Preventive zinc supplementation among infants, preschoolers, and older prepubertal children

Kenneth H. Brown, Janet M. Peerson, Shawn K. Baker, and Sonja Y. Hess

Abstract

Zinc supplementation trials carried out among children have produced variable results, depending on the specific outcomes considered and the initial characteristics of the children who were enrolled. We completed a series of meta-analyses to examine the impact of preventive zinc supplementation on morbidity; mortality; physical growth; biochemical indicators of zinc, iron, and copper status; and indicators of behavioral development, along with possible modifying effects of the intervention results. Zinc supplementation reduced the incidence of diarrhea by ~20%, but the impact was limited to studies that enrolled children with a mean initial age greater than 12 months. Among the subset of studies that enrolled children with mean initial age greater than 12 months, the relative risk of diarrhea was reduced by 27%. Zinc supplementation reduced the incidence of acute lower respiratory tract infections by ~15%. Zinc supplementation yielded inconsistent impacts on malaria incidence, and too few trials are currently available to allow definitive conclusions to be drawn. Zinc supplementation had a marginal 6% impact on overall child mortality, but there was an 18% reduction in deaths among zinc-supplemented children older than 12 months of age. Zinc supplementation increased linear growth and weight gain by a small, but highly significant, amount. The interventions yielded a consistent, moderately large increase in mean serum zinc concentrations, and they had no significant adverse effects on indicators of iron and copper status. There were no significant effects on children's behavioral development, although the number of available studies is relatively small. The available evidence supports the need for intervention programs to enhance zinc status to reduce child morbidity and mortality and to enhance child growth. Possible strategies for delivering preventive zinc supplements are discussed.

Key words: Children, growth, infants, iron status indicators, morbidity, mortality, prevention, zinc supplementation

Background

A considerable number of intervention trials have been conducted in a variety of settings to assess the impact of preventive zinc supplementation on children's health and development. The results of these studies are inconsistent, possibly because of differences in the underlying zinc status or other characteristics of the study populations or discrepancies in the research methods. In this paper, we examine the results of controlled supplementation trials to address the following questions:

Section 1: Does preventive zinc supplementation of infants and young children affect their risk of selected illnesses, survival, physical growth, behavioral development, and serum zinc concentration? Are these effects modified by child- or dose-related factors?

Section 2: Are there adverse effects of preventive zinc supplementation?

Section 3: What are the opportunities to link preventive zinc supplementation programs to existing health and nutrition programs, and what technical, social, behavioral, and programmatic challenges must be confronted?

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Section 1

Does preventive zinc supplementation of infants and young children affect their risk of selected illnesses, survival, physical growth, behavioral development, and serum zinc concentration? Are these effects modified by child- or dose-related factors?

Conclusions

Preventive zinc supplementation reduces the incidence of diarrhea by ~20% among children in lower-income countries, although current evidence indicates that this beneficial effect of zinc is limited to children greater than ~12 months of age. Zinc supplementation also lowers the incidence of acute lower respiratory tract infections (ALRI), reducing pneumonia and ALRI by ~15%. Fewer studies have been completed to assess the effects of zinc supplementation on the incidence and severity of malaria, but the limited available information suggests that zinc supplementation may reduce the number of malaria episodes that result in clinic visits. Overall, zinc supplementation produces a 6% reduction in child mortality, although this benefit may be restricted to children 12 months of age or older, in whom the mortality reduction is approximately 18%. There is some information to suggest that zinc supplementation also may reduce mortality among small-for-gestational-age (SGA) infants, but the number of available studies and the numbers of children enrolled in each are too small to allow definite conclusions to be drawn.

Zinc supplementation produces a small, but significant, increase in linear growth and weight gain. Zinc supplementation consistently increases serum zinc concentration, with a moderately large effect size. We did not find evidence of any overall impact of zinc supplementation on mental or psychomotor development. However, the number of available studies is still relatively small, and the duration of these studies may be too short to permit detection of such outcomes.

Zinc supplementation programs should be considered for children in countries with an elevated risk of zinc deficiency to reduce their incidence of diarrhea, pneumonia, and possibly other infections; reduce mortality among children 12 months of age or older and possibly among SGA infants; and increase growth velocity and thereby reduce their risk of nutritional stunting and underweight.

