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Adding Zinc to Supplemental Iron and Folic Acid Does Not Affect Mortality and Severe Morbidity in Young Children[1]

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Abstract

Abstract Studies have found a substantial reduction in diarrhea and respiratory morbidity in young children receiving zinc supplementation. The impact of daily zinc supplementation administered with iron plus folic acid (IFA) in young children on all-cause hospitalizations and mortality in comparison with IFA alone was evaluated. In a double blind cluster-randomized controlled trial, 94,359 subjects aged 1–23 mo were administered a daily dose of zinc plus IFA or IFA alone for a duration of 12 mo after enrollment. The intervention group tablet contained 10 mg of elemental zinc, 12.5 mg of iron, and 50 μg of folic acid. The control group tablets were similar except that they contained a placebo for zinc. Infants aged <6 mo were administered half a tablet, and those older received 1 tablet dissolved in breast milk or water. Hospitalizations were captured by trained study physicians through the surveillance of 8 hospitals. Deaths and hospitalizations were ascertained through visits to households by study supervisors once every 2 mo. The overall death rates did not differ significantly between the 2 groups when adjusted for cluster randomization (hazard ratio = 1.02, 95% CI 0.87, 1.19). Zinc and IFA supplementation compared with IFA alone did not affect adjusted hospitalization rates (overall rate ratio = 1.08, 95% CI 0.98, 1.19; diarrhea-specific rate ratio = 1.15, 95% CI 0.99, 1.34; or pneumonia-specific rate ratio = 1.09, 95% CI 0.94, 1.25). The lack of impact of zinc on mortality and hospitalization rates in this study may have been due to the use of lower daily zinc dosing than used in some of the morbidity prevention trials or from an interaction between zinc and iron, where the addition of iron may have adversely affected potential effects of zinc on immune function and morbidity. Future research should address iron and zinc interaction effects on important functional outcomes. J. Nutr. 137: 112–117, 2007.

Introduction

Zinc deficiency is common in children of developing countries, including India. Possible causative factors include inadequate dietary intake, limited bioavailability from cereal-based diets, low intake of animal foods, and intestinal zinc losses during repeated diarrheal illnesses (1). Zinc deficiency impairs immunological and nonimmune barriers to infections, particularly those affecting mucosal surfaces (2–6). Randomized placebo-controlled trials in developing countries have shown substantial reduction in diarrhea and respiratory morbidity among young children receiving daily zinc supplementation (1,7–11). Importantly, the reduction in morbidity following supplementation was more for severe than mild infections (11). To facilitate the formulation of a public health policy to combat zinc deficiency, it is also necessary to assess the effect of improved zinc intake on child mortality. We therefore evaluated the impact of daily zinc supplementation, coadministered with iron plus folic acid (IFA),[6] in young children on all-cause hospitalizations and mortality in comparison with the intake of IFA alone.

The decision to administer zinc with IFA was a pragmatic one, as the deficiencies of both these micronutrients coexist. Besides, routine supplementation with IFA is a national program in India. We believed that if zinc supplementation reduced child mortality, a practical way to supplement children would be to administer it along with IFA. We did, however, consider the possibility that coadministration might reduce the bioavailability of zinc; but by the time the study began, our conclusion, based on a review of the literature, was that such an effect would likely be small if supplements were given in a molar ratio close to 1:1, as was done in a current trial (12–16). Formulations that provide the recommended daily allowance (RDA) of multivitamins and 1 RDA of zinc (5 mg for infants and 10 mg for older

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[6] Abbreviations used: CHW, community health worker; IFA, iron plus folic acid; RDA, recommended daily allowance.

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children) are commonly available for young children. The value of this daily zinc dosing is not fully established. Our study, therefore, was deliberately designed to test an intervention that would be deliverable under programmatic conditions.

Methods

The study was a double blind randomized controlled trial in which the unit of randomization was households. The trial was conducted between February 2002 and August 2003 in low-to-middle socio-economic urban neighborhoods of north and northwest Delhi in India covering a population of ~1,900,000 inhabitants and 400,000 households in 25 neighborhoods, typical of the urban low-to-middle income socioeconomic status communities in the city, spread over 80 square kilometers. This list was provided by the Municipal Corporation of Delhi, which is responsible for the entire region. Recent data from similar populations in Delhi indicate that childhood undernutrition, zinc and other micronutrient deficiency, diarrhea, and lower respiratory tract infections are common in this setting (7,8,10,11,17).

