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Substantial Reduction in Severe Diarrheal Morbidity by Daily Zinc Supplementation in Young North Indian Children

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ABSTRACT. *Objective.* **To evaluate the impact of 4 months of daily zinc supplementation on the incidence of severe and recurrent diarrhea in children 6 to 30 months of age.**

Methods. **A double-blind, randomized, placebo-controlled trial was conducted on children who were identified by a door-to-door survey to be aged 6 to 30 months and residing in the urban slum of Dakshinpuri, New Delhi. They were randomized to receive daily zinc gluconate (elemental zinc 10 mg to infants and 20 mg to older children) or placebo. A field attendant administered the syrup daily at home for 4 months except on Sundays, when the mother did so. One bottle that contained 250 mL was kept in the child's home and replaced monthly. Field workers visited households every seventh day during the 4-month follow-up period. At each visit, information was obtained for the previous 7 days on history of fever, number and consistency of stools, and presence of cough. When the child was ill, illness characteristics and treatment seeking outside the home were determined. If the child had diarrhea or vomiting, then dehydration was assessed. At household visits, 2 packets of oral rehydration salts were given when a child had diarrhea. Children who visited the study clinic spontaneously for illness or were referred by the field workers were treated according to the standard national program guidelines. Antibiotics were advised only for diarrhea with bloody stools or for associated illnesses. For using generalized estimating equations for longitudinal analysis of a recurring event such as diarrhea, the follow-up data for each child was divided into 17 child-periods of 7 days each and presence or absence of an incident episode of diarrhea or severe diarrhea within each 7-day period was coded. This method of analysis does not assume independence of events and therefore prevents underestimation of variance that results because of correlation of morbidity within the same child. A logistic generalized estimating equations model with exchangeable correlation covariance-variance matrix was then used to estimate the effect size.**

Results. **Zinc or placebo doses were administered on 88.8% and 91.2%, respectively, of study days during the 4 months of follow-up. There was a small but significant increase in the average number of days with vomiting in the zinc group (4.3 [standard deviation (SD): 5.8] vs 2.6 [SD 3.9] days; difference in means: 1.7 [95% confidence interval (CI): 1.3–2.1] days). At the baseline, mean plasma zinc was 62.0 μg/dL (SD: 14.3 μg/dL) in the zinc and 62.0 μg/dL (SD: 11.2 μg/dL) in the placebo group; 45.8% and 42%, respectively, had low plasma zinc levels below 60 μg/dL. At the end of the study, plasma zinc levels were substantially higher in the zinc group (ratio of geometric means: 1.94 [95% CI: 1.86–2.03]) and the proportion with low plasma zinc was lower (difference in proportions: −46.7% [95% CI: −41.8% to −51.4%]). The incidence of diarrhea during follow-up was lower in the zinc-supplemented as compared with the placebo group (odds ratio [OR]: 0.88; 95% CI: 0.82–0.95). The beneficial impact of zinc was greater on the incidence of diarrhea with progressively increasing duration: episodes of diarrhea that lasted 1 to 6 days (OR: 0.92; 95% CI: 0.85–1.00), 7 to 13 days (OR: 0.79; 95% CI: 0.65–0.95), and ≥14 days (OR: 0.69; 95% CI: 0.48–0.98). The impact was also greater on the incidence of episodes with progressively higher stool frequency: 3 to 5 stools per day (OR: 0.90; 95% CI: 0.83–0.98), 6 to 9 stools per day (OR: 0.87; 95% CI: 0.77–0.98), and ≥10 per day (OR: 0.77; 95% CI: 0.63–0.94). In the zinc group, significantly more children experienced no diarrheal episode during the study period (risk ratio [RR]: 1.22; 95% CI: 1.02–1.44). Furthermore, substantially fewer children (RR: 0.51; 95% CI: 0.36–0.73) experienced recurrent diarrhea, defined as >6 diarrheal episodes in the follow-up period as compared with children in the placebo group. The number of children who were hospitalized for any cause tended to be lower in the zinc group, but the difference was not statistically significant (1.79% vs 2.43%; RR: 0.74; 95% CI: 0.43–1.27). The baseline mean plasma copper (μg/dL) was similar in the 2 groups (difference in means: 1.6; 95% CI: −2.9 to 6.1). The end study plasma copper levels were significantly lower in the zinc group (difference in means: −15.5; 95% CI: −19.9 to −11.1).**

