

# Effect of zinc supplementation on morbidity and growth in hospital-born, low-birth-weight infants<sup>1–3</sup>

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## ABSTRACT

**Background:** Low-birth-weight infants may have impaired zinc status, but little is known about the effect of zinc supplementation.

**Objective:** The objective was to investigate the effect of daily zinc supplementation on morbidity and anthropometric status in hospital-born, low-birth-weight infants.

**Design:** In a double-blind, randomized, placebo-controlled trial, 2052 hospital-born term infants with a birth weight  $\leq 2500$  g were randomly assigned to receive zinc or placebo. The zinc group received elemental zinc: 5 mg/d for those infants between ages 2 wk and 6 mo and 10 mg/d for those infants aged  $>6$  mo. All-cause hospitalizations, prevalence of diarrhea, acute lower respiratory tract infections, visits to health care providers, weights, and lengths were ascertained at 3, 6, 9, and 12 mo of age.

**Results:** The supplement was consumed for  $>85\%$  of the follow-up period. Mean plasma zinc at 12 mo of age was higher in the zinc group (100.2  $\mu\text{g/dL}$ ) than in the control group (73.3  $\mu\text{g/dL}$ ) (difference in means: 26.9; 95% CI: 19.6, 34.2). The 24-h and 7-d prevalence of diarrhea and acute lower respiratory tract infections was similar at 3, 6, 9, and 12 mo. Care-seeking for illness was significantly lower in the zinc group (difference in proportions:  $-5.7$ ; 95% CI:  $-9.9$ ,  $-1.4$ ;  $P < 0.05$ ) at 9 mo. The numbers of hospitalizations, weights, and lengths were all similar at all 4 assessments.

**Conclusion:** Hospital-born, term, low-birth-weight infants do not seem to benefit substantially from zinc supplementation that meets the Recommended Dietary Allowance for zinc in terms of morbidity or physical growth during infancy in this setting. This trial was registered at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) as NCT00272142. *Am J Clin Nutr* 2009;90:385–91.

## INTRODUCTION

Zinc is a micronutrient of biological and public health importance because it is essential for protein synthesis and nucleic acid metabolism. Zinc deficiency impairs innate and acquired immunity (1). Supplementation trials with zinc in children aged 6 mo to 3 y of age have shown significant reduction in diarrheal and lower respiratory tract infections (2–5). However, there are few such supplementation trials in low-birth-weight infants (6, 7).

Of the annual 20 million low-birth-weight neonates,  $\approx 95\%$  are born in developing countries (8). Low birth weight is estimated to be an underlying risk factor in 70% of perinatal deaths, 90% of neonatal deaths, and 50% of infant deaths (9).

Low birth weight is associated with growth faltering and substantially increasing risk of severe infection-related mor-

bidity and mortality. Impaired zinc status has been reported in small-for-date infants (10, 11). Postnatal zinc deficiency has been attributed to factors such as low body stores, limited capacity to absorb and retain micronutrients coupled with increased endogenous losses associated with organ immaturity, high nutrient demand to support catch-up growth, and inadequate intakes because of exclusive breastfeeding (12). Low concentrations of zinc in the cord blood of low-birth-weight infants have been noted in several settings and are correlated with birth weight and gestation (13). Furthermore, significant reduction in zinc concentrations ( $P < 0.05$ ) during lactation is reported, and it has been postulated that the amount of zinc provided by breast milk may be lower than the Recommended Dietary Allowance (RDA) of zinc (13).

Clinical trials to assess potential benefits of zinc supplementation in early infancy need to be done in hospital-born babies and in those delivered at home because socioeconomic and dietary practices differ. We conducted an individually randomized placebo-controlled trial to assess efficacy of daily zinc supplementation between 2 to 4 wk and 12 mo of age in hospital-born, low-birth-weight infants. We hypothesized that hospital-born, term, low-birth-weight infants were likely to be zinc deficient and that supplementation with the RDA in the first year of life would decrease mild and severe diarrhea and acute lower respiratory tract infections (ALRIs) and improve physical growth compared with a group administered a placebo.

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## SUBJECTS AND METHODS

A double-blind, randomized, placebo-controlled trial was conducted between January 2005 and August 2007. The setting was urban low to middle socioeconomic neighborhoods in New Delhi, India. Data indicate that childhood undernutrition and micronutrient deficiency are common in children residing in similar settings (2, 3, 7). The burden of childhood diarrhea and respiratory infections is high (2, 14).

Clearances were obtained from the ethics committee of the All India Institute of Medical Sciences, the World Health Organization review committee, and the Society for Applied Studies.