Resident community health workers (CHW) were recruited; 1 CHW for 200 contiguous households to ensure that each CHW would follow-up on ~60 children. A door-to-door survey was conducted by study field investigators and CHW to identify pregnant women and children aged <2 y.

Randomization and blinding procedures. Two randomization lists were computer generated (one for each stratum) by a staff member of the World Health Organization (WHO). The first list was for households with only 1 infant aged 30–60 d and with a weight ≤3.5 kg (Stratum A). The second list was for households with an infant aged 30 to 60 d and weighing >3.5 kg and/or any child older than 60 d (Stratum B). The purpose of the stratified randomization was to ensure that young infants <2 mo, who were likely to have a low birth weight (weight at 30–60 d ≤3.5 kg; Stratum A), were equally distributed between the intervention and control groups. Infants aged 30–60 d with a weight >3.5 kg and older children (because it was difficult to assume that their current weight could identify whether they were low birth weight) were grouped into Stratum B. Because the unit of randomization was the household rather than the individual child, a very small number of households with 2 eligible children (for example, a 1-mo–old weighing ≤3.5 kg and a 2-y–old child) could only be grouped into 1 of the strata. We arbitrarily decided to include such households in Stratum B. Each list had permuted blocks of 16 participants randomly allocated to 16 letter codes. Half of the 16 letter codes were randomly assigned to the zinc and IFA group and the other half to the IFA group. This code was only available with the WHO and the company that prepared and packaged the supplement. The supplements were packaged in strips with a letter code printed on the back.

Randomization lists containing only serial numbers (that represented household numbers) and respective letter codes were made available to the investigators, but they did not know which of the 16 letter codes represented the 2 study groups.

Households with potential study participants were asked to give consent for screening their child(ren) for eligibility. Households where parents consented to participate were assigned a serial number in sequence of their enrollment. Supplement strips, with the letter code assigned to that serial number from the appropriate randomization list, were labeled with the name(s) of the child(ren). All enrolled children from a household received the supplement with the same letter code.

Ethical clearances were obtained from the Ethics Committee of the All India Institute of Medical Sciences, the Society for Applied Studies, and the WHO Review Committee.

Verbal consent was obtained from community leaders and other opinion makers working in the study neighborhoods. Individual written consent, or the thumb imprint from those who could not write, was taken from the caregiver of each enrolled child and a copy of the form was left with the family.

Enrollment. Twenty supervisors enrolled children through household visits. Eligible children were aged 1–23 mo, of either sex, local residents, and unlikely to move away over the next 6 mo. Children were excluded if they had major congenital anomalies, severe malnutrition, or any serious condition that affected the ability of the child to consume the supplement. Children with illnesses requiring hospitalization were excluded temporarily and screened again after recovery.

Families were given child identification cards and asked to call designated study coordinators and investigators in the case of a problem pertaining to the child's participation or to a specific illness.

The supplement. For each enrolled child, a 30-d supply of dispersible tablets was left in the home and replenished monthly. The intervention group tablet contained 10 mg of elemental zinc, 12.5 mg of iron, and 50 μg of folic acid. The control group tablets were similar in appearance and taste except they contained a placebo for zinc. These tablets were provided by the WHO (Geneva) and prepared by Nutriset. Infants aged <6 mo were administered half a tablet dissolved in 5 mL expressed breast milk, and older children received 1 tablet daily in breast milk or clean water.

Cointerventions. Routine primary health care services, per national government policy, were available in the area through government outpatient facilities and a large number of private health care providers.

Postenrollment activities. Community health workers visited households on alternate days to record the child's health status (hospitalization or death), to administer the supplement if not already done so by the caregiver, and to reinforce continued use of the supplement.