Conclusions. **Zinc supplementation substantially reduced the incidence of severe and prolonged diarrhea, the 2 important determinants of diarrhea-related mortality and malnutrition. This intervention also substantially reduced the proportion of children who experienced recurrent diarrhea. Prompt measures to improve zinc status of deficient populations are warranted. The potential approaches to achieve this goal include food fortification, dietary diversification, cultivation of plants that are zinc dense or have a decreased concentration of zinc absorption inhibitors, and supplementation of selected groups of children. Future studies should assess the impact of increased zinc intakes on childhood mortality in developing countries. For facilitating intervention, there is a need to obtain reliable estimates of zinc deficiency, particularly in developing countries. The functional consequences of the effect of various doses of zinc on plasma copper levels merits additional**

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study. *Pediatrics* 2002;109(6). URL: http://www.pediatrics.org/cgi/content/full/109/6/e86; *zinc supplementation, diarrhea, severe diarrhea, recurrent diarrhea, copper status.*

ABBREVIATIONS. GEE, generalized estimating equations; CI, confidence interval; SD, standard deviation; OR, odds ratio; RR, risk ratio.

Zinc deficiency is common in children in developing countries because the overall food intake as well as the consumption of animal foods is low and the bioavailability of zinc from the phytate-rich cereal-based diets is limited. Stool zinc losses during recurrent diarrheal illnesses are also a contributing factor.[1]

Zinc deficiency impairs innate as well as acquired immunity.[2,3] Zinc deficiency also has direct effects on the gastrointestinal tract that lead to an increased clinical severity of acute enteric infections.[4,5]

Reduced diarrheal morbidity has been documented in zinc supplementation trials,[6] but these were not large enough to assess impact on clinically severe illness. Before public health policy is made, it is important to assess whether zinc supplementation prevents clinically severe and recurrent diarrhea. The clinical features associated with greater severity and risk of death during diarrheal illnesses include high stool frequency or stool output and duration of 14 or more days.[7,8] A significant reduction in the incidence of such severe episodes would justify adoption of measures to prevent zinc deficiency in susceptible populations. We therefore evaluated the impact of daily zinc supplementation in a representative sample of children who were aged 6 to 30 months and enrolled from a New Delhi slum area, with a sample size sufficient to determine the impact on the incidence of severe diarrhea.

METHODS

Study Setting

The trial was implemented in the urban slum of Dakshinpuri, which comprises 15 000 dwellings and a population of approximately 75 000. Available data suggested that malnutrition and zinc deficiency were common in early childhood.[9,10] Approximately one fifth of children who were younger than 5 years were wasted (weight-for-age z score below -2) and half were stunted (height-for-age z score below -2). Subclinical zinc deficiency (serum zinc $\leq 60\ \mu g/dL$) was present in 37% of children who were aged 12 to 59 months and brought for care for diarrhea in a community clinic.[9,10]

Randomization Scheme and Blinding

A simple randomization scheme in blocks of 8 was generated by a person at Statens Serum Institut, who was not involved in the field work or the data analysis, using the SAS software (version 8.1; SAS Institute, Cary, NC). The zinc and placebo syrups were prepared and packaged in unbreakable bottles by GK Pharma ApS (Køge, Denmark), which also labeled the bottles with unique identification numbers according to the randomization code. The zinc and placebo syrups were similar in appearance, taste, and packaging.

Enrollment and Intervention Delivery

Enrollment began on February 15, 1998. In a door-to-door survey, 3802 children who were 6 to 30 months of age were identified. Enrollment required that the parent(s) give informed consent and that the families did not intend to emigrate (Fig 1). Exclusion criteria included refusal of consent, likely to move out of the study area within the next 4 months, requiring urgent hospitalization on the scheduled enrollment day, or having received vitamin A within the previous 2 months. The last exclusion criterion was adopted to avoid toxicity, because all included subjects were given a massive dose of vitamin A (100 000 IU to infants and 200 000 IU to older children) at enrollment in addition to zinc or placebo as required by the national program policy. The 2482 enrolled children were randomized to receive zinc gluconate (10 mg of elemental zinc/d to infants and 20 mg/d to older children) or placebo daily for a period of 4 months. The follow-up of the last child was completed on September 30, 2000.

