Effect of zinc supplementation between 1 and 6 mo of life on growth and morbidity of Bangladeshi infants in urban slums[1–3]

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ABSTRACT

Background: Evidence for an effect of zinc supplementation on growth and morbidity in very young infants in developing countries is scarce and inconsistent.

Objective: We assessed the effect of zinc supplementation on growth and morbidity in poor Bangladeshi infants aged 4–24 wk.

Design: Infants from Dhaka slums were enrolled at 4 wk of age and randomly assigned to receive 5 mg elemental Zn/d (n = 152) or placebo (n = 149) until 24 wk of age. They were followed weekly for information on compliance and morbidity; anthropometric measurements were performed monthly. Serum zinc was assessed at baseline and at 24 wk of age.

Results: At 24 wk of age, serum zinc concentrations were higher in the zinc than in the placebo group (13.3 ± 3.8 and 10.7 ± 2.9 μmol/L, respectively; $P < 0.001$). Significantly greater weight gains were observed in the zinc than in the placebo group for 43 infants who were zinc deficient (< 9.18 μmol/L) at baseline (3.15 ± 0.77 and 2.66 ± 0.80 kg, respectively; $P < 0.04$). In the other infants, no significant differences were observed in mean weight and length gains during the study period. Zinc-deficient infants showed a reduced risk of incidence of acute lower respiratory infection after zinc supplementation (relative risk: 0.30; 95% CI: 0.10, 0.92); among the non-zinc-deficient infants there were no significant differences between treatment groups.

Conclusions: Zinc-deficient Bangladeshi infants showed improvements in growth rate and a reduced incidence of acute lower respiratory infection after zinc supplementation. In infants with serum zinc concentrations > 9.18 μmol/L, supplementation improved only biochemical zinc status. *Am J Clin Nutr* 2002;76:1401–8.

KEY WORDS Zinc supplementation, infants, morbidity, growth, Bangladesh

INTRODUCTION

Zinc deficiency has been associated with reduced growth, impaired immunity, and increased prevalence and incidence of infectious diseases among infants and children in developing countries (1–3). Evidence for a causal relation with morbidity has been provided by randomized controlled intervention trials in infants ≥ 6 mo of age and children in both industrialized and developing countries that showed improved immune functions (4, 5) and reduced morbidity (2) after zinc supplementation. These effects are thought to be more attributable to a correction of the zinc deficiency status that causes an impaired immunity and intestinal mucosal damage (6) than to a pharmacologic effect of zinc (7). Evidence for an effect of zinc supplementation on the growth of children came from a recent meta-analysis that concluded that zinc supplementation during childhood is responsible for a small but statistically significant effect on growth, particularly among growth-retarded children (1).

Most of the intervention trials studying the effect of zinc on growth or morbidity were performed in children > 6 mo of age, when the period of highest growth velocity has already passed. Furthermore, the first 6 mo of life are immunologically characterized by waning passive immunity from maternal antibodies and continued development of the infant's immune system. It was therefore hypothesized that earlier interventions might be more effective in preventing growth faltering and reducing morbidity patterns among children at risk (8). Unfortunately, only limited information is available on the effect of zinc supplementation in younger infants, and the results are not conclusive. Beneficial effects on growth and morbidity were observed after zinc supplementation among low-birth-weight and small-for-gestational-age infants in Brazil (9) and Chile (10), respectively. However, in India no effect of zinc supplementation on diarrheal morbidity was observed in children 6–11 mo of age, in contrast to the strong beneficial effects observed among older children (11). Different prevalences of zinc deficiency caused by varying rates of prematurity, intrauterine growth retardation, exclusivity of breast-feeding, and early morbidity may explain the varying responses to zinc supplementation in very young infants.

To investigate the effect of zinc supplementation on growth and morbidity from infectious diseases in infants < 6 mo of age, we

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performed an intervention trial among 4–24-wk-old Bangladeshi infants living in Dhaka urban slums. Because the incidence of low birth weight among this population is as high as 43%, the majority of which (76%) is caused by intrauterine growth retardation (12), a large proportion of these infants can be considered to have impaired immunity and increased morbidity and to be at risk of growth faltering later in life (13).

SUBJECTS AND METHODS

Study population

The study was performed in 3 selected areas of Dhaka city slums, in a representative sample of households from Dhaka's slum population (14). The slum areas are characterized by high population density, poor housing, multifamily latrines and water sources, poor sewerage and drainage facilities, and irregular garbage collection. The population is relatively young and mostly illiterate (15). Malnutrition is known to be widely prevalent, and prevalences of malnutrition among children of the urban slums are even higher than among children of the rural poor (16).