Hospitalizations were captured through 24-h passive surveillance of 8 major hospitals used by the study population by intensively trained study physicians. These physicians examined the central admission register every 6 h for all admissions in ≤3-y–old children. Those admitted were visited, their addresses ascertained, and after confirming enrollment status, they were asked to show their study identification card. Once ensured that the patient was indeed a study participant, the child was examined. The 8 hospitals were selected prior to study initiation by identifying those commonly used for children (as determined by a limited survey and key informant interviews). A hospitalization was defined as inpatient admission or a short admission to the emergency ward for documented dehydration and oral rehydration, or when the use of oxygen or intravenous fluid therapy was considered essential. The final diagnosis reflected a consensus between the study physician and the treating physician.

Additionally, study supervisors visited households once every 2 mo to ascertain details of hospitalizations and deaths that occurred in the last 2 mo. An inpatient admission was defined as at least a 24-h stay or shorter if resulting in death. A minimum 24-h stay was considered necessary to ensure that, through this 2-mo recall process, actual hospitalizations were reported rather than outpatient visits requiring a long waiting time.

Deaths were identified through CHW and home visits by study supervisors every 2 mo. Households where a child had died were visited by a skilled interviewer to fill a previously validated "verbal autopsy questionnaire" (18) as early as possible after the death was reported.

Trial size. Sample sizes were calculated for 95% CI and 90% power using data from recent studies in similar sites (8,10,11,19). Based on these data, the mortality and hospitalization rates in the control communities were assumed to be 16/1000 child-y and 30/1000 child-y, respectively. Diarrhea and pneumonia related hospitalization rates were each assumed to be 12/1000 child-y. It was assumed that the rates of mortality and hospitalizations across households varied by ±50% of these rates. Approximately 85% of households were assumed to have only 1 child aged <2 y and the remaining 15% to have 2 children. Every child was expected to contribute ~0.78 child-y according to the follow-up strategy and we further assumed a 10% loss to follow-up. Using a trial-size formula appropriate for cluster randomization for comparison of 2 rates (20), we calculated that we needed ~33,000 households per group to detect a 20% relative reduction in mortality rate, a 15% relative reduction in hospital admission rate, and a 25% relative reduction in diarrhea and pneumonia specific hospitalization rates.

The study commenced in February 2002 and, per an a priori trial size, children were enrolled. During the study, the Data-Safety Monitoring

Board observed that the mortality rate was lower than assumed but did not recommend extended enrollment, because to reach the original objective, an additional 5 y of recruitment would be necessary. The study was therefore stopped on 31 August 2003.

Anthropometry and zinc and ferritin assays. Weights, lengths, and blood specimens for estimates of zinc and ferritin were taken in 1000 randomly selected subsamples at baseline and 12 mo postsupplementation.

At enrollment, nonfasting venous blood (5 mL) was drawn in zinc-free heparinized polypropylene tubes (Sarstedt) by one of the physicians. The heparinized blood was centrifuged (447 × *g*; 10 min) and plasma transferred to zinc-free polypropylene vials (Eppendorf), which were stored at −20°C until analysis.

The plasma specimens were analyzed for zinc using a standard flame furnace atomic absorption spectrophotometer technique (GBC Avanta). Seronorm (Sero AS) was used as the reference standard in every batch of 20 samples. Immunoenzymatic colorimetric method (DiaMetra) was used for quantitative determination of ferritin concentration in plasma (21,22).

Measurement of compliance. Fifty percent of randomly selected households were visited by an independent team to obtain an assessment of supplement intake in the previous 24 h and the prevalence of side effects such as vomiting.

Data management. Forms were designed in FoxPro for Windows (Microsoft) and range and consistency checks built in. Data were double entered independently by 2 data entry clerks and validation completed within 72 h after form filling. The validated data were merged in a master file and 2 backup copies made, 1 of which was kept offsite.

Definitions used for assigning causes of hospitalization. Cause of hospitalization was classified as diarrhea, pneumonia, and others. Diarrhea was defined as the passage of 3 or more loose or watery stools in a 24-h period for 1 or more days. Diarrheal symptoms had to be present during 1 of the 2 d preceding hospitalization. Dehydration was classified as severe, some, or none, according to WHO guidelines (23). Pneumonia was defined as the presence of a cough or difficult breathing with crepitations or bronchial breathing on auscultation. When a classification of diarrhea or pneumonia was not made, the hospitalization was assigned to the "other causes" category.

