

# Zinc Supplementation in Infants Born Small for Gestational Age Reduces Mortality: A Prospective, Randomized, Controlled Trial

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**ABSTRACT.** *Background.* Low birth weight infants have been noted to have low zinc concentrations in cord blood, and zinc deficiency in childhood is associated with reduced immunocompetence and increased infectious disease morbidity. This study investigates whether zinc supplementation of infants born full term and small for gestational age affects mortality.

*Methods.* A randomized, double-blind, controlled trial with 2-by-2 factorial design enrolled 1154 full-term small for gestational age infants to receive in syrup 1 of the following: riboflavin; riboflavin and zinc (5 mg as sulfate); riboflavin, calcium, phosphorus, folate, and iron; or riboflavin, zinc, calcium, phosphorus, folate, and iron. A fixed dosage of 5 mL per child was given daily from 30 to 284 days of age. Household visits were made 6 days per week to provide the syrup and conduct surveillance for illness and death. When a child's death was reported, parental reports and medical records were used to ascertain the cause. The effects of zinc and of the combination of iron, folate, calcium, and phosphorus were analyzed by intent to treat. The mortality analysis was performed using a survival analytic approach that models time until death as the dependent variable; all models had 2 terms as independent variables: 1 for the zinc effect and 1 for the vitamin and mineral (calcium and phosphorus, folate and iron) effect.

*Results.* Zinc supplementation was associated with significantly lower mortality, with a rate ratio of 0.32 (95% confidence interval: 0.12–0.89). Calcium, phosphorus, folate, and iron supplementation was not associated with a mortality reduction, although a statistically non-significant trend toward reduction was observed with a rate ratio of 0.88 (95% confidence interval: 0.36–2.15).

*Conclusion.* Zinc supplementation in small for gestational age infants can result in a substantial reduction in infectious disease mortality. *Pediatrics* 2001;108:1280–1286; zinc, micronutrients, mortality, randomized trial.

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ABBREVIATIONS. LBW, low birth weight; SGA, small for gestational age; WHO, World Health Organization; PI, Ponderal index; RR, rate ratio; CI, confidence interval; RDA, recommended daily allowance.

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Despite the success of child survival programs, approximately 12 million children under 5 years old in developing countries still die of preventable causes, half of them of diarrheal diseases and respiratory infections.<sup>1</sup> With the demonstration that vitamin A supplementation reduces child mortality,<sup>2</sup> there has been increasing recognition of the importance of nutrient deficiencies and their role as determinants of infectious diseases. It is becoming clear that a large portion of the risk of infectious disease morbidity and mortality attributed to malnutrition may result primarily from deficiencies of a few critical micronutrients.

Evidence of the importance of zinc deficiency in child health has come from recent randomized, controlled trials of zinc supplementation.<sup>3,4</sup> A pooled analysis of data from 7 trials evaluating preventive effects of zinc supplementation on diarrhea and pneumonia found an overall 18% lower diarrhea incidence and a 41% lower pneumonia incidence in zinc-supplemented preschool children.<sup>3</sup> The significant effects on diarrhea and pneumonia, which are the major causes of death in this age group, lead to the question of whether there is an effect on mortality as well.

Developing countries account for 90% of the 20 million annual low birth weight (LBW) deliveries worldwide; 75% of these are in India, Pakistan, and Bangladesh.<sup>5,6</sup> Birth weight is the single most important determinant of infant survival in developing countries,<sup>7–9</sup> estimated to be an underlying risk factor in >70% of perinatal deaths, 90% of neonatal deaths, and 50% of infant deaths.<sup>10</sup> Unlike in developed countries, where preterm birth is the main cause of LBW, in developing countries most LBW infants are small for gestational age (SGA).<sup>6,10</sup> Nutrient deficiencies during fetal development can cause this intrauterine growth retardation and may also compromise immune function after birth.<sup>12</sup> Low zinc concentrations in the cord blood of LBW newborns have been noted in a number of settings, and birth weight has been shown to be highly correlated with cord zinc concentration in India.<sup>13–16</sup> Because of impaired immunocompetence and other factors, SGA infants have higher rates of respiratory infections<sup>7,8</sup> and diarrhea.<sup>7,9</sup> Therefore, zinc supplementation in SGA infants may reduce infectious disease morbidity and mortality.

We conducted a randomized, double-blind, controlled trial with a 2-by-2 factorial design to assess

the effects of zinc or vitamin and mineral (calcium, phosphorus, folate, and iron) supplements on development, growth, morbidity, and mortality in 1- to 9-month-old SGA infants. The effects on mortality are reported here.

## METHODS

### Study Population, Screening, and Selection of Sample

The study was conducted in Sangam Vihar, a resettlement population in New Delhi, India, between April 18, 1996, and November 7, 1998. The infant mortality rate in this population is 83 per 1000 births; the birth rate is about 30 per 1000. Approximately 14% of the deliveries are preterm, and 42% of newborns weigh <2500 g.