Study participants were term infants (gestational age  $>37$  wk) with a birth weight of  $\leq 2500$  g born in the Kasturba and Hindu Rao Hospitals. These are government institutions that provide treatment free of cost to the population. Infants in the intervention group received elemental zinc, 5 mg daily for those aged  $\leq 6$  mo and 10 mg thereafter, from the day of enrollment (2–4 wk age) until the age of 12 mo. Infants in the control group received placebo daily for the same period.

Consent was sought from community leaders in the study area. Flyers were distributed to raise community awareness about the study. Written consent (or thumb imprints for those who could not write) was obtained from caregivers of enrolled infants, and a copy of the consent form was left with the family.

### Trial size

Estimates for hospitalization rates for infants in the control group were obtained from an earlier trial (15); the all-cause hospitalization rate was 207/1000 child-years of follow-up, and hospitalization rates due to diarrhea and ALRI were 9/1000 child-years and 114/1000 child-years, respectively. To detect a 25% reduction in all-cause hospitalizations, a 35% reduction in hospitalizations for respiratory illness, and a 40% reduction in hospitalizations due to diarrhea, a total of 2000 infants were required after an inflation of 10% for attrition rates. The value of  $\alpha$  was 0.05 (95% CI) and that of  $\beta$  was 0.1 (90% power) for these calculations.

### Randomization and blinding

A simple randomization scheme in permuted blocks of fixed length of 20 was used to guard against possible seasonal variations of diarrheal morbidity. The randomization list and the labeling of the supplement with a subject identification number were done by a statistician not involved with the study.

### Supplement

The supplement was in the form of dispersible tablets packaged in strips containing 15 tablets each. Monthly supplies of tablets were given to the caregiver to be stored in plastic boxes with tight lids to ensure inaccessibility by young children. The tablets for the intervention group contained 5 mg of elemental zinc as zinc sulfate. The placebo tablets were similar in appearance and taste. Tablets were manufactured by Nutriset (Malaunay, France). Caregivers were asked to administer one tablet dissolved in 5 mL of expressed breast milk to infants aged  $\leq 6$  mo. Older infants received 2 tablets daily dissolved in breast milk or water.

## Enrollment procedures

Study supervisors identified new births in the 2 hospitals daily. Caregivers of term infants living  $\leq 10$  km of the hospital were informed about the study and, if they were willing to participate, weight and length measurements were obtained. Supervisors and supplement dispensers visited homes of potentially eligible infants when they were aged 2–4 wk and enrolled them into the study if written consent was given. In addition to the baseline characteristics, mothers of enrolled infants were queried for having been diagnosed with diabetes, hypertension, antepartum hemorrhage, history of convulsions, or severe pallor during pregnancy. Infants with severe malnutrition, twins, or infants who had serious illnesses requiring hospitalization were excluded. If there was more than one eligible infant in a household, only one was enrolled in the trial. The procedure for administration of the supplement was shown to caregivers.

## Co-interventions

Immunizations were provided according to the national program. From 2 mo of age, infants received iron (Tonoferron; East India Pharmaceutical Works Ltd, Kolkata, India)—with each milliliter containing colloidal elemental iron, lysine hydrochloride, vitamin B-12, and folic acid—and multivitamin drops (Visyneral; USV Ltd, Mumbai, India)—with each milliliter containing vitamin A, vitamin B-6, vitamin C, vitamin D<sub>2</sub>, thiamine, riboflavin, niacinamide, D-panthenol, biotin, and tocopheryl acetate and excluded zinc according to hospital policy for infants born at low birth weight. Caregivers were advised not to co-administer iron and multivitamin supplements with zinc and to administer the drops to infants in evenings and the zinc supplement in mornings (16, 17). Enrolled infants had access to the services of both hospitals in addition to several other government and private health care facilities in the area.

## Measurement of outcomes

Research assistants visited homes every 3 mo, and supplement dispensers visited monthly to deliver the tablets and document intake for the previous month through examination of the tablet strip and by querying the mother. At 12 mo of age, a food-frequency questionnaire was also administered at the home visits to obtain information about the types of foods consumed by the infants. Infants were called to the hospital for blood sampling at the end of the study.

Infants were home visited at ages 3, 6, 9 and 12 mo by research assistants. Caregivers were queried about recent (24-h, 7-d, and 1-mo) diarrheal and respiratory morbidity, care-seeking and hospitalizations, and clinical examinations. If an enrolled infant died during the follow-up period, a verbal autopsy (18) was conducted by a trained interviewer.

## Anthropometric measurements and zinc assays

Weights and lengths were measured at home at 3, 6, 9, and 12 mo of age. The portable weighing scale weighed to the nearest 100 g (Seca, Salter Scales, Hamburg, Germany) and length measurement boards manufactured locally measured to the nearest 0.1 cm.