Definitions used for assigning causes of death. Computer-defined algorithms were used to assign the cause of death (18). For diarrhea, mothers' report of the illness was used. The assignment of diarrhea as a cause of death included the presence of acute (≤14 d) or persistent (>14 d) diarrhea or the presence of dysentery, i.e., the presence of visible blood in 1 or more stools. Pneumonia was defined as the presence of cough or difficult breathing along with fast breathing or chest indrawing based on the mother's report (18).

Analysis. Analyses were by intent to treat and conducted using Stata software, version 8.2. We included data from all children until the time they were available for follow-up or completed 12 mo of follow-up. Child-years of follow-up to censorship were calculated. Differences among groups were analyzed using chi-square test for prevalence. For outcomes, we calculated differences in means or proportions and their 95% CI. Cox proportional hazard models were used to estimate the impact on the intervention on mortality adjusted for potential confounding baseline factors. Standard errors of the effect size were adjusted for clustering of the outcome within households to account for the cluster randomization. Poisson models using a generalized estimating equation framework were used to estimate the impact of the intervention on hospitalization rates to allow for the potential nonindependence of hospital admissions in the same household. Robust standard errors were estimated.

Results

A total of 577,258 households were surveyed to yield 102,474 children aged 1–23 mo (**Fig. 1**). Four thousand four hundred and

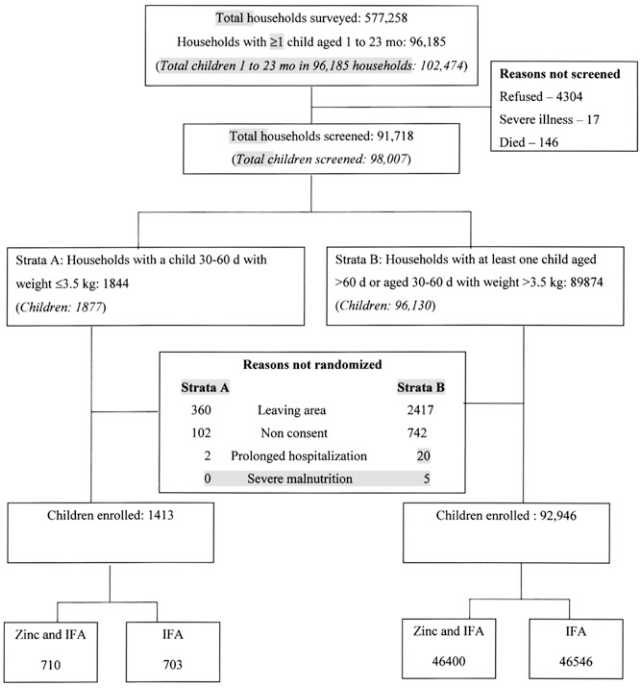

Figure 1 Trial profile.

sixty-seven (4.3%) children could not be screened due to refusal (4304), severe illness on day of screening (17), or death (146). Of the 91,718 households screened (with 98,007 children), 1844 households (with 1877 children) were eligible for randomization to Strata A and 89,874 households (with 96,310 children) to Strata B. After exclusions, a total of 94,359 children were enrolled from 88,940 households (Fig. 1). Of the children enrolled, 647 (0.68%) died, 64 (0.07%) refused further participation, and another 3470 (3.7%) moved away before completing 12 mo follow-up. At the time of study termination, 42,048 had completed the 12-mo follow-up and for 48,130 the follow-up was ongoing.

The 2 groups were similar for various socio-economic, child characteristics (**Table 1**), and baseline biochemical and anthropometry indicators (**Table 2**). Over a third of children had zinc concentrations <60 μg/dL (<9.18 μmol/L). Plasma ferritin concentrations were similar in the 2 groups. Approximately one-fourth of children had iron deficiency (hematocrit <0.33, Table 2). In the subgroup for whom anthropometric measures were conducted, 49.7 and 50.7% were underweight (weight-for-age <−2 Z score) and 43.6 and 45.3% were stunted (height-for-age <−2 Z score) at baseline in intervention and control groups, respectively. In the 50% of households visited by an independent team to assess compliance to supplement administration, over three-fourths of children (77.5% in the zinc plus IFA group and 79% in the IFA group; difference in proportions 1.5%, 95 CI 0.69, 2.3) had been administered the supplement in the 24 h prior to the visit either by the caregiver or the CHW. In the previous 24 h, 2.6 and 2.1% of children in the zinc and IFA and IFA groups experienced vomiting, respectively (difference in proportions = 0.5%, 95% CI 0.33, 0.67; $P = 0.002$).