Detailed review of evidence

Overview

To address the aforementioned set of questions, we conducted a systematic review of relevant supplementation trials of infants and prepubertal children. The following sections describe the procedures used to identify individual studies and select those for inclusion in the meta-analyses, the analytic methods that were used, and the specific outcomes of interest.

Identification of references. We sought information on controlled zinc supplementation trials conducted among prepubertal children by completing a computerized bibliographic search in May 2007, using the PubMed bibliographic database with the key word "zinc" and limiting for human studies, English language, clinical trial, and randomized, controlled trials. The results of the search were further expanded by contacting experts in the field and examining subsequent PubMed notifications and one conference report. The search strategy yielded a total of 1,625 individual references for consideration (**fig. 1**).

Selection of studies. The title or abstract of each article was scanned by a research assistant and two of the authors. Full articles were retrieved for further assessment if the available information suggested that zinc was provided as a supplement (exclusive of infant formula), the presence or absence of zinc in the supplement was the only factor that differed between any two intervention groups, and zinc supplementation was provided for prevention of deficiency rather than for treatment of a current disease. Zinc supplementation was considered to be therapeutic when it was provided as a component of the treatment regimen for diarrhea, pneumonia, malaria, or inpatient nutritional rehabilitation of children with severe malnutrition (marasmus or kwashiorkor), and therefore studies of these conditions were excluded from the present analysis. All other zinc supplementation studies were considered preventive zinc supplementation trials.

A total of 95 references were identified from controlled trials of preventive zinc supplementation in children; 8 of these publications were excluded because the article described a prior meta-analysis [1, 2] or pooled analysis [3], insufficient data were presented to address the questions of interest [4, 5], subjects were selected because of sickle-cell disease [6], or some subjects were no longer prepubertal [7, 8]. For two studies that included both prepubertal and postpubertal individuals, we were able to include the results just for the prepubertal children, either as presented in the paper [9] or as provided subsequently by the authors [10].

The 87 acceptable articles were then screened to combine results from those that presented data on the same intervention trial by using key trial characteristics, such as the country site, supplementation scheme, and study population. In some cases, several articles were published from the same study under the names of different first authors, so we refer to individual studies by using the country site and year of first publication. A total of 55 individual trials were identified, which enrolled a total of 202,692 children. If a trial included more than two sets of treatment groups that differed

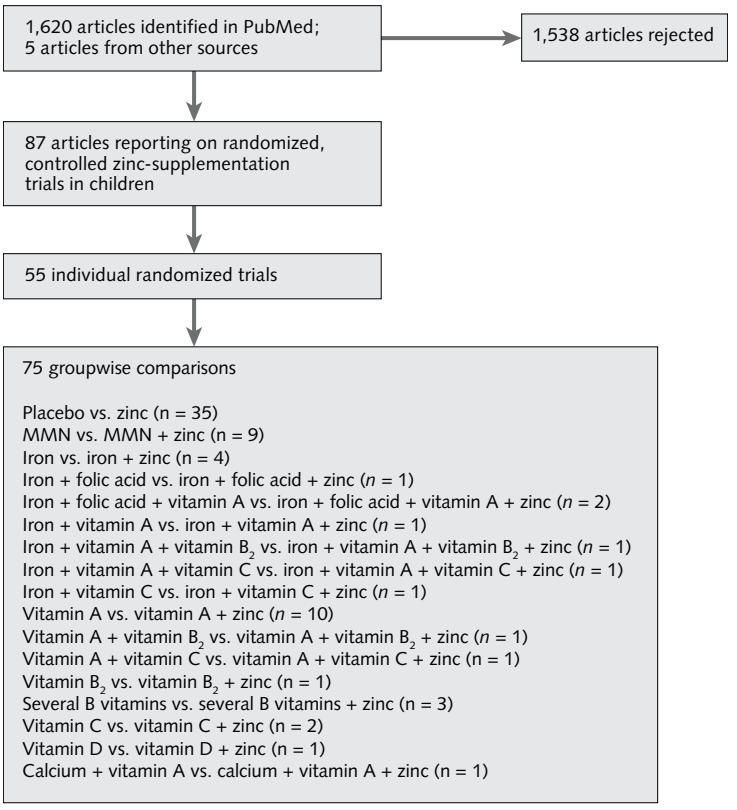

FIG. 1. Number of articles and individual studies included in the meta-analysis on preventive zinc supplementation in children. For groupwise comparisons, the two treatment groups differed only by the presence or absence of zinc in the supplement provided. MMN (multiple micronutrients) indicates at least four micronutrients. For more information on characteristics of the studies and participants, see **table 1.**