Blood samples were obtained in 15% of the randomly selected infants at baseline and at 12 mo of age. A 5-mL nonfasting, venous blood sample was drawn in zinc-free, heparinized polypropylene

tubes (Sarstedt, Numbrecht, Germany). After centrifugation (447 × g, 10 min), plasma was transferred to zinc-free polypropylene vials (Eppendorf, Hinz, Germany) and stored at -20°C until analysis. Zinc assays were performed by using standard flame furnace atomic absorption spectrophotometer technique (GBC Avanta, Dandenong, Australia). Seronorm was used as the reference standard (Sero AS, Billingstad, Norway) in every batch of 20 samples. Hemoglobin concentration and hematocrit were estimated from capillary blood by using HemoCue AB 201 (Angleholm, Sweden) (19).

### Training and standardization

Teams were trained in obtaining consent, filling out forms, answering families' queries, supplement administration, and referral. Standardization exercises for inter- and intraobserver variability in weights and lengths were conducted in which each child was measured twice (10 sets of 10 infants each, aged <1 y). Exercises ceased only when all research assistants obtained identical readings in both their weight measurements on a child and were in perfect agreement with the group mean, ie, the arithmetic mean of the measurement obtained for a set of 10 infants by all research assistants (20). For length, a difference of ≤0.5 cm between the readings of a research assistant and the group mean was considered acceptable. The accuracy of weighing scales was checked daily against known standard weights and the accuracy of infantometers was checked by using standard steel rods.

### Definitions used

Diarrhea was defined as the passage of ≥3 loose or watery stools in a 24-h period. ALRI was defined the presence of cough

or difficult breathing associated with a respiratory rate ≥50 breaths/min (21). Severe diarrhea was defined as the presence of diarrhea in the previous 24 h with the maximum number of loose or watery stools greater than the median frequency of all diarrheal stools in the previous 24 h, or presence of signs of dehydration in the previous 24 h. Severe ALRI was defined as the presence of ALRI in the previous 24 h associated with one or more of the following: nasal flaring, grunting or stridor, lower chest indrawing, or an infant drinking poorly. Hospitalization was defined as admission to an inpatient facility of ≥6 h duration or as an inpatient death irrespective of duration of admission. For the purpose of analysis, hospitalizations of the same infant were separated by a ≥2-wk time frame.

### Data management and analysis

Forms were designed in FoxPro for Windows version 6 (Microsoft Corporation, Redmond, WA), and range and consistency checks were programmed during the designing of the database. Double data entry was followed by validation and merging of clean data into a master database. Analysis was conducted by using Stata software version 8.2 (Stata Corp LP, College Station, TX).

Characteristics of all infants who were randomly assigned to the 2 groups were displayed in the baseline table. For the 3 monthly visits, infants were included in the analysis if the home visit was conducted within the predefined time frame. The maximum delay or advance of measurement allowed was 10% of the child age at each visit (ie, ±9, ±18, ±27, and ±36 d for the visits at ages 3, 6, 9, and 12 mo, respectively). Hospitalization data were included for the period that an infant was available for follow-up.

The proportion of children who were wasted (weight for height ≤2 SD), stunted (height for age 2 SD), or underweight (weight