We chose twice the recommended dietary allowance for supplementation in this study to allow for possible impairment in absorption of ingested zinc among children as a result of consumption of a predominantly phytate-rich cereal-based diet, bacterial overgrowth, and protozoal or parasitic infestations. A higher intake may also be required to compensate for excessive losses of zinc during the diarrheal illnesses that are common in this setting.[1]

A field attendant administered the syrup daily at home for 4 months except on Sundays, when the mother was asked to administer it. One bottle that contained 250 mL was kept in the child's home and replaced monthly.

The study was approved by the ethics committee of the All India Institute of Medical Sciences. Informed written consent was obtained from the community leaders. Details of the study were given in writing and also read aloud to the parents in the presence of a witness. Signatures or thumb impressions were obtained on a consent form, and a copy of the document was left with the family.

Trial Size Calculations

Trial size was estimated using information from earlier studies in the same population,[11] which reported a diarrhea incidence of 6 episodes/child/y. For detecting a 15% reduction in diarrhea incidence, 996 children were required per group for the 4-month follow-up period. For detecting a 25% reduction in the incidence of diarrhea with a duration of 7 or more days and a similar reduction in episodes with ≥ 10 stools per day, 1100 and 1050 children per group, respectively, were required with the same study duration. The value of α was taken as 0.05 (95% confidence) and that of β as 0.1 (90% power) for these calculations. To allow for approximately a 10% attrition rate, we enrolled approximately 1240 children per group.

Outcomes and Their Measurement

Field workers visited households every seventh day during the 4-month follow-up period. At each visit, information was obtained for the previous 7 days on history of fever, number and consistency of stools, and presence of cough. When the child was ill, illness characteristics and treatment seeking outside the home were determined. If the child had diarrhea or vomiting, then dehydration was assessed. Growth was assessed through weight and length measurements at enrollment and at the end of the study using Seca Salter Scales and locally manufactured infantometers that read to the nearest 0.1 kg and 0.1 cm, respectively.

At household visits, 2 packets of oral rehydration salts were given when a child had diarrhea. At enrollment, caregivers were informed that clinical services for their children would be available at the study clinic established in the community. Children who visited the clinic spontaneously or sick children who were referred to the clinic by field workers were treated according to the World Health Organization guidelines for Integrated Management of Childhood Illnesses.[12]

Plasma Zinc

At enrollment, nonfasting venous blood (approximately 5 mL) was drawn in zinc-free heparinized polypropylene tubes (Sarstedt, Nümbrecht, Germany) between 9 AM and 4 PM by 1 of the physicians. The heparinized blood was centrifuged, and plasma was transferred to zinc-free polypropylene vials (Eppendorf, Hinz, Germany), which were stored at $-20°C$ until analysis. In a randomly selected 30% subsample, a second blood sample was taken at the end of the study to assess the compliance as reflected by a change in plasma zinc concentration. Approximately half of the plasma specimens were analyzed for zinc using