only by the presence of zinc (e.g., placebo vs. zinc alone, iron vs. zinc plus iron, or multiple micronutrients (MMN) with or without zinc), each set of groups that differed by zinc only was considered a separate groupwise comparison (**fig. 1**). A total of 75 separate controlled comparisons were identified. Of these comparisons, 73 were derived from studies considered to be well designed because the treatments were randomly assigned to individuals and the research protocol used a double-blind, controlled design. Only one study did not specifically indicate whether treatments were randomly assigned [11]. In the study Brazil 1998 [12, 13], one of the three treatment groups (5 mg of zinc daily) was excluded from consideration because that group was not enrolled concurrently with the placebo group.

Data extraction and management. For studies that fulfilled the inclusion criteria, three research assistants summarized relevant information regarding the study population and intervention design, using a standard data-extraction template. Any relevant information concerning the trial that was missing from the published report was obtained from the original author(s) of the article, if possible. One of the reviewers verified all extracted information by comparing the data with the original publication. When there were differences of opinion among reviewers, these were discussed and resolved by consensus.

Data analyses. The outcomes examined were incidence of diarrhea; incidence of ALRI; incidence of malaria; mortality; change in height (length or stature), expressed in centimeters or height-for-age z-score (HAZ); change in body weight, expressed in kilograms or weight-for-age z-score (WAZ); change in weight-for-height z-score; change in mid-upper-arm circumference; change in serum or plasma zinc concentration; final mental development index score; final physical development index score; change in blood hemoglobin concentration; change in serum ferritin concentration; and change in serum copper concentration. For all outcomes, except morbidity variables and final developmental scores, studies were included in the analyses only if information was available for both the

children's initial status and change during the course of the intervention. Morbidity and mortality variables were converted to rate ratios, and anthropometric, biochemical, and development variables were converted to effect size, which was calculated as the difference between the mean of the values for the zinc and the corresponding control group divided by their pooled standard deviation. In general, effect sizes of ~0.2 are considered of small magnitude, effect sizes of ~0.5 are considered moderately large, and those of ~0.8 or greater are considered large [14].

The overall mean effect size for each outcome variable was estimated from a random-effects model [15]. This model assumes that the observed effect size or log(relative risk) from a particular study is the sum of the true effect for that study plus a normally distributed random error term, which is related to the sample size and effect size or relative risk for that study and, in turn, that the true effects are themselves normally distributed. Because the total variance for the study effect size is different from one study to the next, the best estimate of the overall mean is a weighted mean effect size, in which the weights are equal to the inverse of the total variance. The SAS for WINDOWS (release 9) MIXED procedure was used to estimate the weighted mean effect size and its standard error.

Additionally, the heterogeneity of responses was assessed by using the chi-square test, as described by Hedges [16]. We explored possible sources of heterogeneity with random-effects meta-regression analyses, in which study characteristics were used to explain effect sizes [17, 18]. As with any regression, the number of possible explanatory variables was strictly limited by the number of observations, which in this case is the number of comparisons available. Explanatory variables were examined separately in a series of bivariate models; then a subset of explanatory variables was entered into a regression model and nonsignificant predictors were removed in a stepwise fashion. When appropriate, nonlinearity was initially assessed with polynomial models and, in one case (relation between diarrheal incidence and age), was followed up with the use of a two-phase regression model. The SAS for WINDOWS MIXED procedure was used for all of these procedures except the two-phase regression model, for which the SAS NLMIXED procedure was used.