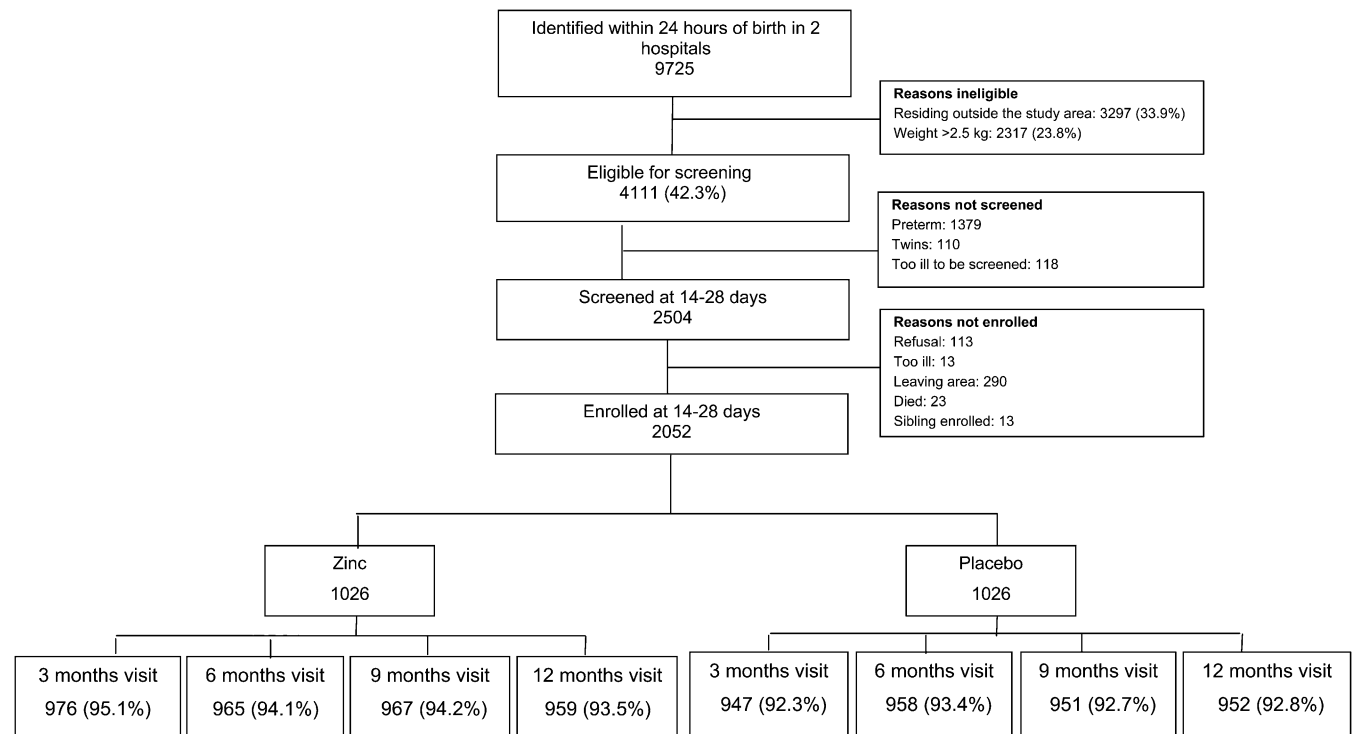


FIGURE 1. Trial profile.

for age 2 SD) according to the World Health Organization Child Growth Standards median at different ages was estimated (22).

The differences in means or proportions and their 95% CIs were estimated for all outcomes. Categorical outcomes were compared by using the chi-square test for proportions or chi-square for trend for multiple strata.

## RESULTS

A total of 9725 infants were identified  $\leq 24$  h of birth in 2 hospitals. Of these, 2504 were screened between 2 and 4 wk of age. Of the 2504 infants screened, 2052 (81.9%) were enrolled, 1026 each in the zinc and placebo groups. Of all enrolled infants,  $>92\%$  were available for each of the visits at ages 3, 6, 9, and 12 mo within predefined time frames (Figure 1). Of visits not made, the primary reason was that families were away. The numbers of families who withdrew consent during the 1-y follow-up period were 7 and 10: 4 and 6 infants at the 3-mo visit and an additional 3 and 4 infants at the 12-mo visit in the zinc and placebo groups, respectively.

The mean age at enrollment was 15 d, and  $\approx 50\%$  of the enrolled infants were male (Table 1). Infants in the zinc and placebo groups were similar for several infant and family characteristics. Ninety-nine percent of enrolled infants were breastfed. Prevalence of morbidity in the previous 24 h, mean weights and lengths, and zinc and hemoglobin concentrations in blood were similar at baseline. Approximately three-fourths of

**TABLE 1**

Baseline characteristics of families and infants 2–4 wk of age enrolled in the zinc and placebo groups<sup>1</sup>

Characteristics	Zinc (n = 1026)	Placebo (n = 1026)
Age (d) at enrollment	15.3 $\pm$ 2.1 <sup>2</sup>	15.3 $\pm$ 2.1
Male infants [n (%)]	463 (45.1)	448 (43.7)
Breastfed [n (%)]	1020 (99.4)	1020 (99.4)
24-h morbidity [n (%)]		
Diarrhea <sup>3</sup>	47 (4.6)	41 (4.0)
Acute lower respiratory tract infection <sup>4</sup>	231 (22.5)	200 (19.5)
Fever	22 (2.1)	23 (2.2)
Literate mothers [n (%)]	789 (76.9)	763 (74.4)
Literate fathers [n (%)]	848 (82.7)	864 (84.2)
Total no. of family members	7.0 $\pm$ 3.5	6.8 $\pm$ 3.3
Family income (rupees/mo)	4000 (2700, 6000) <sup>5</sup>	4000 (2500, 6000)
Weight (kg)	2.3 $\pm$ 0.2	2.3 $\pm$ 0.2
Length (cm)	46.0 $\pm$ 1.3	46.1 $\pm$ 1.3
Plasma zinc ( $\mu\text{g/dL}$ ) <sup>6</sup>	63.4 $\pm$ 20.9	64.7 $\pm$ 30.1
$<60$ $\mu\text{g/dL}$ [n (%)]	92 (50.2)	107 (56.8)
$<55$ $\mu\text{g/dL}$ [n (%)]	66 (36.1)	82 (42.9)
Hemoglobin (g/L) <sup>7</sup>	15.9 $\pm$ 2.4	15.9 $\pm$ 2.4
Hematocrit (%) <sup>7</sup>	49.9 $\pm$ 7.8	49.3 $\pm$ 7.5

<sup>1</sup> No differences between the 2 groups were statistically significant (t test for comparison of means and chi-square test for proportions).