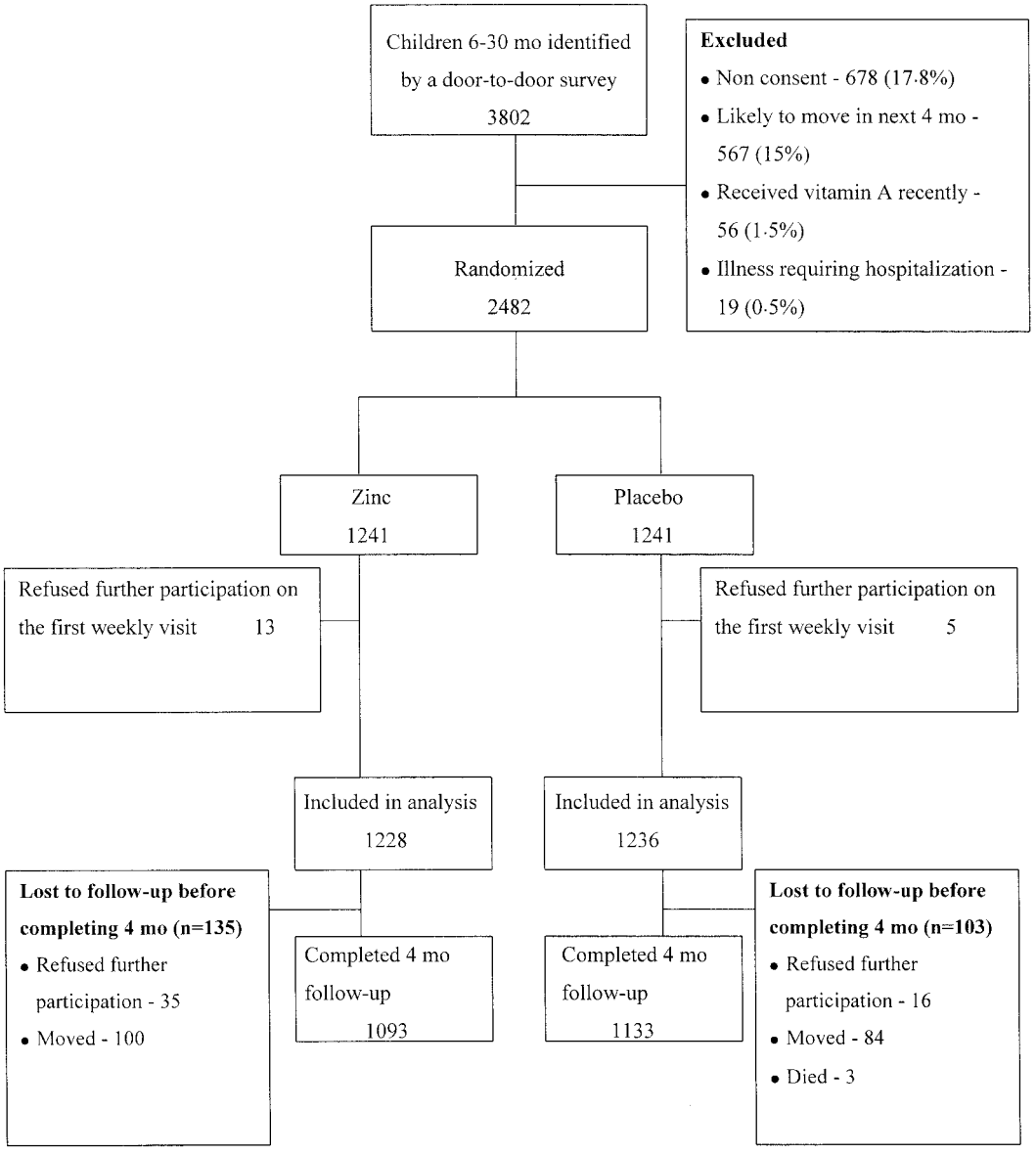

Fig 1. Trial profile.

a standard flame furnace atomic absorption spectrophotometer technique (GBC Avanta, Dandenong, Victoria, Australia), and the other half were assessed by inductively coupled plasma atomic emission spectrometry (Ash IRIS/AP, Thermo Jarell, Franklin, MA).[13,14] Seronorm (Sero AS, Billingstad, Norway) was used as the reference standard in every batch of 20 samples in both methods. The 2 methods were calibrated to give the same results before initiating the analysis of study samples. Plasma copper was analyzed simultaneously with plasma zinc in the same sample by inductively coupled plasma atomic emission spectrometry.[14]

Standardization and Quality Control

A study manual that described all operating procedures was used during training and throughout the study. Standardization exercises were conducted to achieve agreement within and between study personnel for questionnaire filling, assessment of dehydration, and weight and length measurements. Retraining exercises were conducted every 3 months.

Supervisors monitored the field workers' activities. Independent supervisory checks were made to inquire about daily dispensing of the syrup (0.5% of total visits) and to verify the data collected at morbidity visits (1% of total visits). Field workers were also observed at home visits (1% of visits) for assessing the interaction with the family, assessment of dehydration, measurement of temperature and lower chest indrawing, and so forth.

Data Management and Analysis

The data entry system with range and consistency checks was designed using FoxPro for Windows (Microsoft Corporation, Redmond, WA). The data were double-entered independently by 2 data clerks. Data were entered and validated within 48 hours after completion of the questionnaires in the field.