A census and baseline survey covered 2066 households with a population of 10 003. Current pregnancies were recorded, and this register was updated by surveys every 3 months. Pregnant women were offered free antenatal services, and those who attended the clinic were given tetanus toxoid and iron supplements according to current World Health Organization (WHO) and Government of India policy. Pregnant women were followed monthly until 36 weeks of gestation, then weekly for 2 weeks, and finally daily until delivery. They were advised to inform the field clinic of a delivery, at which time a physician, nutritionist, and field assistant visited the home. A birth assessment form was completed, and birth weight, length, and head circumference were recorded. Weight was measured to 10 g with an electronic scale (SECA Corporation, Columbia, MD) by 2 independent observers. Gestational age was assessed according to Capurro et al.<sup>17</sup> Only children with gestational age >37 weeks were considered for the study. The newborn was designated SGA if the birth weight was less than the 10th percentile for that gestational age compared with the reference population.<sup>18</sup> Parents of the newborns who were SGA were invited to participate in the study. All mothers were advised to exclusively breastfeed and to bring the infant for immunizations.

The Ponderal index (PI = weight [g]/length [cm]<sup>3</sup>) for each child was calculated and compared with the 10th percentile of gestational age-specific values from Indian children.<sup>19</sup> The values for gestational age 36–37, 38, 39, 40, 41, and 42 weeks were 2.23, 2.25, 2.26, 2.24, 2.20, and 2.14 g/cm<sup>3</sup>, respectively. A child below this value was considered to be wasted.

Eligible neonates were visited at home 2 weeks after birth. Each child was given an identification number in 1 of the 2 PI strata (wasted or not wasted); this number was used for random allocation of the child to 1 of the 4 treatment groups.

Before enrollment, a parent was given a full explanation of the study, and written informed consent was obtained. The study was approved by the human research review committees at the Center for Micronutrient Research, Annamalai University, Society for Essential Health Action and Training (a nongovernment organization in Delhi, India), the Johns Hopkins Bloomberg School of Public Health, and the WHO.

### Experimental Maneuver

The supplements (prepared by Ranbaxy Research Laboratories, Gurgaon, India) were assigned 1 of 16 letter codes (4 codes for each study group). A statistician then made lists for each PI stratum, using permuted blocks of 10. The serial identification number given at enrollment was used to allocate a child to 1 of the 16 codes (and thus to 1 of the 4 treatment groups). A pharmacy assistant, using the list of assigned letter codes, labeled each bottle with a child's name and identification. No one at the field site, including the investigators, had information about the assignment of the 16 letter codes or their corresponding micronutrient content. Because of the presence of calcium and phosphorus, the bottles of 2 groups (ie, bottles with 8 of the 16 letter codes) were more viscous, but the taste, color, and smell of the 2 pairs of zinc and nonzinc preparations were identical.

The randomization process allocated enrolled children to receive in 5 mL of syrup either riboflavin (0.5 mg/day); riboflavin and zinc (5 mg/day); riboflavin, calcium (180 mg/day), phosphorus (90 mg/day), folate (60 μmol/day), and iron (10 mg/day); and riboflavin, zinc, calcium, phosphorus, folate, and iron. Sulfate salts of zinc and iron were used.

When the neonate was 15 days old the mother was given a bottle of the supplement and advised to start giving the supplement beginning with 1 mL and increasing to 5 mL within 15 days. From 30 days of age, daily supplementation with 5 mL was given. Field assistants visited the family to feed the supplement to the child every day except Sundays and holidays, for which they left a measured dose in a separate vial for the mother to feed.

### Baseline Assessment and Surveillance

At the first household visit soon after birth, weight, length, gestational age, and conditions of delivery were recorded. The additional baseline information was collected at the start of the illness surveillance at 30 days of age, including socioeconomic indicators and family characteristics. Each enrolled child was visited at home by a trained field worker every day, except Sundays or holidays, between 30 and 284 days of age. If the child was not available, an attempt was made to make a second visit later in the day, failing which the information was collected, if possible, on the next day. At each visit, information on the previous 24 hours, including the number and consistency of stools, the presence of fever or vomiting, and the pattern of feeding, were recorded, respiratory rate was counted, and compliance with supplement consumption was checked. During the study, compliance was 76.9% (76.7%, 77.7%, 76.3%, and 76.9% in groups 1 through 4), the mother gave the supplement two thirds of the time, and the field worker fed the supplement one third of the days it was taken. Treatment of diarrhea, dysentery, and pneumonia under WHO guidelines was provided free to the participating children throughout the study. When a death was reported, recall information and records available from the family and study physicians were used to describe the illness leading to the death. Two independent physicians blinded to study group allocation assigned a cause of death for each child.

### Data Management

The data for each child visit were entered the day after the visit. By the end of that day the records were sent back to the field, along with a printout of the entered data and a list of range and logical errors. These were corrected by return household visit, if necessary. The printout was checked manually by the supervisor, who corrected entry errors. In addition, a second data entry was performed.