<sup>2</sup> Mean  $\pm$  SD (all such values).

<sup>3</sup> Passage of  $\geq 3$  loose or watery stools with recent change in frequency and character of stools.

<sup>4</sup> Cough or difficult breathing and fast breathing.

<sup>5</sup> Median; interquartile range in parentheses (all such values).

<sup>6</sup> n = 183 and 191 for the zinc and placebo groups, respectively.

<sup>7</sup> n = 182 and 193 for the zinc and placebo groups, respectively.

mothers and four-fifths of fathers were literate (Table 1). The prevalence of diabetes, hypertension or antepartum hemorrhage, history of convulsions, or severe pallor as reported by mothers during the antenatal period was similar in the 2 groups (data not shown,  $P > 0.05$ ).

The total days of follow-up were 355,460 d and 355,989 d in the zinc and placebo groups, respectively. Infants in the zinc group were supplemented on 85.8% of the days and those in the placebo group for 86.1% of the days. The common reasons for nonadministration of the supplement were that the families were temporarily away or the mother forgot;  $<1\%$  of mothers cited unwillingness of the infant to take the supplement as a reason. The prevalence of vomiting in the previous 24 h at different ages, comparing zinc with placebo groups, was 7.3% compared with 6.9% at 3 mo, 5.3% compared with 3.9% at 6 mo, 5.6% compared with 5.4% at 9 mo, and 3.7% compared with 4.5% at 12 mo ( $P > 0.05$  for all comparisons).

The mean plasma zinc concentrations were higher in the zinc group infants 12 mo postsupplementation than in the placebo group infants (100.2 compared with 73.3  $\mu\text{g/dL}$ ; difference in means: 26.9  $\mu\text{g/dL}$ ; 95% CI: 19.6, 34.2  $\mu\text{g/dL}$ ). The proportion of infants with zinc deficiency using a cutoff of  $<60$   $\mu\text{g/L}$  was also significantly lower in the zinc group (difference in proportions:  $-11.8\%$ ; 95% CI:  $-20\%$ ,  $-3.4\%$ ;  $P < 0.005$ ). Zinc supplementation had no effect on iron status; hemoglobin concentrations and hematocrit were similar in infants in the 2 groups 12 mo postsupplementation (Table 2).

The prevalence of diarrhea and ALRI in the previous 24 h and 7 d was similar at the 3-, 6-, 9-, and 12-mo visits in the zinc and placebo groups. The prevalence of severe diarrhea and ALRI in the previous 24 h at each of these visits also was similar (Table 3). The proportion of infants who sought care for any illness, diarrhea, or pneumonia in the 1 mo preceding the home visit was similar at the 3-, 6-, and 12-mo visits. Care-seeking rates for illness were significantly lower (difference in proportions:  $-5.7$ ; 95% CI:  $-9.9$ ,  $-1.4$ ;  $P < 0.05$ ) at the 9-mo visit in infants who had zinc supplements than in those in the placebo group. The proportion of infants who were never hospitalized or hospitalized once, twice, or  $\geq 3$  times also was similar (chi-square for

**TABLE 2**

Effect of zinc supplementation on plasma zinc hemoglobin and hematocrit concentrations at 12 mo of age in the zinc and placebo groups

	Zinc (n = 151)	Placebo (n = 168)	Difference in means/proportions <sup>1</sup>
Plasma zinc ( $\mu\text{g/dL}$ )	100.2 $\pm$ 41.9 <sup>2</sup>	73.3 $\pm$ 22.5	26.9 (19.6, 34.2) <sup>3</sup>
$<60$ $\mu\text{g/dL}$ [n (%)]	19 (12.6)	41 (24.4)	$-11.8$ ( $-20$ , $-3.4$ ) <sup>4</sup>
$<55$ $\mu\text{g/dL}$ [n (%)]	13 (8.6)	24 (14.3)	$-5.7$ ( $-12.6$ , 1.3)
Hemoglobin (g/L) <sup>5</sup>	9.4 $\pm$ 1.4	9.6 $\pm$ 1.4	$-0.23$ ( $-0.54$ , 0.07)
$<10$ g/L [n (%)]	102 (66.7)	93 (54.7)	12.0 (1.4, 22.5) <sup>6</sup>
Hematocrit (%) <sup>5</sup>	32.7 (4.2)	33.1 (4.3)	$-0.41$ ( $-1.34$ , 0.52)
$<33\%$ [n (%)]	65 (42.5)	71 (41.8)	0.7 ( $-10$ , 11.5)

<sup>1</sup> Derived by using a t test for comparison of means and test of proportion for comparison of difference in proportions; 95% CI in parentheses ( $P > 0.05$  unless noted otherwise).