Plasma zinc concentrations, after 12 mo of supplementation, were higher in the zinc and IFA group [difference in means = 7.9 μg/dL (1.2 μmol/L); 95% CI 6.0, 9.8 μg/dL (0.92, 1.49 μmol/L), $P < 0.0001$]; the proportion of deficiency was also lower (difference in proportions = −10%; 95% CI –15.6, –4.4;

TABLE 1 Baseline socio-economic and child characteristics of enrolled children[1]

Characteristics	Zn and IFA	IFA
Subjects, *n*	47,110	47,249
Total family members, *n*	5.93 ± 2.62	5.94 ± 2.63
Mothers' schooling, *y*	4.86 ± 4.91	4.87 ± 4.91
Fathers' schooling, *y*	7.59 ± 4.54	7.59 ± 4.53
Families with, *n (%)*		
Piped water supply or ownership of hand pump	39,639 (84.1)	39,758 (84.1)
Toilet ownership	34,164 (72.5)	34,228 (72.4)
Age at enrollment, *mo*	11.77 ± 6.71	11.68 ± 6.69
Males, *n (%)*	24,679 (52.4)	25,049 (53.0)
Children born in hospitals, *n (%)*	19,777 (42.0)	19,946 (42.2)
Birth weight reported by mother,[2] *kg*	2.69 ± 0.613	2.68 ± 0.622
Currently breast-fed, *n (%)*	37,870 (80.4)	38,150 (80.7)
Morbidity reported in the previous 24 h, *n (%)*		
Diarrhea	3883 (8.2)	4010 (8.5)
Pneumonia	809 (1.7)	811 (1.7)
Fever	2747 (5.8)	2749 (5.8)
Families who experienced ≥1 child deaths, *n (%)*	3990 (8.5)	3861 (8.2)

[1] Values are means ± SD, $n = 94359$, or *n* (%).
[2] Zinc and IFA, $n = 8730$, IFA alone, $n = 8810$.

TABLE 2 Baseline biochemical and anthropometric indicators in a subsample of enrolled children[1]

Characteristics	Zn and IFA	IFA
Subjects, *n*	738	741
Plasma zinc,[2] *μg/dL*	64.0 ± 13.3	64.2 ± 11.3
Plasma zinc <60 μg/dL, *n (%)*	265 (35.9)	264 (35.6)
Subjects, *n*	676	666
Plasma ferritin,[2] *ng/mL*	86.8 ± 126.0	86.0 ± 124.4
Subjects, *n*	753	753
Hematocrit	0.348 ± 0.046	0.349 ± 0.045
Hematocrit <0.33, *n (%)*	212 (28.1)	193 (25.6)
Subjects, *n*	879	869
Weight for age <−2 Z scores, *n (%)*	437 (49.7)	441 (50.7)
Height for age <−2 Z scores, *n (%)*	383 (43.6)	394 (45.3)

[1] Values are means ± SD unless indicated otherwise.
[2] SI unit factor conversion: zinc (μmol/L) = 0.153; ferritin (pmol/L) = 2.247.

$P = 0.0005$, **Table 3**). Only 7.7 and 7.3% of children had low hematocrit (24) in the zinc and IFA and IFA alone groups, respectively.

There were a total of 980 hospitalizations identified through the passive surveillance of hospitals in the zinc and IFA and 916 in the IFA alone group. Zinc and IFA supplementation, compared with IFA supplementation, had no impact on overall hospitalization rates adjusted for cluster randomization (rate ratio = 1.08, 95% CI 0.98, 1.19). The diarrhea-specific (rate ratio = 1.15, 95% CI 0.99, 1.34) and pneumonia-specific (rate ratio = 1.09, 95% CI 0.94, 1.25) hospitalization rates were also similar in the 2 groups. The CI around the effect sizes preclude the possibility of a clinically meaningful effect (**Table 4**).