### Study Profile

Of 1302 eligible SGA children, 52 died or moved before being randomized at 15 days of age (Fig 1). A total of 1250 children were randomized to the 4 groups, but 96 children dropped out before the surveillance began at 30 days of age (22, 23, 25, and 26 for groups 1 through 4, respectively). All 1154 children (292 control group, 292 zinc group, 281 vitamin and mineral group, and 289 zinc and vitamin and mineral group) on whom the surveillance was started were included in the analysis regardless of their compliance in taking the supplement. Of 290 364 days of potential surveillance, if each of the 1154 children had information for the complete 254 days or till the day of death if they died, we had information on 216 805 days, indicating that death, withdrawal, or temporary nonavailability accounted for 25.3% of days (this was similar in all 4 groups: 26.7%, 24.5%, 24.3%, 25.9%, respectively). Of 385 children who did not die and did not complete full 254 days of surveillance, 339 (88.1%) outmigrated and 46 (11.9%) withdrew consent to continue. Children not completing the study were included in the analysis using information available.

### Statistical Analysis

The effects of zinc and of the combination of calcium, phosphorus, folate, and iron were analyzed by intent to treat (Fig 2). The amount of person-time contributed by each study participant was calculated for this analysis. We first verified whether the effect of 1 treatment (zinc or vitamin and mineral combination) was modified by the other before using a factorial analysis. The mortality analysis was performed using a survival analytic approach that models time until death as the dependent variable, specifically a Cox proportional hazards model using SAS 7.0.<sup>20</sup> In the first analysis the model had 2 terms as independent variables, 1 for the zinc effect (1 = yes, 0 = no) and another for the vitamin and mineral (calcium, phosphorus, folate, and iron) effect (1 = yes, 0 =

Fig 1. Profile of enrollment in the 4 study groups.

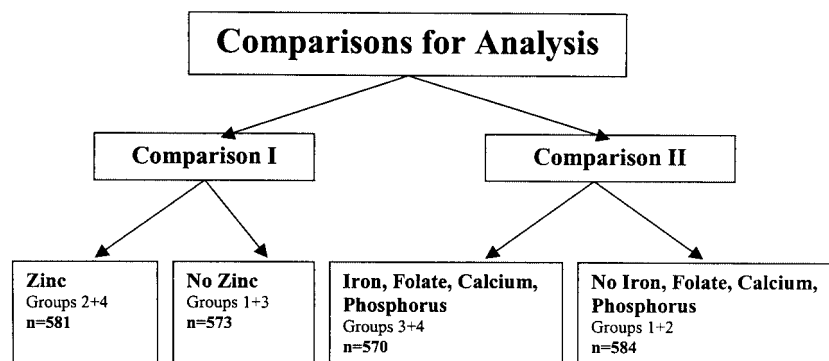
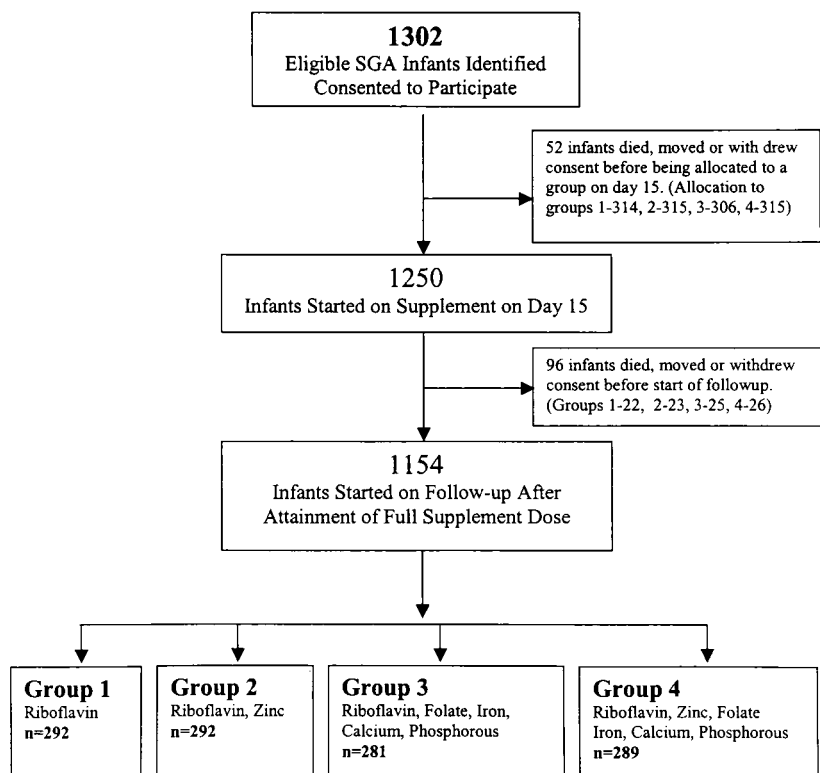