<sup>2</sup> Mean  $\pm$  SD (all such values).

<sup>3</sup>  $P < 0.0001$ .

<sup>4</sup>  $P < 0.005$ .

<sup>5</sup> n = 153 and 170 for the zinc and placebo groups, respectively.

<sup>6</sup>  $P < 0.003$ .

**TABLE 3**Diarrhea and respiratory morbidity at different ages in the zinc and placebo groups<sup>1</sup>

	Zinc (n = 976)	Placebo (n = 947)	Difference in proportions <sup>2</sup>
Age 3 mo, past 24 h			
Diarrhea	183 (18.8) <sup>3</sup>	193 (20.4)	-1.6 (-5.2, 1.9)
Severe diarrhea	91 (9.3)	80 (8.5)	0.9 (-1.7, 3.4)
ALRI	117 (12.0)	113 (11.9)	0.1 (-2.8, 2.9)
Severe ALRI	41 (4.2)	48 (5.1)	-0.9 (-2.7, 1.0)
Age 3 mo, past 7 d			
Diarrhea	306 (31.4)	321 (33.9)	-2.5 (-6.7, 1.6)
ALRI	139 (14.2)	137 (14.5)	-0.2 (-3.4, 2.9)
Age 6 mo, past 24 h <sup>4</sup>			
Diarrhea	145 (15.0)	153 (15.9)	-0.9 (-4.2, 2.3)
Severe diarrhea	72 (7.4)	72 (7.5)	-0.1 (-2.4, 2.3)
ALRI	98 (10.2)	78 (8.1)	2.0 (-0.6, 4.6)
Severe ALRI	40 (4.2)	26 (2.7)	1.4 (-0.2, 3.1)
Age 6 mo, past 7 d			
Diarrhea	283 (29.3)	264 (27.6)	1.8 (-2.3, 5.8)
ALRI	122 (12.6)	89 (9.3)	3.4 (0.6, 6.1)
Age 9 mo, past 24 h <sup>5</sup>			
Diarrhea	129 (13.3)	152 (15.9)	-2.6 (-5.8, 0.5)
Severe diarrhea	55 (5.7)	59 (6.2)	-0.5 (-2.6, 1.6)
ALRI	49 (5.1)	51 (5.4)	-0.3 (-2.3, 1.7)
Severe ALRI	15 (1.6)	14 (1.5)	0.1 (-1.0, 1.2)
Age 9 mo, past 7 d <sup>5</sup>			
Diarrhea	244 (25.2)	271 (28.5)	-3.3 (-7.2, 0.7)
ALRI	59 (6.1)	57 (6.0)	0.1 (-2.1, 2.2)
Age 12 mo, past 24 h <sup>6</sup>			
Diarrhea	117 (12.2)	118 (12.4)	-0.2 (-3.1, 2.8)
Severe diarrhea	51 (5.3)	50 (5.2)	0.1 (-1.9, 2.1)
ALRI	34 (3.6)	26 (2.7)	0.8 (-0.7, 2.4)
Severe ALRI	13 (1.4)	9 (0.9)	0.4 (-0.5, 1.4)
Age 12 mo, past 7 d <sup>6</sup>			
Diarrhea	227 (23.7)	222 (23.3)	0.4 (-3.5, 4.2)
ALRI	37 (3.9)	28 (2.9)	0.9 (-0.7, 2.5)

<sup>1</sup> ALRI, acute lower respiratory tract infection.<sup>2</sup> Derived by using a test of proportions for comparison of difference in proportions; 95% CI in parentheses ( $P > 0.05$  for all comparisons).<sup>3</sup> n; percentage in parentheses (all such values).<sup>4</sup> n = 965 and 958 for the zinc and placebo groups, respectively.<sup>5</sup> n = 967 and 951 for the zinc and placebo groups, respectively.<sup>6</sup> n = 959 and 952 for the zinc and placebo groups, respectively.

trend:  $P = 0.72$ ) in the 2 groups (**Table 4**). There were 21 deaths in the zinc group and 19 in the placebo group ( $P > 0.05$ ).