Description of intervention trials

The general characteristics of the studies included in the meta-analyses are shown in **table 1**. Of the 55 studies included in the analyses, 7 were from Africa, 23 were from Asia, 12 were from South America, 11 were from North America, 1 was from Australia, and 1 was from Europe. The supplementation periods ranged from 2 weeks [19] to 15 months [11], and the number of subjects ranged from 18 to 94,359. The periodic zinc supplementation doses ranged from 1 to 70 mg per dose (median, 10 mg, with one dose unknown). These doses were provided daily [9, 20–68], several times per week [10–13, 69–94], or once per week [94–99], resulting in a daily dose equivalents ranging from 0.9 to 21.4 mg of zinc/day. Most studies provided zinc as zinc sulfate ($n = 36$), although a few distributed other compounds, including zinc acetate ($n = 5$), zinc gluconate ($n = 5$), zinc amino acid chelates ($n = 3$), and zinc oxide ($n = 1$). In four studies, the zinc compound was not stated [22, 48, 71, 73], and in another study zinc acetate was provided during the first phase of the study and zinc gluconate was given later [11]. We attempted to evaluate the possible modifying effect of current breastfeeding on the response to zinc supplementation, but this was not possible because of the lack of relevant information in the available reports.

Selected initial characteristics of the subjects enrolled in the trials are presented in **table 1**. The mean initial age at enrollment varied greatly among studies. Some studies enrolled infants within a few days after birth [12, 27, 30, 78], whereas one study enrolled children with a mean initial age of 11.1 years [10].

Results

Diarrhea morbidity. Information on diarrhea incidence was available from 24 studies, which enrolled a total of 16,339 children. These studies provided 33 distinct comparisons of zinc supplements, with or without other nutrients, versus the same preparations without zinc. The treatment groups received just zinc or placebo in 16 comparisons. In five comparisons, both groups also received iron, with or without vitamin A; and in four comparisons, the treatment groups received vitamin A plus a micronutrient other than iron. Three comparisons provided vitamin C or B vitamins, with or without zinc. Five additional comparisons investigated MMN, with and without zinc. The mean age of the study participants ranged from newborns to approximately 4 years.

There was a significant 20% lower incidence of diarrhea among children who received zinc supplementation (relative risk, 0.80; 95% CI, 0.71 to 0.90; $p = .0004$, random-effects model) (**fig. 2**). Because of significant heterogeneity among studies ($p < .0001$), a meta-regression analysis was completed. The mean initial age of the study subjects was highly significantly associated with the magnitude of the effect of zinc supplementation ($p < .001$), and the groupwise comparisons are displayed by mean initial age in **figure 3**. Inspection of the figure indicates that the beneficial effect of zinc supplements on diarrhea incidence was limited to studies of children with a mean initial age greater than 12 months. Among studies of children with mean age initial age greater than 12 months, the relative risk of diarrhea incidence was 0.73 (95% CI, 0.61 to 0.87; $p = .0014$).

TABLE 1. Selected characteristics of double-blind, randomized, controlled trials in prepubertal children and study subjects for each group comparison

Country, year [reference] author	Selection criteria for study population[a]	Group comparison[b]	Sample size[c]	% male	Supplementation scheme				Mean initial characteristics[c]			
					Duration (mo)	Frequency	Zinc dose (mg)	Other micronutrients[d]	Age (mo)	Serum zinc concentration (μg/dL)	HAZ	WAZ
Bangladesh, 2001 [19–21] Rahman	Unselected infants	Placebo Zinc	325	50.5	0.46	Daily	20	None	23.7	73.5	−2.41	−2.35
		Vitamin A Vitamin A + zinc	328	55.5	0.46	Daily	20	200,000 IU vitamin A[e]	23.7	70.9	−2.41	−2.42
Bangladesh, 2002 [22] Osendarp [23] Hamadani	Unselected children	Placebo Zinc	301	44.5	4.6	Daily	5	None	0.9	NA	NA	NA
Bangladesh, 2003a [24] Albert	Unselected infants	Placebo Zinc	126	57.0	1.38	Daily	20	None	39.0	62.0	NA	NA
		Vitamin A Vitamin A + zinc	123	55.0	1.38	Daily	20	200,000 IU vitamin A[e]	41.0	62.0	NA	NA
Bangladesh, 2003b [95, 97] Baqui [96] Black	Unselected infants[f]	Vitamin A + vitamin B_2 Vitamin A + vitamin B_2 + zinc	318	44.4	6	Weekly	20	100,000 IU vitamin A[e]; 1 mg vitamin B_2	6.3	67.9	−1.20	−1.00
		Vitamin A + vitamin B_2 + iron Vitamin A + vitamin B_2 + iron + zinc	327	44.9	6	Weekly	20	100,000 IU vitamin A[e]; 1 mg vitamin B_2, 20 mg iron	6.3	66.7	−1.20	−1.05
Bangladesh, 2005 [98] Brooks	Unselected infants	Placebo Zinc	1,621	52.0	12	Weekly	70	None	5.3	64.5	−1.30	−1.62
Brazil, 1998 [12] Lira [13] Ashworth	LBW infants	Placebo Zinc	134	44.5	1.84	6/wk	1	None	0.0	NA	NA	NA
Brazil, 2000 [25] Sayeg Porto	Children with HAZ < −2	Placebo Zinc	18	50.0	6	Daily	42	None	118.2	100.5	−2.67	NA
Burkina Faso, 2001 [69, 70] Müller	Unselected pre-schoolchildren	Placebo Zinc	685	49.5	6	6/wk	12.5	None	18.1	76.5	−1.55	−2.00
Canada, 1989 [26] Gibson	Boys with HAZ < 15%	Placebo Zinc	60	100.0	12	Daily	10	None	75.8	104.9	−1.39	−0.18