Diarrhea was defined as the passage of 3 or more liquid or watery stools in a 24-hour period. Recovery was defined as the first day of a 72-hour period when the child had no diarrhea. Episodes of severe diarrhea were computed using 2 indicators of severity: duration of episodes or the highest stool frequency on any day of the episode. Recurrent diarrhea was defined as >6 diarrheal episodes during the 4-month study period. For using generalized estimating equations (GEE) for longitudinal analysis, the follow-up data for each child was divided into 17 child-periods of 7 days each. This method of analysis does not assume independence of events and therefore prevents underestimation of variance that results because of correlation of morbidity within the same child. For a child-period to be included in the analysis, the child had to contribute at least 50% (≥4 days) of the given 7-day period. Presence or absence of an incident episode of diarrhea or severe diarrhea within each 7-day period for a child was coded. A logistic GEE model with exchangeable correlation covariance-variance matrix was then used to estimate the effect size. The propor-

tion of days of follow-up with diarrhea was calculated for each child, and the mean prevalence in each group was estimated.

The distribution of the end-of-study plasma zinc in the zinc group was not normal. Therefore, we log-transformed the plasma zinc results in both the groups, and the effect size is presented as the ratio of geometric means with their 95% confidence intervals (CIs). Statistical analysis was performed using Stata, version 6 (Stata Corp, Union Station, TX). Blinding was also maintained during analyses by coding the groups as A and B.

RESULTS

Baseline Characteristics

The children in the 2 groups were comparable for a number of baseline characteristics, including age, anthropometry, child feeding practices, maternal literacy, family size, morbidity in the previous 24 hours, and family socioeconomic characteristics (Table 1). The flow diagram of study participants and reasons for loss to follow-up is shown in Fig 1. Of those randomized, 1093 (88.1%) children in the zinc group and 1133 (91.3%) in the placebo group were available at the last scheduled follow-up visit.

Plasma Zinc

The mean plasma zinc at baseline was 62 μg/dL (standard deviation [SD] 12.8). Approximately 44% of children had plasma zinc concentration below 60 μg/dL, and 27% had plasma zinc concentration below 55 μg/dL. The plasma zinc concentration was significantly higher at the end of the study in the zinc-supplemented children (ratio of geometric means: 1.94; 95% CI: 1.86–2.03). The difference in plasma zinc between end-of-study and baseline concentrations was also substantially higher in the zinc group as compared with the placebo group (ratio of geometric means: 2.0; 95% CI: 1.91–2.09; Table 2).

Acceptability and Side Effects

Zinc or placebo doses were administered on 88.8% and 91.2%, respectively, of study days during the 4 months of follow-up. There was a small but significant increase in the average number of days with vomiting in the zinc group (4.3 [SD 5.8] vs 2.6 [SD 3.9] days; difference in means: 1.7; 95% CI: 1.3–2.1 days).

Eight children (0.3%), all in the zinc group, reported vomiting immediately after the supplement was given on each day during the first 2 weeks of supplementation. As per a priori decision, they were not supplemented any further. In none of these cases was the vomiting severe or reported at times other than immediately after administration of the supplement.

Effect on Overall and Severe Diarrhea Incidence

There were 2794 episodes (7.7 episodes/child-year) of diarrhea in the zinc group and 3165 (8.6 episodes/child-year) in the placebo group during the follow-up period. Of these, 36 episodes in the zinc group and 44 episodes in the placebo group occurred in the same 7-day child-period and were therefore ignored in the GEE analysis.

In the GEE logistic regression model, zinc supplementation was associated with lower risk of diarrhea (odds ratio [OR]: 0.88; 95% CI: 0.82–0.95). The beneficial effect of zinc supplementation was greater on diarrhea that lasted 7 to 13 days (OR: 0.79; 95% CI: 0.65–0.95) and on episodes that lasted ≥14 days (OR: 0.69; 95% CI: 0.48–0.98). The effect on incidence of diarrhea with stool frequency of ≥10 on any day was also greater than that on all diarrhea in the zinc-supplemented children (OR: 0.77; 95% CI: 0.63–0.94; Table 2). The mean prevalence of diarrhea per 100 days of follow-up was 6.6 in the zinc group and 7.9 in the placebo group (difference in means: −1.30; 95% CI: −0.61 to −2.0).