The mean ( $\pm$ SD) weights and lengths at 3, 6, 9, and 12 mo in the zinc and placebo infants are shown in **Figure 2**. The proportions of infants wasted, stunted, and underweight in the zinc compared with placebo groups were 14.9% compared with 16.1%, 43.3% compared with 42%, and 59.0% compared with 56.7% at 3 mo; 16.9% compared with 18.6%, 38.3% compared with 35.5%, and 46.5% compared with 45.8% at 6 mo; 19.1% compared with 19.2%, 45.3% compared with 42.9%, and 48.2% compared with 46.4% at 9 mo; and 23.9% compared with 23.8%, 53.8% compared with 50.1%, and 51.9% compared with 51.1% at 12 mo, respectively. All comparisons were statistically not significant ( $P > 0.05$ ).

Dietary recalls at 12 mo of age in enrolled infants revealed that cereals were consumed daily in 75% of infants and legumes daily in 15% of infants and 2 to 4 times/wk by an additional 41% of

**TABLE 4**Treatment-seeking and hospitalization rates in the zinc-supplemented and control groups<sup>1</sup>

	Zinc	Placebo	Difference in proportions <sup>2</sup>
Sought treatment $\geq 1$ time in the past month for the following illnesses			
Age 3 mo <sup>3</sup>			
Any	538 (55.1) <sup>4</sup>	524 (55.3)	-0.2 (-4.7, 4.2)
Diarrhea	194 (36.1)	201 (38.4)	-2.3 (-8.1, 3.5)
ALRI	90 (16.7)	89 (17.0)	-0.3 (-4.8, 4.2)
Age 6 mo <sup>5</sup>			
Any	612 (63.4)	595 (62.1)	1.3 (-3.0, 5.6)
Diarrhea	232 (37.9)	238 (40.0)	-2.1 (-7.6, 3.4)
ALRI	139 (22.7)	115 (19.3)	3.4 (-1.2, 7.9)
Age 9 mo <sup>6</sup>			
Any	595 (61.5)	639 (67.2)	-5.7 (-9.9, -1.4) <sup>7</sup>
Diarrhea	246 (41.3)	264 (41.3)	0.0 (-5.5, 5.5)
ALRI	118 (19.8)	122 (19.1)	0.7 (-3.7, 5.2)
Age 12 mo <sup>8</sup>			
Any	567 (59.1)	555 (58.3)	0.8 (-3.6, 5.2)
Diarrhea	235 (41.5)	235 (42.3)	-0.9 (-6.7, 4.9)
ALRI	79 (13.9)	83 (14.9)	-1.0 (-5.1, 3.1)
Infants hospitalized <sup>9</sup>			
Never	837 (81.9)	849 (83.2)	
Once	160 (15.6)	147 (14.4)	
Twice	22 (2.1)	19 (1.9)	
Three or more times	3 (0.3)	5 (0.5)	
Hospitalizations (no./1000 child-years of follow-up)	189.9	175.3	1.10 (0.87, 1.39) <sup>10</sup>

<sup>1</sup> ALRI, acute lower respiratory tract infection.<sup>2</sup> Derived by using a test of proportions for comparison of difference in proportions; 95% CI in parentheses ( $P > 0.05$  for all comparisons unless noted otherwise).<sup>3</sup> n = 976 and 947 for the zinc and placebo groups, respectively.<sup>4</sup> n; percentage in parentheses (all such values).<sup>5</sup> n = 965 and 958 for the zinc and placebo groups, respectively.<sup>6</sup> n = 967 and 951 for the zinc and placebo groups, respectively.<sup>7</sup>  $P < 0.05$ .<sup>8</sup> n = 959 and 952 for the zinc and placebo groups, respectively.<sup>9</sup> n = 1022 and 1020 for the zinc and placebo groups, respectively;  $P = 0.71$  (chi-square test for trend).<sup>10</sup> Odds ratio; 95% CI in parentheses.

infants. Animal milk or other milk products were consumed daily by 66% of infants. Egg, lamb, or chicken was fed to 45% of infants  $\geq 1$  time/wk; of these infants, 21% received these foods 2 to 4 times/wk.