Fig 2. Comparisons used in the analysis.

no). In the second analysis, multivariate models with additional factors such as sex, birth weight, PI, and socioeconomic variables (literacy and number of preschool children in the household) were investigated. For socioeconomic status evaluation 2 variables were constructed, 1 based on reported income (including income of both mother and father) and 1 based on possessions (these included owning the house, rooms in the house, having a personal water pump, ownership of taxi, scooter, cycle, television, animals, fans, or refrigerator). On the property scale, each family got a score of 0 to 16. To evaluate whether the difference in mortality resulting from zinc supplementation occurred over the entire study period or was limited to children >6 months old, as is the case with vitamin A supplementation, we plotted a Kaplan–Meier survival analysis comparing the zinc and nonzinc groups.<sup>21</sup> To evaluate effect of zinc supplementation including breastfeeding as a covariate, the follow-up was divided into monthly intervals, and the record of breastfeeding at the start of the month was used as the covariate. A Cox regression model similar to that described previously was fitted with 3 terms as independent variables: zinc effect (yes or no), vitamin and mineral effect (yes or no), and breastfeeding status (exclusive, predominant, partial, or non-breastfed). The breastfeeding term was entered as a categorical variable with nonbreastfed as the reference category.

The sample size of the trial was based on a reduction in diarrhea morbidity, not total mortality, because we did not anticipate

a difference of the magnitude that was actually found. At the current sample size of about 570 per group and a 0.05 1-sided alpha, using a log-rank test for equality of survival curves, the trial had a power of 71% to detect a hazard rate ratio (RR) of 0.30.

## RESULTS

There were no significant or clinically meaningful differences between the 4 groups at baseline (data not shown). The very similar baseline characteristics of the 2 analyzed comparisons (Table 1) also indicated success of randomization. Of 1154 SGA infants enrolled in the study, 57% were LBW ( $\leq 2500$  g), and 50% of infants were wasted.

The univariate analysis (Table 2) using factorial design compared 581 children in the 2 groups who received zinc (groups 2 and 4) with 573 children in the 2 groups that did not receive zinc (groups 1 and 3). Zinc supplementation was associated with significantly lower mortality in the period of surveillance, with an RR of 0.32 (95% confidence interval [CI]: 0.12–0.89). It also compared 570 children who re-

**TABLE 1.** Percentage of Selected Characteristics in 4 Comparison Groups at Baseline

Characteristic		Zinc		Calcium, Phosphorus, Iron, Folate	
		Yes ( <i>n</i> = 581)	No ( <i>n</i> = 573)	Yes ( <i>n</i> = 570)	No ( <i>n</i> = 584)
Place of delivery	Home	73.1%	70.7%	70.5%	73.3%
	Hospital	20.7	23.4	22.8	21.2
	Other	6.2	5.9	6.7	5.5
Mode of delivery	Normal	96.2	96.2	95.3	97.1
	Cesarean section	2.8	2.4	2.8	2.4
	Others	1.0	1.4	1.9	0.5
Breastfeeding	Exclusive	43.4	45.4	42.5	46.2
	Predominant	22.0	22.7	21.6	23.1
	Partial	12.4	12.6	13.9	11.7
Gestational age (wks)	None	22.2	19.3	22.0	19.0
	<37	3.8	3.1	3.3	3.6
	37–38	15.5	19.5	17.2	17.8
	39–40	71.8	69.6	71.4	70.0
Birth weight (g)	41–42	9.0	7.7	8.1	8.6
	1500	0.5	1.2	0.5	1.2
	1500–2500	57.8	56.9	60.0	54.8
	2500–3500	41.7	41.9	39.5	44.0
Low Ponderal index		48.9	50.1	48.9	50.0
Male		43.2	45.4	46.0	42.6
Literacy of mother	Read and write	40.8	39.3	39.4	40.9
Number of children	<3	43.8	43.3	40.6	46.4
Income	≤1500 (median)	55.4	58.5	57.4	56.5
Property score	≤5	53.5	50.8	51.2	53.1

**TABLE 2.** Effect of Zinc or Calcium, Phosphorus, Folate, and Iron Supplementation on Mortality at 1 to 9 Months of Age

	Supplementation Comparison	Number of Children	Days of Follow-Up	Number of Deaths	Mortality Hazards	
					RR (95% CI)*	<i>P</i> Value
Zinc	Yes	581	118 458	5	0.32 (0.12–0.89)	.028
	No	573	114 999	15		
Calcium phosphorus, folate, and iron	Yes	570	115 711	9	0.83 (0.34–2.0)	.677
	No	584	117 746	11		

\* RRs are from a Cox's survival analysis that had terms for both the zinc effect (1 = yes, 0 = no) and the calcium, phosphorus, folate, and iron effect (1 = yes, 0 = no) entered in the model simultaneously; there were no significant interactions.

ceived calcium, phosphorus, folate, and iron supplementation (groups 3 and 4) with 584 children who did not (groups 1 and 2). Calcium, phosphorus, folate, and iron supplementation was not associated with lower mortality, although a statistically nonsignificant trend toward lower mortality was observed, with an RR of 0.83 (95% CI: 0.34–2.0). There was no interaction between the 2 effects ( $P > .1$ ).