Effect on Recurrent Diarrhea

In a child-based analysis, more children in the zinc-supplemented group experienced no episodes of diarrhea during the study period than those in the placebo group (risk ratio [RR]: 1.22; 95% CI: 1.02–1.44). Furthermore, substantially fewer children had recurrent diarrhea, defined as experiencing >6 diarrheal episodes during the study period in the zinc-supplemented group than those given placebo (RR: 0.51; 95% CI: 0.36–0.73; Table 3). The number of children who were hospitalized as a result of any cause tended to be lower in the zinc group, but the difference was not statistically significant (1.79% vs 2.43%; RR: 0.74; 95% CI: 0.43–1.27). Three children, all in the placebo group, died.

TABLE 1. Baseline Characteristics of Children Who Were Aged 6 to 30 Months and Enrolled in the Zinc and Placebo Groups*

Characteristic	Zinc Group (n = 1228)	Placebo Group (n = 1236)
Age (mo) at enrollment (mean [SD])	15.6 (7.5)	15.0 (7.5)
Male	610 (49.7)	679 (54.9)
Breastfed	849 (69.1)	861 (69.7)
24-h prevalence		
Cough	369 (30.0)	375 (30.3)
Fever	104 (8.5)	91 (7.4)
Fast breathing	56 (4.6)	54 (4.4)
Reported diarrhea	141 (11.5)	153 (12.4)
Literate mother	798 (65.1)	785 (64.3)
Family income (Rupees) per year (median [IQR])	36 000 (24 000, 54 000)	36 000 (24 000, 54 000)
Weight (mean [SD])	8.1 (1.6)	8.0 (1.6)
Length/height (mean [SD])	73.0 (7.1)	72.4 (7.2)

IQR indicates interquartile range.
* All values are number (%) except those marked mean (SD) or median (IQR).

TABLE 2. Zinc and Copper Concentrations at Baseline and End of Study in Zinc-Supplemented and Placebo-Group Children

	Zinc Group (n = 1210)	Placebo Group (n = 1221)	Difference in Means or Difference in Proportions (95% CI)
Baseline			
Plasma zinc (μg/dL; mean [SD])	62.0 (14.3)	62.0 (11.2)	0 (−1.0 to 1.0)
<60 (μg/dL; n [%])	553 (45.8%)	513 (42.0%)	3.8% (−0.3% to 7.6%)
	(n = 478)	(n = 472)	
Plasma copper (μg/dL; mean [SD])	166.8 (33.3)	165.2 (37.3)	1.6 (−2.9 to 6.1)
End of study	(n = 450)	(n = 499)	
Plasma zinc (μg/dL; mean [SD])	129.1 (66.3)	60.8 (13.8)	68.3 (62.3–74.2)
<60 (μg/dL; n [%])	21 (4.6%)	256 (51.3%)	−46.7% (−41.8% to −51.4%)
	(n = 440)	(n = 490)	
Plasma copper (μg/dL; mean [SD])	140.4 (36.5)	155.9 (31.6)	−15.5 (−19.9 to −11.1)

TABLE 3. Impact of Zinc Supplementation on the Incidence of All and Severe Diarrhea Corrected for Correlation of Episodes Occurring in the Same Child by GEE Logistic Regression Models Analysis

	Zinc (n = 1228)	Placebo (n = 1236)	OR (95% CI)
Total child-years of follow-up	361.7	368.2	
Number of 7-d child-periods with ≥4 d of follow-up	18 841	19 179	
Child-periods with an incident episode of diarrhea	2758	3121	0.88 (0.82–0.95)
Child-periods with an incident diarrhea episode lasting			
1–6 d	2348	2567	0.92 (0.85–1.00)
7–13 d	243	312	0.79 (0.65–0.95)
≥14 d	52	77	0.69 (0.48–0.98)
Child-periods with an incident diarrhea episode with maximum stools/d			
3–5	2204	2453	0.90 (0.83–0.98)
6–9	791	918	0.87 (0.77–0.98)
≥10	235	310	0.77 (0.63–0.94)

Effect on Incidence of Diarrhea and Severe Diarrhea in Subgroups

There was a trend toward lower incidence of diarrhea and severe diarrhea in the zinc group in all subgroups examined (Fig 2). The reductions were significant only in children who had plasma zinc ≥60 μg/dL, were 12 months or older, and were not wasted or stunted. The number of children was relatively larger in these subgroups and may partly explain the narrower CIs.