## DISCUSSION

The main findings of the study are that zinc supplementation at one RDA started between 2 and 4 wk of age and given until the age of 12 mo in hospital-born, low-birth-weight infants had no significant effect on diarrheal or respiratory morbidity or on anthropometric status at 3, 6, 9, and 12 mo of age. These findings based on hospital-born babies in an urban setting may not necessarily apply to infants at similar ages delivered at home under different socioeconomic circumstances, in those following different dietary practices, or in those residing in rural areas. The

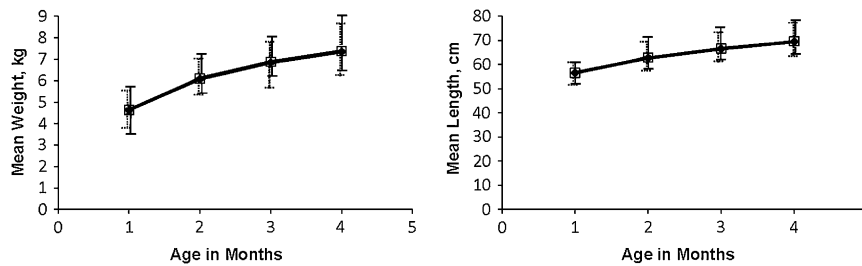


FIGURE 2. Attained weights and lengths at different ages in the zinc and placebo groups. ●: zinc; □: placebo.  $P > 0.05$  for all comparisons.

consumption of animal foods, literacy rates of both parents, and family income in the study subjects was substantially higher than in other neighboring communities (23).

Although the effect of improved zinc intake in reducing diarrheal and respiratory morbidity has been observed in children aged 6 mo to 3 y, few studies have assessed the effect of zinc supplementation in the initial 6 mo of life of children who were born with a low birth weight (4).

Sur et al (6) assessed the effect of zinc sulfate supplementation (5-mg daily dose) in low-birth-weight infants selected from a poor urban community during their first year of life and reported a significant reduction in the incidence of diarrhea. Interestingly, the effect was observed only at ages when breastfeeding had declined. In another trial, in which mothers were administered a zinc supplement or placebo during pregnancy, a significant reduction in diarrheal morbidity during the first 6 mo of life was observed in their offspring in the intervention group; this effect was substantially greater in the low-birth-weight subset (24).

In the only study that measured effect of zinc supplementation on mortality in neonates who were small for gestational age, Sazawal et al (7) reported significant reduction in all-cause mortality in those supplemented daily with zinc; the reduction in mortality was apparent as early as 4 mo of age.

The lack of significant effect on morbidity at 9 and 12 mo of age is surprising because previous studies have shown a positive effect (2, 3). A possible reason may be that most previous studies used a 20-mg rather than a 10-mg daily dose of zinc. Furthermore, most previous trials were community based rather than hospital based, with possible socioeconomic and dietary differences.

We did not observe any significant effect on weight or length gain. The findings from the literature on this issue vary. In very-low-birth-weight infants, Freil et al (25) reported significant increase in linear growth velocity but not in weight gain. On the other hand, Sur et al (6) reported significant increases in both length and weight gain at 12 mo of age after zinc supplementation in low-birth-weight infants. The effect on weight gain became apparent after 4 mo of age and that in length only at 10 mo of age.

A recent meta-analysis on effect of micronutrients on physical growth in children aged <5 y did not report improvement in linear growth with zinc supplementation (26). The difference from a previous meta-analysis that reported a positive effect on linear growth was attributed by the authors to the fact that the recent trials were done in children with relatively better nutritional status (27).

Factors other than socioeconomic status also need consideration. Noncompliance is unlikely to explain the lack of effect in the current trial, because >85% of participants reported having consumed the supplement and the prevalence of zinc deficiency was  $\geq 50\%$  lower at 12 mo in the intervention group.

The zinc salts and dosing used in the study were similar to those used in the study done in Kolkata (6). A notable difference was that the incidence of diarrheal illness was reported in Kolkata, whereas diarrhea prevalence was estimated in our study.

Furthermore, although severity parameters used for defining severe ALRI were similar to those used in earlier studies, the ones used for diarrhea were less stringent than those used by others. This difference in severity parameters may be relevant because zinc supplementation has a greater effect on incidence of severe diarrhea.

Notably, the studies by Sazawal et al (7) and Sur et al (6), which showed a positive effect, used liquid formulations compared with the current study, which used tablets. The fact that plasma zinc concentrations at 12 mo of age were significantly improved in the intervention group indicates that this is an unlikely explanation for the differences in results.

In conclusion, although low zinc concentrations were common in infants born at low birth weight, supplementation with one RDA did not reduce morbidity or improve physical growth. Because the socioeconomic status of families enrolled in the trial was better than that observed in neighboring communities, further trials in community settings with varying zinc dosages are required.

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The authors' responsibilities were as follows—ST and TR-C: responsible for the daily implementation of the study; and NB, DM, MKB, and OF: provided technical input during all stages of the project and analysis. All authors contributed substantially to the design and undertaking of the study, its analysis, and the writing of this article and approved the final manuscript. None of the authors had a conflict of interest.

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