Singleton infants were eligible for inclusion in the study if they met entry criteria of age (4 ± 1 wk) and residence, were in good general health without known underlying illnesses, were not included in any other intervention trial, and had not received immunizations through other sources. A total of 301 infants aged 3–5 wk (152 in the zinc and 149 in the placebo group) were identified through an established household-surveillance system and enrolled in the study between April and June 1997. As is the case in most of Bangladesh, the vast majority of these infants (87%) were born at home, and gestational age and birth weight assessments were therefore not available. Before enrollment, written, informed consent was obtained from each infant's parents. The study was approved by the Ethical Review Committee of the International Centre for Diarrhoeal Disease Research, Bangladesh and the Committee on Human Research of the Johns Hopkins School of Hygiene and Public Health.

Study design

Infants were randomly allocated to receive 5 mL/d of a liquid with or without 5 mg elemental Zn (as zinc acetate). Both liquids contained sucrose, flavors, and preservatives; were indistinguishable in both appearance and taste; and were prepared and coded by Opsonin Chemical Industries Ltd, Dhaka. The zinc content of both supplement and placebo was independently confirmed by 2 different laboratories. Health workers delivered a bottle containing a 1-wk supply of 40 mL of the supplement to the houses of the participants and instructed the mothers to give a daily dose to their infants, when possible in between feedings, using a marked dropper or feeding spoon. Compliance with supplement consumption was 85% (of total days), and the average (± SD)daily consumption was 4.2 ± 1.3 mL, as assessed by measuring liquid levels at the weekly visits. Unannounced compliance checks between the regular visits were also performed monthly in a 10% subsample of the population. No differences in compliance were observed between the 2 treatment groups. The codes of the supplements were unknown to both participants and study staff and were broken only after data editing and cleaning were completed.

Before randomization, information was collected on the household's socioeconomic status, demographic characteristics, maternal and infant anthropometry, characteristics of the delivery (place, duration, complications) and infant vaccination history. The infants were provided with the standard immunizations by the study nurses. The bacille Calmette-Guérin vaccine was administered at enrollment, and the infants were immunized with the trivalent oral polio vaccine and the combined diphtheria, tetanus toxoid, and pertussis–*Haemophilus influenza* type B vaccine (TETRAMUNE, Wyeth Lederle Vaccines, Pearl River, NY) at 8, 12, and 16 wk of age (± 2 wk). A subsample of 171 infants who had not yet reached the age of 4 mo ± 15 d at the time of arrival of the vaccine, received in addition the 7-valent pneumococcal conjugate vaccine (Wyeth Lederle Vaccines) at 4-wk (± 2 wk) intervals (17).

The infants' serum zinc concentration was determined at 4 and 24 wk of age. The infants were followed weekly for assessment of compliance and morbidity of diarrheal and respiratory diseases. Information on infant feeding practices was collected every 2 wk, and the infants were classified as either exclusively, predominantly (infant receiving breast milk and water or sugar water), or partially breast-fed or not breast-fed at all. The age of introduction of complementary foods was also determined. Anthropometric measurements (weight and length and arm, head, and chest circumference) were performed monthly until the infants were aged 6 mo.

Data collection procedures

During monthly home visits, infant weight was measured to the nearest 10 g on beam-balance scales (Seca 725; Seca, Hamburg, Germany) that were regularly calibrated against standard weights. Recumbent lengths were measured to the nearest 0.1 cm on a length board, and head, chest, and arm circumferences were measured to the nearest millimeter with numeral insertion tapes. The mean of 2 measurements was recorded as the observed value for all indexes. Intra- and interobserver variations were assessed and found to be acceptable, with CVs < 2% for all anthropometric indexes. Underweight (low weight-for-age), stunting (low length-for-age), and wasting (low weight-for-length) were defined as SD scores (z scores) of less than −2.00 compared with the US National Center for Health Statistics reference charts with the use of EPI INFO software (version 6.1; Centers for Disease Control, Atlanta; 18).

A detailed history of the past week's respiratory infections, diarrhea, fever, and other illnesses was recorded during the weekly home visits. The infants were investigated for signs of dehydration during the monthly visits. Infants who required medical treatment were examined by study physicians following standard treatment protocols and were referred to appropriate health care facilities if necessary. All data were collected by the same trained fieldworkers and manually checked and coded by registered nurses.

Acute lower respiratory infection (ALRI) was defined as a history of cough or difficult breathing, with or without fever, lasting > 1 d and accompanied by rapid breathing, chest indrawing, or both. Upper respiratory tract infection was defined as *1*) a history of cough or difficult breathing, with or without fever, for > 1 d not associated with rapid breathing or chest indrawing, or *2*) a cough for > 1 d with nasal discharge.

Acute diarrhea was defined as unusually loose or unusually frequent stool, or both, according to the mother's perception. If the stool contained blood, the episode was classified as dysentery. Persistent diarrhea was defined as diarrhea lasting for ≥ 14 d.