In the multivariate analysis using Cox regression models, zinc supplementation was associated with lower mortality and wasting with higher mortality (Table 3). There was a trend toward lower mortality in children with uneducated mothers, but it was not statistically significant. There was no association with either of the socioeconomic status variables. The Kaplan–Meier curves indicated that the difference in mortality resulting from zinc supplementation started as early as the second month of life (Fig 3). The sample size in this trial was small to evaluate age-specific effects, however, and these data are at best interpreted as qualitative indications of the effects by age. The effect of zinc supplementation was similar in wasted and nonwasted children (data not presented).

In the analysis including breastfeeding as a covariate, both breastfeeding and zinc supplementation

**TABLE 3.** Multivariate Analysis of Effects of Zinc or Calcium, Phosphorus, Folate, and Iron Supplementation and Other Factors on Mortality at 1 to 9 Months of Age

Variable	RR	95% CI	<i>P</i> Value
Calcium, phosphorus, folate, iron group	0.86	0.36–2.15	.770
Zinc group	0.32	0.12–0.89	.028
Low birth weight	1.59	0.55–4.63	.395
Father's ability to read	1.13	0.31–4.12	.859
Mother's ability to read	2.36	0.95–5.86	.065
Property group	0.51	0.20–1.31	.161
Income group	0.90	0.36–2.28	.831
Children under 5 in house	1.27	0.36–4.44	.714
Wasting	0.26	0.08–0.82	.021
Gender	0.72	0.28–1.84	.494

\* Cox's survival analysis for mortality with the calcium, phosphorus, folate, and iron group (1 = yes, 0 = no), zinc group (1 = yes, 0 = no), low birth weight (1 = yes, 0 = no), father's or mother's ability to read and write (1 = yes, 0 = no), property or income group (1 = >median, 0 < = median), children under 5 (1 = >2, 0 = 0–2), wasting (1 = no, 0 = yes), gender (1 = male, 0 = female).

were independently associated with mortality. The effect of zinc supplementation on mortality in this analysis was similar to that of the previous analysis RR 0.34 (95% CI: 0.12–0.94;  $P = .038$ ). Breastfeeding status was significantly associated with mortality

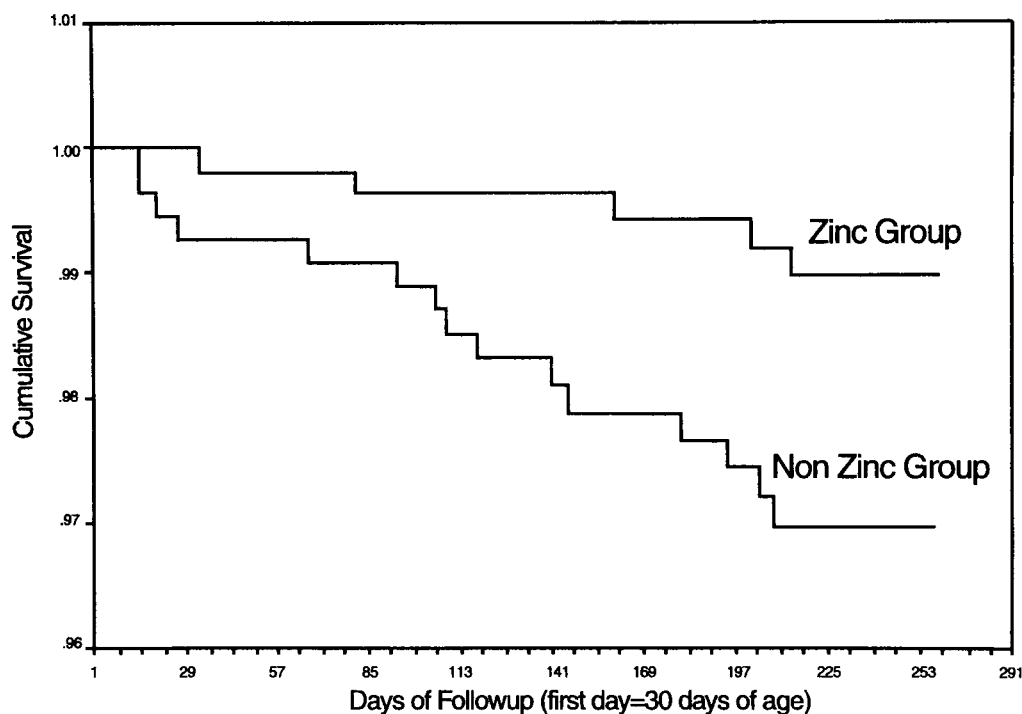


Fig 3. Survival curves for zinc-supplemented and non-zinc-supplemented groups.