Effect on Plasma Copper

The children in the 2 groups were comparable for mean copper levels at baseline (Table 4). At the end of the study, the mean copper levels were substantially lower in the zinc group (difference in means: −15.5 μg/dL; 95% CI: −19.9 to −11.1). The proportion of children at the end of the study who had plasma copper <80 μg/dL was 4.8% in the zinc group compared with 0.6% in the placebo group (difference in proportions: 4.2%; 95% CI: 2%–6.2%).[15]

DISCUSSION

Daily zinc supplementation of infants and young children in a representative sample from a population with low socioeconomic status reduced the odds by 12% for all diarrheal illnesses, 23% for diarrheal episodes with very high stool frequency, and 31% for persistent diarrheal episodes. In acute infectious enteritis among children, stool frequency of 10 or more is associated with a high risk of complications,[16] and diarrheal episode duration is strongly associated with the risk of death. In a north Indian cohort study, the case fatality ratio for diarrheal episodes that lasted ≥14 days (11.94%) was several times higher than for episodes that lasted 7 to 13 days (0.8%) or <7 days (0.6%).[7]

Zinc supplementation also resulted in a substantial decline in the proportion of children who experienced recurrent diarrhea, suggesting that zinc deficiency may be an important underlying factor. Previous studies have shown that in developing countries, diarrheal morbidity has a skewed distribution and a subset of children experience exceptionally high diarrhea morbidity that is not explained by socioeconomic factors or anthropometric status.[16] The impact on recurrent diarrhea has important implications, as recurrent diarrhea is an established risk factor for malnutrition.[17,18]

The baseline plasma copper levels were substantially above the upper limit of the range for young children; this may be related to the use of brass utensils in the study households or may be a manifestation of an acute-phase response to infections, common in this setting. The lower, end-of-study copper levels in the intervention group may be attributable to the effect of zinc on copper absorption[19,20] or decreased prevalence of infections at the time of measurement of end-of-study plasma copper and therefore lesser proportion of children with an acute-phase response. The functional consequences of the effect of various doses of zinc on plasma copper levels merits additional study.

When the current and other available studies are viewed together, the preventive impact of zinc supplementation against diarrhea does not seem to be