The number of actual surveillance days was counted by subtracting the days on which no recall data were available from the total days of follow-up. When a mother had been absent for > 15 d

(2 consecutive visits), recall data were only collected for the 14 d before the first interview after the period of absence. An episode of illness was considered resolved if the child was free of symptoms for at least 3 consecutive days according to definitions used in similar studies (2, 11).

Specimen collection and laboratory procedures

At 4 and 24 wk of age, nonfasting blood specimens were obtained by antecubital venipuncture during morning hours for serum zinc determination with the use of trace mineral–free plastic syringes, stainless steel needles, and plastic tubes. Serum was separated a maximum of 6 h after collection and after separation stored at –20 °C until analysis. Before analysis, the serum samples were diluted (1:12) with 0.03% polyoxyethylene 4 lauryl ether (Brij 30) and HNO_3 (10 mmol/L). Zinc concentration was measured with flame atomic absorption spectrophotometry (19) (AA-6501S Atomic Absorption Flame Emission Spectrophotometry, Shimadzu, Japan). A standard curve was established by using a commercial zinc reference (BDH Laboratory Supplies, Dorset, United Kingdom) in concentrations of 0.1, 0.25, 0.5, and 1.0 mg/L. Commercial serum with known concentrations of zinc was used as a measure of quality control. The following concentrations (±SD) were measured in our laboratory: 1.42 ± 0.049 μmol/L against reference value 1.42 μmol/L and 4.39 ± 1.38 μmol/L against reference value 4.28 μmol/L. The measured values were therefore within 3% of the reference values. The CV of the measurements was always < 5%.

Statistical methods

Differences between the zinc and placebo groups for serum zinc at 6 mo of age and for the difference in serum zinc at 1 and 6 mo of age were tested with analysis of variance. Before this analysis we had performed a regression analysis and observed that the differences in serum zinc between 1 and 6 mo of age were independent of the absolute serum zinc concentrations.

For each outcome variable, possible interactions between the effect of supplementation and infant's sex, baseline nutritional status, or baseline serum zinc status were evaluated by introducing separate interaction terms in the linear regression models. We had selected these variables because there is evidence in the literature that sex, nutritional status, and serum zinc status might interact with a possible supplementation effect of zinc (1, 2, 11). The effect of zinc supplementation on the following outcome variables was dependent on baseline serum zinc concentration: weight gain ($P = 0.04$), change in head circumference ($P = 0.02$), length gain ($P = 0.002$), incidence of dysentery ($P = 0.049$), incidence of persistent diarrhea ($P = 0.02$), and prevalence of dysentery ($P = 0.02$). We also observed an interaction between effect of supplementation and sex for the prevalence of ALRIs ($P = 0.058$). There were no significant interactions between treatment effect and baseline nutritional status. We therefore created separate models based on subgroups for sex and baseline serum zinc < or ≥ 9.18 μmol/L. The cutoff for low serum zinc as a measure of zinc deficiency was selected according to the literature (2).

Differences between the zinc and placebo groups in anthropometric indexes and *z* scores at 6 mo of age were tested by using analysis of covariance for repeated measurements. Selected baseline values were added as covariates (SPSS 7.5 for WINDOWS; SPSS Inc, Chicago). Subsequently, differences in mean weight and length gain between the zinc and placebo groups were assessed by using analysis of covariance. The covariates had been selected before the analysis of covariance through a multiple stepwise regression identifying variables that contributed significantly to the variation in outcome variable.

Longitudinal prevalence of diseases was calculated for each individual as percentage of actual surveillance days with illness. The nonparametric Mann-Whitney *U* test was used to compare differences in longitudinal prevalence between infants from the zinc and placebo groups. Log-transformed values of prevalence were used in the multivariate regression models because the distribution of longitudinal prevalence was highly skewed. Before the log transformation, a constant (1) was added to all values to enable log transformation of the zero values.

Differences between groups in incidence of diseases were assessed with Poisson regression models (EGRET statisitical software; SERC Inc, Seattle) including number of episodes as dependent, treatment group as independent, and total days of actual surveillance as off-set term in the model (20). Potential confounders were added to the regression models as additional independent variables.

P values of < 0.05 were considered statistically significant. Results are presented as means (±SDs) unless otherwise indicated.

RESULTS

During the course of the study 31 infants (10%) were lost to follow-up [14 (9%) in the zinc and 17 (11%) in the placebo group; NS]. Fifteen of the 31 infants either permanently or temporarily out-migrated, 8 infants died during the study period, 4 parents refused further participation, and 4 infants received immunizations through other sources and were excluded from further participation. There were no differences in reasons for being lost to follow-up between the 2 treatment groups. Infants who were lost to follow-up from the study still contributed to the analysis for morbidity for the number of days on which there were observations.

