duration[1]	38% Lower stool output[1]	—
Bangladesh	(29)	55% Reduced probability of continuing diarrhea[1]	—	75% Less[1]
Nepal	(30)	26% Reduced probability of continuing diarrhea[1]	8% Less stool frequency[1]	—

[1] Statistically significant, i.e., $P < 0.05$.

DISCUSSION

The substantial prevalence of zinc deficiency in children in developing countries and its important consequences for higher rates of illness and death from infectious diseases in children in developing countries leads to the conclusion that the global burden of disease due to this nutritional problem is very large. This unnecessary burden can be reduced by existing means of improving the available zinc in the diet (34). Although this may be possible in some settings by using dietary modification, e.g., consumption of additional animal products or reduction in the consumption of foods that interfere with zinc absorption (35), in other settings such as in poor, vegetarian populations, this may prove difficult. Additional dietary approaches particularly including fortification are needed to address the problem of dietary inadequacy of zinc and other micronutrients such as iron (34). Supplements may play a role as well, and there is a need to understand more about the interactions of iron and other micronutrients when given together (36).

The efficacy of zinc in treating both persistent and acute diarrhea is now clear. Recommendations have already been made by WHO for its use in the treatment of persistent diarrhea. Furthermore, a WHO meeting in 2001 reviewed the studies presented here along with five as-yet unpublished studies (31). These unpublished studies reveal benefits that are consistent with those reported here and are briefly summarized in the meeting report. The report concludes that "there is now enough evidence demonstrating the efficacy of zinc supplementation on the clinical course of acute diarrhea." Although there is encouraging information from several large-scale, community-based studies that use zinc supplements to treat diarrhea, more information is needed on this in different settings. In particular, there is a need to understand how to promote zinc supplements to treat diarrhea without interfering with oral rehydration therapy, which will remain the mainstay of treatment. The meeting concludes that future studies should "investigate the feasibility, sustainability, and cost-effectiveness of different zinc delivery mechanisms and monitor variables, such as consumption of ORS (oral rehydration therapy), antibiotic use rate, non-diarrheal morbidity and overall mortality." It also indicates that it is important to determine the best formulation of zinc to minimize side effects and maximize adherence to therapy.

The important role of zinc deficiency in childhood infectious diseases is now clear. The challenge is to develop the public health response to address this deficiency and thereby improve child health.

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