Through supervisor home-visit assessments made every 2 mo, there were a total of 1752 hospitalizations in the zinc and IFA group and 1768 hospitalizations in the IFA group. In this assessment too, hospitalization rates per 1000 child-y were similar (44.8 in the zinc and IFA and 45.0 in the IFA group; the rate ratio adjusted for cluster randomization = 0.99, 95% CI 0.93, 1.06).

There were 326 deaths in the zinc and IFA and 321 deaths in the IFA group. The overall death rates adjusted for cluster randomization did not differ between the 2 groups (hazard ratio = 1.02, 95% CI 0.87, 1.19). In the zinc and IFA group, the cause-specific death rate for pneumonia seemed to be lower, but an overall test did not indicate that the distribution for causes of death differed between the 2 groups ($P = 0.281$, **Table 5**).

Discussion

Zinc deficiency is common in this population. Zinc, when supplemented with IFA, had no significant effect on overall mortality and hospitalization rates. Whereas zinc supplementation trials (without coadministration of other micronutrients) have consistently shown that reduced morbidity is due to diarrhea and pneumonia, these results are somewhat unexpected (1,7–11). There are several possible explanations for these findings. One possibility is that compliance rates may not have been high enough; however, the rates reported in our study were >70%. That compliance may not be a major factor is also indicated by the fact that only 7% children at the end of the study had low hematocrit in a population where iron deficiency anemia is

TABLE 3 Effect of zinc and IFA supplementation compared with IFA alone on zinc, hematocrit, and ferritin plasma concentrations 12 mo after supplementation[1]

	Zinc and IFA	IFA	Difference in means/ proportions, *95% CI*
Subjects, *n*	551	545	
Plasma zinc,[2] *μg/dL*	70.7 ± 20.3	62.8 ± 10.9	7.9 (6.0, 9.8)*
Plasma zinc <60 μg/dL, *n (%)*	162 (29.4)	215 (39.4)	−10 (−15.6, −4.4)*
Subjects, *n*	555	547	
Hematocrit	0.370 ± 0.03	0.371 ± 0.03	−0.001 (−0.004, 0.003)
Hematocrit <0.33, *n (%)*	43 (7.7)	40 (7.3)	0.4 (−2.7, 3.5)
Subjects, *n*	436	412	
Plasma ferritin,[2] *ng/mL*	55.0 ± 67.7	57.2 ± 66.3	−2.2 (−11.2, 6.8)
Plasma ferritin <20 ng/mL, *n (%)*	178 (40.8)	152 (36.9)	3.9 (−2.6, 10.4)
Plasma ferritin <12 ng/mL, *n (%)*	130 (29.8)	112 (27.2)	2.6 (−3.4, 8.7)

[1] Values are means ± SD unless indicated otherwise.
[2] SI unit factor conversion: zinc (μmol/L) = 0.153; ferritin (pmol/L) = 2.247.
* $P < 0.001$.

TABLE 4 Effect of zinc and IFA supplementation compared with IFA alone on all-cause and cause-specific hospitalization rates

	Zn and IFA	IFA	Rate ratio for cluster randomization,[1] *95% CI*
	n		
Total child-y of follow-up	39,103	39,243	
All-cause hospitalizations	980	916	
Admissions/1000 child-y	25	23	1.08 (0.98, 1.19)
Hospitalizations due to diarrhea irrespective of associated causes	384	335	
Admissions/1000 child-y	9.82	8.53	1.15 (0.99, 1.34)
Hospitalizations due to pneumonia irrespective of associated causes	456	424	
Admissions/1000 child-y	11.66	10.8	1.09 (0.94, 1.25)
Hospitalizations due to other causes excluding pneumonia and diarrhea	217	233	
Admissions/1000 child-y	5.45	5.94	0.93 (0.77, 1.13)

[1] Additional adjustment for potential confounders included sex, mother's years of schooling, birth in hospital, breast-feeding status; previous child death in the family did not change effect size or CI.

expected to be very common (25). The alternate-day visits by community health workers were also intended to minimize this possibility.