A total of 270 infants (138 in the zinc and 132 in the placebo group) completed the study until 24 wk of age. This final sample size was sufficient to detect the following differences with 80% power and type I error of 5% between the zinc and placebo groups for the main outcome variables: 1.2 ± 3.5 μmol/L (10%) for serum zinc at 24 wk of age, 0.24 ± 0.7 kg (9%) for increase in body weight between 4 and 24 wk of age, and 0.7 ± 0.2 episodes per child per 6 mo (12%) for incidence of acute diarrhea.

All the infants were breast-fed for the duration of the study, but the rate of exclusive breast-feeding was low because of the early introduction of water provided along with breast milk. At 24 wk of age, 16% of all the infants were exclusively or predominantly breast-fed (breast milk and water) and 80% were partially breast-fed (breast milk and other complementary fluids or foods). There was no significant relation between breast-feeding status at 1 or 6 mo of age and the main outcome variables of interest in stepwise multiple regression analysis to identify potential confounding variables. There was a significant relation with the age of introduction of water for some outcome variables. Therefore we controlled for this variable in the multivariate analysis.

Baseline characteristics of infants in the zinc and placebo groups were not different (**Table 1**). At baseline 43 infants (14%)

TABLE 1
Baseline characteristics of infants in the zinc and placebo groups[1]

	Zinc group (n = 152)	Placebo group (n = 149)
Age (mo)	0.89 ± 0.13	0.90 ± 0.12
Sex, male (%)	41	48
Socioeconomic status (%)[2]		
Poor	41	44
Very poor	30	34
Weight (kg)	3.47 ± 0.48	3.44 ± 0.50
Length (cm)	51.3 ± 2.3	51.1 ± 2.1
Midupper arm circumference (mm)	104 ± 9	104 ± 9
Head circumference (cm)	35.6 ± 1.4	35.6 ± 1.3
Serum zinc (μmol/L)	11.9 ± 2.9	11.7 ± 3.0

[1] $\bar{x}$ ± SD. There were no statistically significant differences between groups.
[2] Based on an index of household assets (12).

had serum zinc concentrations < 9.18 μmol/L (22, or 15%, in the zinc group and 21, or 14%, in the placebo group; NS).

Serum zinc

At 24 wk of age, the zinc group had significantly higher concentrations than did the placebo group (13.3 ± 3.8 compared with 10.7 ± 2.9 μmol serum Zn/L; $P < 0.001$). Concentrations significantly decreased between 4 and 24 wk in the placebo group (−1.1 ± 4.1 μmol serum Zn/L), whereas they increased in the zinc group (1.5 ± 4.7 μmol serum Zn/L; P for difference < 0.001). At 24 wk of age, a total of 28 infants (22%) in the placebo group were classified as zinc deficient (< 9.18 μmol serum Zn/L; 2) compared with 12 infants (9%) in the zinc group ($P < 0.005$).

Assessment of growth

No differences were observed for changes in weight, length, and head circumference between 4 and 24 wk of age for infants in the zinc and placebo groups (**Table 2**). Mean weight and length at 24 wk of age were 6.33 ± 0.94 kg and 62.7 ± 2.6 cm for the zinc group and 6.23 ± 1.01 kg and 62.5 ± 2.7 cm, respectively, for the placebo group (difference NS). Mean length-for-age, weight-for-age, and weight-for-length z scores between 4 and 24 wk of age were not different between treatment groups (data not shown).

When data were analyzed separately for infants with (n = 43) or without (n = 257) zinc deficiency at baseline (< 9.18 μmol serum Zn/L), significant differences were observed after zinc supplementation for total weight gain between 4 and 24 wk of age and weight at 24 wk of age (6.52 ± 0.85 kg compared with 5.82 ± 0.99 kg in the zinc and placebo groups, respectively; $P < 0.05$) in 43 infants who were zinc deficient at baseline (Table 2). A similar trend was observed for total length gain, but this difference was not significant. Weight-for-age and weight-for-length z scores at 4, 5, and 6 mo of age were significantly higher in the zinc than in the placebo group (**Figures 1–3**). After zinc supplementation, significantly greater changes in weight, length, head circumference, and chest circumference were observed in the zinc-deficient infants than in the non-zinc-deficient infants (Table 2). No differences were observed in the infants from the placebo group or between treatment groups in infants with normal baseline concentrations (≥ 9.18 μmol serum Zn/L; Table 2 and Figures 1–3).