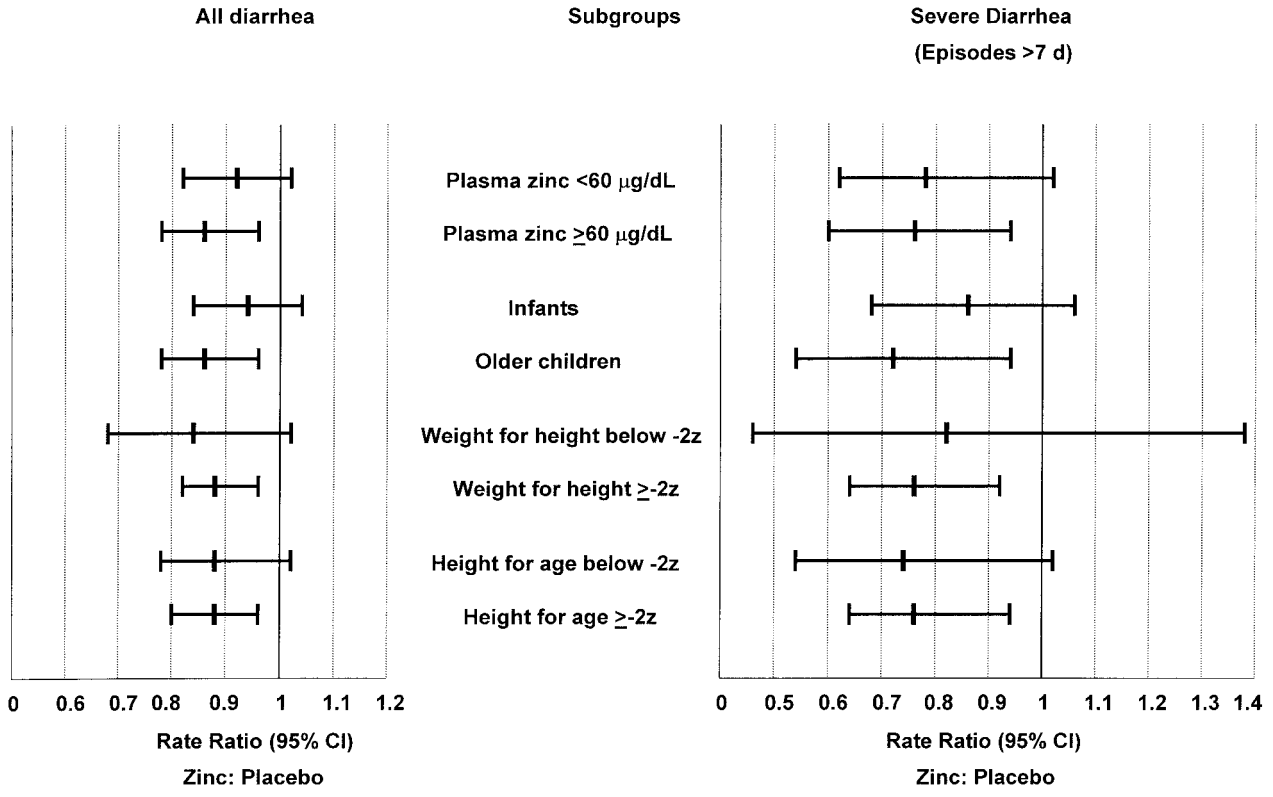

Fig 2. Effect of zinc supplementation on incidence of diarrhea in subgroups of enrolled children.

restricted to those with wasting, stunting, or low plasma zinc. This makes it difficult to select a target group on whom the intervention may be focused. The limitations of plasma zinc as a measure of zinc status may partly explain these findings.[12] Alternatively, the impact of zinc may not be attributable only to correction of deficiency, ie, there may be some pharmacologic effect even in those with normal zinc status.[21]

Prevention of diarrhea by optimizing zinc intakes is biologically plausible. The low mean plasma zinc shows that deficiency was common in the trial subjects. In experimental models, zinc deficiency has been shown to impair cellular and humoral immune function.[3,22] Supplementation in such individuals improves immune function, including delayed cutaneous hypersensitivity, and increases the number of CD4 (helper) lymphocytes.[3] Zinc deficiency also has direct effects on the gastrointestinal tract, such as impaired intestinal brush border, increased secretion in response to bacterial enterotoxins, and perturbations in intestinal permeability.[4,23] Finally, zinc in the treatment of acute diarrhea has been shown consistently to reduce episode duration and severity.[24]

An important strength of the study design is that subjects of the present trial constituted a representative sample of a well-defined, low-income urban community. The findings of the study are therefore generalizable to low-income populations with similar dietary habits and morbidity patterns. Although we did not include children who were younger than 6 months, recent reports of a mortality decline in zinc-supplemented 1- to 9-month-old small-for-gestational-age infants suggests likely benefits on morbidity in early infancy as well, particularly in countries where low birth weight is common.[25]

The findings of the current and previous studies suggest that improving zinc status in deficient populations is expected to reduce substantially diarrheal and respiratory morbidity.[6,24] For facilitating intervention, there is a need to obtain reliable estimates of zinc deficiency, particularly in developing countries. Prompt measures to improve zinc status of deficient populations are warranted. The potential approaches to achieve this goal include food fortification, dietary diversification, cultivation of plants that are zinc dense or have a decreased concentration of zinc absorption inhibitors, and supplementation of selected groups of children. Future studies should assess the impact of increased zinc intakes on childhood mortality in developing countries.

TABLE 4. Impact of Zinc Supplementation on the Risk of Recurrent Diarrhea

	Zinc (n = 1228) (n [%])	Placebo (n = 1236) (n [%])	RR (95% CI)
Children with			
0 episodes	237 (19.3)	196 (15.8)	1.22 (1.02–1.44)
1–3 episodes	688 (56.0)	683 (55.2)	1.01 (0.94–1.09)
4–6 episodes	257 (20.9)	267 (21.6)	0.97 (0.83–1.13)
>6 episodes	46 (3.7)	90 (7.3)	0.51 (0.36–0.73)

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