( $P = .001$ ). Compared with nonbreastfed infants, exclusively breastfed infants had the lowest mortality RR 0.03 (95% CI: 0.003–0.29;  $P = .002$ ), followed by predominantly breastfed RR 0.054 (95% CI: 0.01–0.27) and partially breastfed RR 0.12 (95% CI: 0.03–0.42).

The 20 observed deaths were caused by diarrhea (1 in the zinc and 9 in the nonzinc group), pneumonia (3 in the zinc and 2 in the nonzinc group), septicemia (all 3 in the nonzinc group), and malnutrition (1 in the zinc and 1 in the nonzinc group). Although in the preceding analysis a single cause of death was indicated, 2 diarrheal deaths and 1 septicemia death also had underlying malnutrition.

#### DISCUSSION

In this study zinc supplementation decreased the risk of infant mortality in children born SGA, whereas supplementation with calcium, phosphorus, folate, and iron did not. Although these data should be considered preliminary because of the small sample size and number of deaths in this study, confounding is an unlikely explanation for these results given the baseline comparability between groups in this masked, randomized, controlled trial. To our knowledge this is the first report of the impact of zinc supplementation on the mortality of children in a developing country. The supplements in this study did not contain vitamin A, consistent with the policy of the Indian Ministry of Health of not providing it to children in this age group. However, vitamin A supplementation probably does not affect mortality in first 6 months of life,<sup>2,22,23</sup> and it is unlikely that vitamin A supplementation would have altered the results of this study. The lack of effect of the calcium, phosphorus, folate, and iron supplement found in

this study does not exclude the possibility of a small reduction in mortality that might be demonstrable in a larger trial.

The data from 10 trials evaluating the preventive effects of zinc supplementation<sup>3</sup> have been subjected recently to pooled analyses, which indicated that there was a significant homogeneity in the results across the studies conducted in 9 developing countries. The substantial reduction in diarrhea and pneumonia rates in these trials and in the diarrhea rates in recently published studies from Ethiopia<sup>4</sup> and Burkina Faso<sup>24</sup> suggest that mortality could be affected as well. However, the magnitude of the effect on mortality found in this trial is more than can be expected given the previously demonstrated impact on morbidity, suggesting that there is an additional effect on the severity of episodes. We have previously documented effects of supplementation on the severity of diarrheal illness.<sup>25,26</sup> Reductions in duration, stool volume, and treatment failure or death have also been found in therapeutic trials of zinc supplementation in acute and persistent diarrhea.<sup>27</sup> Roy et al<sup>28</sup> reported a reduction of mortality in hospitalized patients with persistent diarrhea and malnutrition given zinc supplements (relative risk 0.18,  $P = .06$ ).

Although there is strong evidence of widespread zinc deficiency in children >1 year of age, the data on zinc deficiency in young breastfed children have been mixed. We did not estimate plasma zinc concentrations in this study but have previously documented that 36% of children in this population had a plasma zinc concentration <60  $\mu\text{g}/\text{dL}$  and that the proportion of zinc-deficient children was similar in 6- to 11-month-olds and older children.<sup>29</sup> Low concentrations of zinc in the cord blood of LBW infants

have been noted in a number of settings and shown to be highly correlated with birth weight and gestational age at birth in India.<sup>13-16,30-32</sup> Three studies reported lower zinc concentrations in SGA births,<sup>13,14,33</sup> but 2 studies did not find this association.<sup>16,30</sup>

A possibility of zinc deficiency among exclusively breastfed LBW infants has been suggested based on the findings that after the first few months of lactation a large proportion of women may have breast milk zinc concentrations lower than that needed to provide the recommended daily allowance (RDA) of zinc to infants,<sup>34</sup> and because the RDA is based on healthy infants, the need to provide for catch-up growth would make it a conservative estimate of the zinc need for SGA infants. Poor maternal nutritional status in these settings may also lead to lower breast milk production, so the breast milk zinc concentration needed to provide an RDA would be even higher.<sup>35</sup> The infant's zinc balance may also be affected by excess losses that can occur during diarrhea, resulting in the need for a zinc intake greater than that calculated for healthy children.<sup>36</sup> There are reports of symptomatic zinc deficiency in breastfed infants in the literature.<sup>37-41</sup> The beneficial effects of zinc supplements demonstrated in this study supports the finding that zinc deficiency can occur in breastfed SGA infants.

This study demonstrates that infants born with low PI (wasted) are at substantially greater risk of dying in the postneonatal period than nonwasted infants. SGA infants are born with impaired immune function, potentially an important factor leading to increased respiratory<sup>7</sup> and diarrhea<sup>8</sup> morbidity and mortality in infancy.<sup>12,41-43</sup> Nutritional deficits, including micronutrient deficiencies, have been suggested to be responsible, at least in part.<sup>44</sup> Our findings suggest that zinc deficiency occurs in SGA infants and that the lower mortality found with zinc supplementation results from reduced rates of severe diarrhea, possibly related to enhanced immunocompetence.