TABLE 2
Changes in anthropometric indicators between 4 and 24 wk of age by baseline serum zinc status for infants in the zinc and placebo groups[1]

	Zinc group	Placebo group
Weight growth (kg)		
All infants	2.85 ± 0.73	2.79 ± 0.72
Infants with low serum zinc[2]	3.15 ± 0.77	2.66 ± 0.80[3]
Infants with normal serum zinc[4]	2.79 ± 0.71[5]	2.81 ± 0.72
Weight growth ($g \cdot kg^{-1} \cdot mo^{-1}$)		
All infants	131 ± 29	129 ± 29
Infants with low serum zinc[2]	144 ± 29	130 ± 33
Infants with normal serum zinc[4]	128 ± 28[5]	128 ± 28
Linear length growth (cm)		
All infants	11.5 ± 1.9	11.4 ± 2.1
Infants with low serum zinc[2]	12.5 ± 2.0	11.5 ± 2.2
Infants with normal serum zinc[4]	11.3 ± 1.8[5]	11.4 ± 2.1
Change in head circumference (cm)		
All infants	5.1 ± 1.1	5.2 ± 1.1
Infants with low serum zinc[2]	5.9 ± 1.0	5.1 ± 1.2[3]
Infants with normal serum zinc[4]	5.0 ± 1.1[5]	5.2 ± 1.1
Change in chest circumference (cm)		
All infants	6.8 ± 2.1	6.6 ± 2.1
Infants with low serum zinc[2]	7.8 ± 2.1	6.7 ± 2.4
Infants with normal serum zinc[4]	6.6 ± 2.0[5]	6.6 ± 2.1
Change in midupper arm circumference (cm)		
All infants	2.5 ± 1.1	2.6 ± 1.0
Infants with low serum zinc[2]	2.9 ± 1.2	2.5 ± 1.1
Infants with normal serum zinc[4]	2.5 ± 1.0	2.6 ± 1.0

[1] $\bar{x}$ ± SD; n = 138 for the zinc group, 133 for the placebo group.
[2] Baseline serum zinc concentration < 9.18 μmol/L (n = 21 for the zinc group, 16 for the placebo group).
[3] Significantly different from the zinc group, $P < 0.04$ (ANCOVA control for sex, baseline length-for-age z score, baseline infant weight, baseline serum zinc, and household income).
[4] Baseline serum zinc concentration ≥ 9.18 μmol/L (n = 117 for the zinc group, 115 for the placebo group).
[5] Significantly different from the low serum zinc group, $P < 0.05$ (ANCOVA control for sex, baseline length-for-age z score, baseline infant weight, baseline serum zinc, and household income).

In male infants, total weight gain between 4 and 24 wk of age (3.21 ± 0.68 compared with 2.99 ± 0.62 kg in the zinc and placebo groups) was higher in the zinc than in the placebo group. However, this difference was not statistically significant after controlling for confounding variables in the multivariate analyses. No differences in growth were observed between treatment groups among female infants.

Morbidity

No differences were observed between the treatment groups for percentage of days ill and number of episodes of diarrheal and respiratory diseases (**Tables 3** and **4**). However, when the data were analyzed separately for zinc-deficient infants (baseline concentration < 9.18 μmol serum Zn/L), fewer episodes with ALRIs were observed in the zinc group (0.3 ± 0.7 episodes per child per 6 mo) than in the placebo group (0.9 ± 1.3 episodes per child per 6 mo; relative risk: 0.30; 95% CI: 0.10, 0.92). No significant differences were observed between the zinc and placebo groups for infants with normal baseline concentrations (≥ 9.18 μmol serum Zn/L; Table 4) (2). There were no differences in the effect of zinc on morbidity for infant's sex.

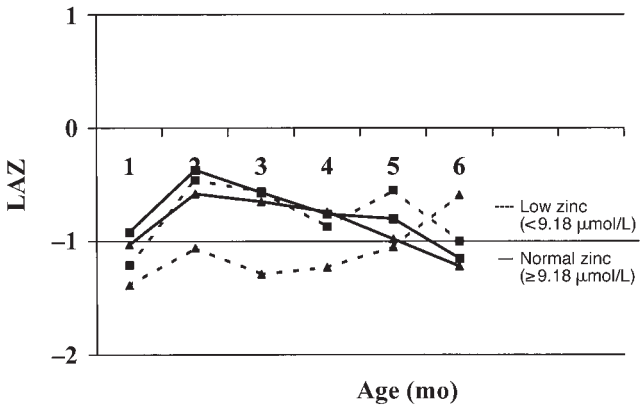

FIGURE 1. Mean length-for-age *z* scores (LAZ) between 1 and 6 mo of age for infants in the zinc (■) and placebo (▲) groups.

DISCUSSION

Supplementation with 5 mg elemental Zn/d between 4 and 24 wk of age did not improve infant growth nor reduce morbidity from diarrheal and respiratory diseases in Bangladeshi infants with normal serum zinc concentrations. However, in infants with low serum zinc concentrations (2) at baseline, beneficial effects were observed after zinc supplementation: these infants had significantly greater weight gain and improved (though not significantly) linear growth, and they experienced significantly fewer episodes of ALRIs.