Chile, 1994 [9] Castillo-Duran	Children with HAZ < 5% percentile	Placebo Zinc	42	52.4	12	Daily	10	None	104.3	NA	−2.42	NA
Chile, 1995 [27] Castillo-Duran	SGA infants	MMN MMN + zinc	68	47.1	6	Daily	3	1,500 IU vitamin A, 50 mg vitamin C, 400 IU vitamin D; 1–2 mg/kg iron[g]	0.1	NA	NA	NA
Chile, 1997 [28] Ruz	Unselected preschoolchildren	Placebo Zinc	98	50.0	14	Daily	10	None	39.8	114.1	−0.52	0.13
Chile, 2001 [29] Castillo-Duran	Infants with birthweight > 2,300 g	Placebo Zinc	112	50.9	12	Daily	5	1–2 mg/kg iron[g]	0.3	NA	NA	NA
China, 1992 [30] Hong	Infants of high-risk pregnancy	B vitamins B vitamins + zinc	65	50.0	6	Daily	7.6	B vitamins[h]	0.1	86.0	NA	NA
China, 1998 [71] Sandstead [72] Penland	Unselected children	MMN MMN + zinc	230	50.0	2.3	6/wk	20	2,500 IU vitamin A, 0.9 mg vitamin B_1, 1.1 mg vitamin B_2, 12 mg vitamin B_3, 1.1 mg vitamin B_6, 35 µg folic acid, 400 IU vitamin D, 7 mg vitamin E, 20 µg vitamin K, 1 mg copper, 20 µg selenium, 90 µg iodine, 1 mg fluoride, 1.5 mg manganese, 30 µg molybdenum, 30 µg chromium	90.0	86.3	NA	NA
China, 2002 [73] Yang	Preschoolchildren with HAZ < −1	Placebo Zinc	61	49.2	12	5/wk	3.5	None	49.1	NA	NA	NA
		Vitamin A + calcium Vitamin A + calcium + zinc	55	50.9	12	5/wk	3.5	200 µg vitamin A, 150 mg calcium	47.1	NA	NA	NA
Ecuador, 1994 [74] Dirren	Unselected preschoolchildren	Placebo Zinc	96	60.0	15	6/wk	10	None	31.5	74.3	−2.90	−1.76
Ecuador, 1996 [31] Sempertegui	Preschoolchildren with WAZ < 10th percentile or HAZ < 10th percentile	Placebo Zinc	48	56.0	2	Daily	10	None	42.3	86.5	−2.00	−1.40

continued

TABLE 1. Selected characteristics of double-blind, randomized, controlled trials in prepubertal children and study subjects for each group comparison *(continued)*