The potential of interventions to improve zinc status and reduce infant mortality has important implications for child survival in developing countries. The findings of this study must be confirmed in larger trials, preferably enrolling both small- and appropriate-for-gestational age infants.

#### Contribution of the Authors

Principal investigators S.S. and R.E.B. formulated the hypotheses, secured funding, developed the data collection instruments, coordinated the study implementation, conducted the analysis, and wrote the article; V.P.M. and P.D. supervised field work, contributed to development of forms and field procedures, and supervised field data collection and supplementation; L.E.C. provided input in design and development of gestational age assessment instruments; U.D. was responsible for programming, data management, quality control, and analysis; and A.B. was responsible for supplement design and development and quality control.

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#### REFERENCES

1. UNICEF. *The State of the World's Children*. New York, NY: Oxford University Press; 1999
2. Beaton GH, Martorell R, Aronson KJ, et al. *Effectiveness of Vitamin A Supplementation in the Control of Young Child Morbidity and Mortality in Developing Countries*. United Nations ACC/SCN State of Art Series, Nutrition Policy Discussion Paper No 13. Geneva, Switzerland: World Health Organization; 1993
3. Zinc Investigators' Collaborative Group (Bhutta ZA, Black RE, Brown KH, et al). Prevention of diarrhea and pneumonia by zinc supplementation in children in developing countries: pooled analysis of randomized controlled trials. *J Pediatr*. 1999;135:689-697
4. Umeta M, West CE, Haidar J, Deurenberg P, Hautvast JG. Zinc supplementation and stunted infants in Ethiopia: a randomised controlled trial. *Lancet*. 2000;355:2021-2026
5. World Health Organization. The incidence of low birth weight: an update. *Wkly Epidemiol Rec*. 1984;59:205-212
6. World Health Organization, Division of Family Health. The incidence of low birth weight: a critical review of available information. *World Health Stat Q*. 1980;33:197-224
7. Ashworth A. Effects of intrauterine growth retardation on mortality and morbidity in infants and young children. *Eur J Clin Nutr*. 1998;52:S1534-S42
8. Victora CG, Kirkwood BR, Ashworth A, et al. Potential interventions for the prevention of childhood pneumonia in developing countries: improving nutrition. *Am J Clin Nutr*. 1999;70:309-320
9. Ashworth A, Feachem RG. Interventions for the control of diarrhoeal diseases among young children: prevention of low birth weight. *Bull WHO*. 1985;63:165-184
10. Singh M, Paul VK. Strategies to reduce perinatal and neonatal mortality. *Indian Pediatr*. 1988;25:499-509
11. Villar J, Belizian JM. The relative contribution of prematurity and fetal growth retardation to low birth weight in developing and developed societies. *Am J Obstet Gynecol*. 1982;143:793-798
12. Ferguson AC. Prolonged impairment of cellular immunity in children with intrauterine growth retardation. *J Pediatr*. 1978;93:52-56
13. Gupta AP, Bhandari B, Gupta A. Serum copper, zinc, magnesium and calcium in neonates. *Indian Pediatr*. 1984;21:569-573
14. Singh PP, Khushlani K, Veerwal PC, Gupta RC. Maternal hypozincemia and low-birth-weight infants. *Clin Chem*. 1987;33:1950
15. Goel R, Mishra PK. Study of plasma zinc in neonates and their mothers. *Indian Pediatr*. 1982;19:611-614
16. Jeswani RM, Vani SN. A study of serum zinc levels in cord blood of neonates and their mothers. *Indian J Pediatr*. 1991;58:683-686
17. Capurro H, Konichezky S, Fonseca D, Caldeyro-Barcia R. A simplified method for diagnosis of gestational age in the newborn infants. *J Pediatr*. 1978;93:120-122
18. Brenner WE, Edelman DA, Hendricks CH. A standard of fetal growth for the United States of America. *Am J Obstet Gynecol*. 1976;126:555-564
19. Mohan M, Prasad SR, Chellani HK, Kapani V. Intrauterine growth curves in north Indian babies: weight, length, head circumference and Ponderal index. *Indian Pediatr*. 1990;27:43-51
20. Allison PD. *Survival Analysis Using SAS System. A Practical Guide*. Cary, NC: SAS Institute Inc; 1995:233-249
21. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc*. 1958;53:457-481
22. Humphrey JH, Agoestina T, Wu L, et al. Impact of neonatal vitamin A supplementation on infant morbidity and mortality. *J Pediatr*. 1996;128:489-496
23. West KP Jr, Katz J, Shrestha SR, et al. Mortality of infants <6 months of age supplemented with vitamin A: a randomized, double-masked trial in Nepal. *Am J Clin Nutr*. 1995;62:143-148