These findings were somewhat unexpected because we had anticipated a beneficial effect of zinc supplementation on growth and morbidity among all infants in this deprived population. The study was performed among young infants < 6 mo of age who are at high risk for growth faltering and contracting diseases, in a population where zinc deficiency is thought to be common. We believe that a lack of effect in the apparently non-zinc-deficient infants (based on concentrations ≥ 9.18 μmol serum Zn/L) may be due to one or more of the following reasons: *1*) the age of these infants did not allow us to show an effect of zinc supplementation on morbidity because of the low incidence of diseases among this young age group and the fact that at this age predominantly breast-fed infants have probably not yet developed a zinc deficiency, *2*) zinc might not have been the primary growth-limiting nutrient for these predominantly breast-fed infants, and *3*) the dosage we provided may not have been sufficient.

We provided 5 mg elemental Zn/d, the recommended daily allowance for this age group (21). Because the infants in our study were predominantly breast-fed during most of the study period, most of the dietary zinc intake was from breast milk, and differences between the zinc and placebo groups in dietary zinc intake, other than the supplement, were therefore thought to be random and caused by natural variability in breast milk zinc (22). Compliance with supplement consumption was good, and we observed significant improvements in serum zinc values in the zinc but not in the placebo group, indicating that the zinc supplementation was successful in improving the zinc status of these infants.

We do not know whether a higher dosage of zinc would have given different results in our population. Positive effects of zinc supplementation on growth or morbidity of infants or children have been observed in studies using higher (23–26) but also similar (27, 28) or even lower dosages (10) than used in our study, although most of these studies were performed in older infants and children. A significantly higher mortality was observed among severely malnourished children in Bangladesh receiving a high-dose (6 mg · kg body $wt^{-1} \cdot d^{-1}$) zinc treatment, suggesting that some caution is warranted in supplementing malnourished children with high dosages of zinc (29).

The lack of effect on growth in the general, ie, non-zinc-deficient, population as observed in our study is in contrast with findings of other studies among the same age group (10, 28) showing improvements in growth after supplementation with 3 and 5 mg elemental Zn/d in Chile and France, respectively. The Chilean study (10) was carried out in small-for-gestational-age infants, whereas in our cohort of infants ≈31% of the infants were expected to be intrauterine growth–retarded based on information from a previous study carried out in the same study area (12). The study in France (28) was performed in infants who were also receiving complementary foods in addition to breast milk, whereas in our study 16% of the infants were not receiving any complementary foods other than water at 24 wk of age. Beneficial effects of zinc supplementation on linear and ponderal growth have also been observed among older infants, in both well-nourished and malnourished populations (1, 23). However, some studies among older children in malnourished populations (24, 27, 30) were not able to show an effect of zinc supplementation on growth. It has

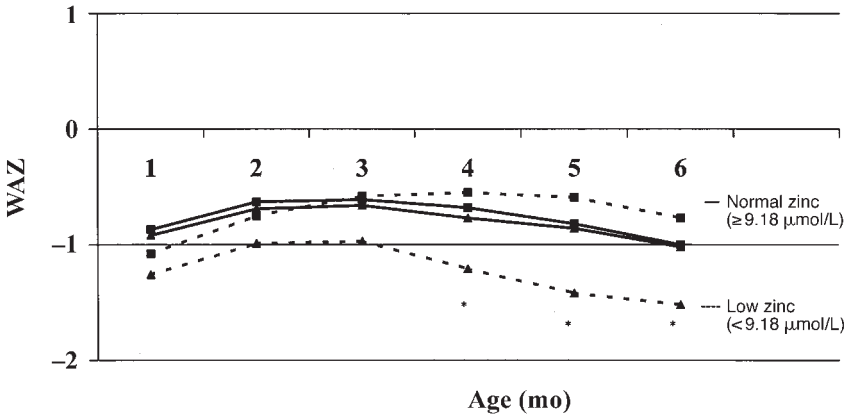

FIGURE 2. Mean weight-for-age *z* scores (WAZ) between 1 and 6 mo of age for infants in the zinc (■) and placebo (▲) groups. *Significantly different from the zinc group, $P < 0.05$.