Interactions between zinc and iron as a possible explanation for the study findings deserve consideration. An earlier review by Lonnerdal (26) suggested that excess iron affects zinc uptake when iron and zinc are administered together in a water solution, and during a fasting state, but not when consumed with meals, and this effect also increases the relative amount of iron in the combination. Recently, Walker et al. (27) reviewed randomized trials assessing the effects of iron and zinc supplementation on iron and zinc status. In the several studies that have assessed the effects of iron-zinc combinations on zinc status and on morbidity, there were no adverse effects of adding iron to zinc supplementation on plasma zinc concentrations; but iron and zinc were given nearly in equivalent ratios. The authors, however, concluded that the effects on morbidity have not been well evaluated (27). Overall, the available data do not allow for a firm conclusion as to whether, when combined supplements are used, iron adversely affects the absorption or utilization of zinc and its favorable effects on morbidity and physical growth, as reported in many studies based in developing countries, such as India, when it was administered alone without other nutrients (26,27).

Therefore, the possibility that adding iron to zinc supplements may have adversely affected the potential effects of zinc on immune function and morbidity in the current study cannot be excluded as a possible explanation for the lack of effect of the combined supplement on the overall severe morbidity and mortality in our study.

The optimal daily supplement doses deserve consideration. In the pooled analysis of zinc preventive trials, 4 trials used a 20 mg daily dose, 5 trials used a 10 mg daily dose, and 1 trial used a 5 mg dose on infants who were small for their gestational age. There were no differences in the effect by dose (9). It is still unclear whether the decreased morbidity with zinc supplementation in children of developing countries results entirely from the correction of the deficiency or whether it also reflects other direct effects of zinc. We chose this dose because a meta-analysis did not find differences in effect by dose (9), and many public health experts do not support the use of a dose larger than the RDA to be used on a long-term basis because of the risk of toxicity. Also, the safety of administering higher doses of zinc for long periods of time has not been fully established.

The prevalence of iron deficiency anemia was similar in the 2 groups at the end of the study, and the rates in both were far lower than previous reports (25) of this population at this age. This suggests that coadministration of zinc and iron in the relative dosing used in this study did not substantially reduce the effect of zinc on iron status.

In conclusion, we found that, in a setting where zinc deficiency is common and zinc supplementation has been clearly shown to reduce diarrhea and pneumonia morbidity, the combined supplementation of iron and zinc is unlikely to result in a substantial reduction in overall mortality and hospitalization rates. This study does not resolve whether the lack of benefit on these outcomes is the result of an adverse effect of iron on zinc absorption or utilization. Recently completed studies in Tanzania and Nepal, where the mortality impact of zinc was assessed without added iron, are likely to provide greater clarity on this issue. Iron and zinc deficiency are common in developing countries, and identifying common strategies to address these deficiencies is of great interest. Future research should address iron and zinc interaction effects on important functional outcomes to facilitate formulation of a scientific and evidence-based public health policy.

TABLE 5 Effect of zinc and IFA supplementation compared with IFA alone on all-cause and cause-specific mortality rates

	Zn and IFA	IFA	Hazard ratio for cluster randomization,[1] *95% CI*
Total child y of follow-up	39,103	39,243	
Number of deaths	326	321	
Mortality rate	8.3	8.2	1.02 (0.87,1.19)
Cause-specific mortality[2]	—	—	
Number of diarrhea-related deaths[3]	73	70	
Mortality rate for diarrhea related deaths	1.86	1.78	
Number of pneumonia-related deaths[3]	85	117	
Mortality rate for pneumonia-related deaths	2.17	2.98	
Number of deaths due to other causes[3]	188	176	
Mortality rate for other causes	4.80	4.48	

[1] Additional adjustment for potential confounders included sex, mother's years of schooling, birth in hospital, breast-feeding status; previous child death in the family did not change effect size or CI.
[2] The distribution of causes of death did not differ among groups. Statistical comparisons of cause-specific mortality rates, therefore, were not made.
[3] Irrespective of associated cause(s).

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