24. Miller O, Becher H, Van Zweeden AB, et al. Effect of zinc supplementation and other causes of morbidity in west African children: randomized double blind placebo controlled trial. *BMJ*. 2000;322:1-6
25. Sazawal S, Black RE, Bhan MK, Jalla S, Sinha A, Bhandari N. Efficacy of zinc supplementation in reducing the incidence and prevalence of acute diarrhea: a community-based, double-blind, controlled trial. *Am J Clin Nutr*. 1997;66:413-418
26. Sazawal S, Black RE, Bhan MK, et al. Zinc supplementation reduces the incidence of persistent diarrhea and dysentery among low socioeconomic children in India. *J Nutr*. 1996;126:443-450
27. Zinc Investigators' Collaborative Group (Bhutta ZA, Bird SM, Black RE, et al). Therapeutic effects of oral zinc in acute and persistent diarrhea in children in developing countries: pooled analysis of randomized controlled trials. *Am J Clin Nutr*. 2000;72:1516-1522
28. Roy SK, Tomkins AM, Mahalanabis D, et al. Impact of zinc supplementation on persistent diarrhoea in malnourished Bangladeshi children. *Acta Paediatr*. 1998;87:1235-1239
29. Sazawal S, Black RE, Bhan MK, Bhandari N, Sinha A, Jalla S. Zinc supplementation in young children with acute diarrhea in India. *N Engl J Med*. 1995;333:839-844
30. Prasad LS, Ganguly SK, Vasuki K. Role of zinc in foetal nutrition. *Indian Pediatr*. 1974;11:799-802
31. Veena R, Narang AP, Banday AW, Bhan VK. Copper and zinc levels in maternal and fetal cord blood. *Int J Gynaecol Obstet*. 1991;35:47-49
32. Kapoor RK, Misra PK, Dixit S, Wakhulu I, Sharma B, Seth TD. Zinc and intrauterine growth. *Indian J Pediatr*. 1988;25:972-976
33. Bahl L, Chaudhuri LS, Pathak RM. Study of serum zinc in neonates and their mothers in Shimla hills (Himachal Pradesh). *Indian J Pediatr*. 1994; 61:571-575
34. Lehti KK. Breast milk folic acid and zinc concentrations of lactating, low socioeconomic, Amazonian women and the effect of age and parity on the same two nutrients. *Eur J Clin Nutr*. 1990;44:675-680
35. Jelliffe DB, Jelliffe EF. The volume and composition of human milk in poorly nourished communities. A review. *Am J Clin Nutr*. 1978;31: 492-515
36. Castillo-Duran C, Vial P, Uauy R. Trace mineral balance during acute diarrhoea in infants. *J Pediatr*. 1988;113:452-457
37. Leigh IM, Sanderson KV, Atherton DJ, Wells RS. Hypozincemia in infancy. *Br J Dermatol*. 1979;101(suppl 17):73-75
38. Aggett PJ, Atherton DJ, More J, Davey J, Delves HT, Harries JT. Symptomatic zinc deficiency in a breast-fed preterm infant. *Arch Dis Child*. 1980;55:547-550
39. Weymouth RD, Kelly R, Lansdell BJ. Symptomatic zinc deficiency in a premature infant. *Aust Paediatr J*. 1982;18:208-210
40. Blom I, Jameson S, Krook F, Larsson-Stymne B, Wranne L. Zinc deficiency with transitory acrodermatitis enteropathica in a boy of low birth weight. *Br J Dermatol*. 1981;104:459-464
41. Bilinski DL, Ehrenkranz RA, Cooley-Jacobs J, McGuire J. Symptomatic zinc deficiency in a breast-fed, premature infant. *Arch Dermatol*. 1987; 123:1221-1224
42. Haas JD, Balcazar H, Caulfield L. Variation in early neonatal mortality for different types of fetal growth retardation. *Am J Phys Anthropol*. 1987;73:467-473
43. McCormick MC. The contribution of low birth weight to infant mortality and childhood morbidity. *N Engl J Med*. 1985;312:82-90
44. Walther FJ, Ramaekers LH. Neonatal morbidity of SGA infants in relation to their nutritional status at birth. *Acta Paediatr Scand*. 1982;71: 437-440
45. Chandra RK. McCollum Award lecture. Nutrition and immunity: lessons from the past and new insights into the future. *Am J Clin Nutr*. 1991;53:1087-1101

## GAY COUPLES FOUND TO HEAD MORE HOMES

“Census data shows that same-sex couples head nearly 600,000 homes in the United States, with a gay or lesbian couple heading a household in nearly every American county . . . Of the 594,391 such homes in the 50 states and the District of Columbia, nearly 16% were in California and 8% were in New York, data from the 2000 census shows. San Francisco had one of the highest shares among metropolitan areas, but gay and lesbian partners were also found in rural parts of the Midwest and the Deep South.”

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Noted by JFL, MD