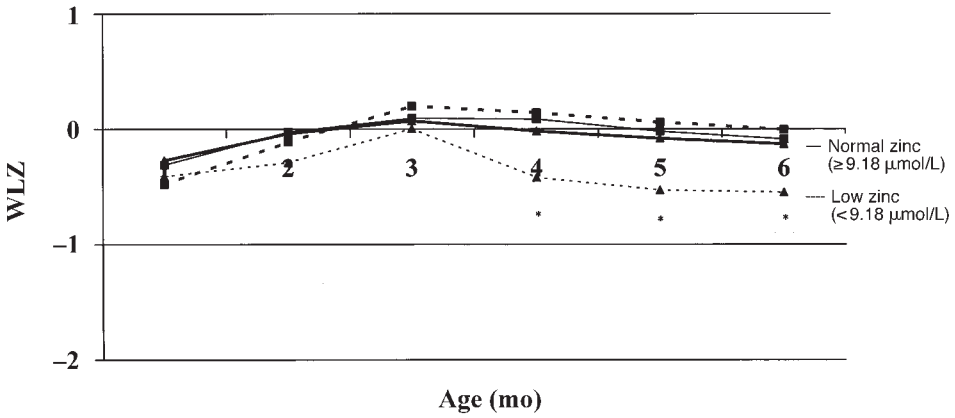

FIGURE 3. Mean weight-for-length (WLZ) *z* scores between 1 and 6 mo of age for infants in the zinc (■) and placebo (▲) groups. *Significantly different from the zinc group, $P < 0.05$.

been hypothesized that zinc was probably not the primary growth-limiting nutrient in these populations (31), and single-nutrient interventions might therefore not improve growth in populations with multiple-nutrient deficiencies (32).

We believe that the very young age, in combination with the breast-feeding practices, in our population is the most likely explanation for a lack of effect of zinc supplementation observed among the general population of infants in our study and in fact has prevented rather than enhanced an effect of zinc both on growth and morbidity. Firstly, we supplemented infants between 4 and 24 wk of age, and the overall burden of morbidity in this age group was low. A stronger reduction in morbidity after zinc supplementation has been observed in older compared with younger age groups (11, 25), possibly because of the higher incidence of diseases in older age groups, where exposure to antigens is usually higher and the protective effect of maternal anti-

TABLE 3
Longitudinal prevalence of morbidity between 4 and 24 wk of age for infants in the zinc and placebo groups[1]

Morbidity	Percentage of days ill			
	Zinc group		Placebo group	
	Mean	Median (range)	Mean	Median (range)
	%	%	%	%
Acute diarrhea				
All infants	5.9	4.8 (0.0–37.0)	5.8	3.6 (0.0–33.3)
Infants with low serum zinc[2]	5.8	5.2 (0.0–26.4)	6.7	4.1 (0.0–26.5)
Infants with normal serum zinc[3]	6.0	4.4 (0.0–37.0)	5.6	3.6 (0.0–33.3)
Persistent diarrhea				
All infants	4.2	0.0 (0.0–48.1)	4.7	0.0 (0.0–86.4)
Infants with low serum zinc[2]	4.3	0.0 (0.0–30.8)	3.1	0.0 (0.0–28.0)
Infants with normal serum zinc[3]	4.2	0.0 (0.0–48.1)	5.0	0.0 (0.0–86.4)
Dysentery				
All infants	0.7	0.0 (0.0–18.6)	1.1	0.0 (0.0–73.0)
Infants with low serum zinc[2]	0.0	0.0 (0.0–0.0)	0.2	0.0 (0.0–4.1)
Infants with normal serum zinc[3]	0.8	0.0 (0.0–18.6)	1.3	0.0 (0.0–73.0)
Cough (upper respiratory infection)				
All infants	36.9	35.3 (0.0–100.0)	35.1	32.2 (0.0–94.6)
Infants with low serum zinc[2]	38.5	40.6 (0.0–100.0)	38.5	44.6 (2.00–94.6)
Infants with normal serum zinc[3]	36.6	33.8 (0.0–91.8)	34.1	29.1 (0.0–89.8)
Acute lower respiratory infection				
All infants	7.6	0.0 (0.0–93.9)	7.5	0.0 (0.0–87.2)
Infants with low serum zinc[2]	5.8	0.0 (0.0–69.4)	8.0	0.0 (0.0–45.5)
Infants with normal serum zinc[3]	7.9	0.0 (0.0–93.9)	7.4	0.0 (0.0–87.2)

[1] n = 152 in the zinc group, 149 in the placebo group. Only infants with ≥15 d follow-up were included. There were no statistically significant differences between groups (linear regression with log-transformed values).

[2] Baseline serum zinc concentration <9.18 μmol/L (n = 22 for the zinc group, 21 for the placebo group).

[3] Baseline serum zinc concentration ≥9.18 μmol/L (n = 130 for the zinc group, 127 for the placebo group).

TABLE 4
Incidence of diseases between 4 and 24 wk of age for infants in the zinc and placebo groups[1]

	Zinc group	Placebo group	RR (95% CI)[2]
Total surveillance days	20547	20238	—
Acute diarrhea			
Total episodes	244	216	—
Episodes per child per 6 mo			
All infants	2.1 ± 2.0[3]	2.0 ± 2.1	1.13 (0.94, 1.36)
Infants with low serum zinc[4]	2.1 ± 2.0	2.6 ± 2.1	0.87 (0.60, 1.72)
Infants with normal serum zinc[5]	2.1 ± 2.1	1.9 ± 2.1	1.14 (0.93, 1.39)
Persistent diarrhea			
Total episodes	40	38	
Episodes per child per 6 mo			
All infants	0.4 ± 0.8	0.4 ± 1.5	1.17 (0.74, 1.83)
Infants with low serum zinc[4]	0.4 ± 0.7	0.3 ± 0.6	1.58 (0.31, 7.96)
Infants with normal serum zinc[5]	0.4 ± 0.9	0.5 ± 1.6	1.04 (0.64, 1.69)
Dysentery			
Total episodes	10	13	
Episodes per child per 6 mo			
All infants	0.09 ± 0.3	0.12 ± 0.4	0.72 (0.31, 1.66)
Infants with low serum zinc[4]	0.0 ± 0.0	0.1 ± 0.3	NA[6]
Infants with normal serum zinc[5]	0.1 ± 0.3	0.1 ± 0.5	0.77 (0.33, 1.78)
Cough (upper respiratory infection)			
Total episodes	511	500	
Episodes per child per 6 mo			
All infants	3.4 ± 1.7	3.4 ± 1.5	1.00 (0.89, 1.14)
Infants with low serum zinc[4]	4.5 ± 2.1	4.5 ± 1.9	0.95 (0.65, 1.39)
Infants with normal serum zinc[5]	4.6 ± 2.0	4.6 ± 2.2	1.01 (0.88, 1.15)
Acute lower respiratory infection			
Total episodes	75	74	
Episodes per child per 6 mo			
All infants	0.7 ± 1.2	0.7 ± 1.2	0.99 (0.71, 1.37)
Infants with low serum zinc[4]	0.3 ± 0.7	0.9 ± 1.3	0.30 (0.10, 0.92)[7]
Infants with normal serum zinc[5]	0.7 ± 1.3	0.7 ± 1.2	1.10 (0.77, 1.56)

[1] n = 150 in the zinc group, 149 in the placebo group. Only infants with ≥15 d follow-up were included. RR, rate ratio; NA, not applicable.
[2] Estimated by Poisson regression with 95% CI in parentheses, adjusted for baseline infant weight, length, socioeconomic status, problems during delivery reported, delivery duration, and age of introduction of water.
[3] $\bar{x}$ ± SD.
[4] Baseline serum zinc concentration <9.18 μmol/L (n = 22 for the zinc group, 21 for the placebo group).
[5] Baseline serum zinc concentration ≥9.18 μmol/L (n = 128 for the zinc group, 127 for the placebo group).
[6] Could not calculate RR because of empty cells.
[7] $P < 0.05$.

bodies is waning. However, reductions in morbidity after zinc supplementation have been observed even during the first 6 mo of life in a study among low-birth-weight infants in Brazil (9). The dosage used in this study was similar to our dosage, but the supplementation in the Brazilian study started at birth and continued for 12 wk only.

Secondly, in our study we observed statistically significant differences in growth and morbidity after zinc supplementation among infants who were zinc deficient at baseline. These findings and the fact that at 4 wk of age only 14% of our population had not yet developed zinc deficiency of a sufficient magnitude to reduce serum concentrations <9.18 μmol Zn/L suggest that most infants of this age had not yet developed a zinc deficiency. At 24 wk of age, almost all infants in our study (96%) were still predominantly or partially breast-fed. In developed countries zinc deficiency is known to be relatively rare among term breast-fed infants during the first months of life (33) because of large concentrations of highly bioavailable zinc in early breast milk and utilization of hepatic metallothionein as a source of zinc during the first months of life (34). The results of our study indicate that similar mechanisms may also occur in less affluent societies in breast-fed children below 6 mo of age, although more research is required to confirm this.

In conclusion, supplementation with 5 mg elemental Zn/d between 4 and 24 wk of age improved zinc status but did not improve growth or reduce morbidity in poor Bangladeshi infants, among infants with serum zinc concentrations >9.18 μmol/L at 4 wk of age. However, improvements in growth and morbidity were observed in infants with low serum zinc concentrations at 4 wk of age, suggesting that zinc supplementation might be beneficial in some infants who are zinc deficient at this very early age.

We previously reported results from another study in the same population showing that supplementation with 30 mg elemental Zn/d during the last 2 trimesters of pregnancy reduced morbidity from diarrheal diseases among low-birth-weight infants during the same age period (12, 35). The differences in results between our 2 studies indicate that compared with infant supplementation, zinc supplementation during pregnancy may be a more effective way to reduce some of the increased health risks associated with low birth weight or zinc deficiency in infants <6 mo of age.

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