Country, year [reference] author	Selection criteria for study population[a]	Group comparison[b]	Sample size[c]	% male	Supplementation scheme				Mean initial characteristics[c]			
					Duration (mo)	Frequency	Zinc dose (mg)	Other micronutrients[d]	Age (mo)	Serum zinc concentration (μg/dL)	HAZ	WAZ
Ecuador, 2008[i] [32] Wuehler	Nonanemic preschool-children with HAZ < –1.3 for children 12–23 mo of age, < –1.5 for children 24–30	Placebo	251	53.1	6	Daily	3	None	21.1	71.6	–2.3	–1.3
		Zinc (3 mg)										
		Placebo	253	53.1	6	Daily	7	None	21.0	71.7	–2.3	–1.3
		Zinc (7 mg)										
		Placebo	253	53.1	6	Daily	10	None	20.9	72.0	–2.3	–1.3
		Zinc (10 mg)										
Ethiopia, 2000 [75] Umeta	Stunted infants with HAZ < –2	Placebo	90	53.3	6	6/wk	10	None	9.6	NA	–2.81	–2.58
		Zinc (stunted)										
	Nonstunted infants matched by age and sex	Placebo	94	46.8	6	6/wk	10	None	9.3	NA	–0.64	–1.40
		Zinc (nonstunted)										
France, 1992 [33] Walravens	Breastfed infants	Vitamin D	57	52.7	3	Daily	5	Vitamin D[h]	5.5	NA	0.12	0.76
		Vitamin D + zinc										
Gambia, 1993 [11] Bates	Unselected preschoolchildren	Placebo	109	50.0	15	2/wk	70	None	17.7	NA	NA	NA
		Zinc										
Guatemala, 1993 [76] Cavan [77] Grazioso	Unselected children	MMN	162	50.0	5.75	6/wk	10	1.5 mg vitamin B_1, 1.2 mg vitamin B_2, 20 mg vitamin B_3, 10 mg vitamin B_5, 1 mg vitamin B_6, 6 μg vitamin B_{12}, 100 μg folic acid, 100 mg vitamin C, 10 μg vitamin D, 3.3 mg vitamin E, 50 μg copper, 2 mg chromium, 110 μg iodine, 50 μg selenium, 110 mg magnesium	81.8	93.5	–1.38	–0.85
		MMN + zinc										
Guatemala, 1997 [34] Ruel [35] Bentley [36] Rivera	Unselected infants	Placebo	89	57.1	7	Daily	10	None	7.6	NA	–2.16	–1.18
		Zinc										

India, 1996 [37–42] Sazawal	Preschoolchildren with diarrhea in past 24 h	MMN MMN + zinc	609	52.3	6	Daily	10	240 RE vitamin A, 0.6 mg vitamin B_1, 0.5 mg vitamin B_2, 10 mg vitamin B_3, 0.5 mg vitamin B_6, 100 IU vitamin D, 3 mg vitamin E	16.0	64.8	NA	NA
India, 2001 [43] Sazawal [44] Black	SGA infants	Vitamin B_2 Vitamin B_2 + zinc	584	50.0	9	Daily	5	0.5 mg vitamin B_2	0.5	NA	NA	NA
		MMN MMN + zinc	570	50.0	9	Daily	5	0.5 mg vitamin B_2, 60 μmol folic acid, 180 mg calcium, 90 mg phosphorus, 10 mg iron	0.5	NA	−1.80	NA
India, 2002 [45, 47] Bhandari [46] Taneja	Unselected preschoolchildren	Vitamin A Vitamin A + zinc	2,482	52.4	4	Daily	20[j]	200,000 IU vitamin A[e,j]	15.3	62.0	NA	NA
India, 2003a[i] [94] Gupta	Unselected preschoolchildren	Placebo Daily zinc	189	46.1	3.68	5/wk	10	None	23.5	NA	NA	NA
		Placebo Weekly zinc	185	46.0	3.68	Weekly	50	None	23.5	NA	NA	NA
India, 2003b [78] Sur	LBW infants	B vitamins B vitamins + zinc	100	50.0	12	5/wk	4.5	B vitamins[h]	0.1	114.1	NA	−2.14
India, 2007a [48] Bhandari	Unselected infants and preschoolchildren	Folic acid + iron Folic acid + iron + zinc	94,359	52.7	12	Daily	10[k]	12.5 mg iron,[k] 50 μg folic acid[k]	11.7	64.1	NA	NA
India, 2007b [99] Gupta	Unselected preschoolchildren	B vitamins B vitamins + zinc	1,712	49.0	6	Weekly	49.3	B vitamins[h]	NA	NA	NA	NA
Indonesia, 2001 [79] Dijkhuizen [80, 81] Wieringa	Unselected infants	Placebo Zinc	238	50.0	6	5/wk	10	None	4.2	NA	−0.79	−0.05
		Iron Iron + zinc	240	50.0	6	5/wk	10	10 mg iron	4.2	NA	−0.90	−0.06
		Vitamin A Vitamin A + zinc	129	50.0	6	5/wk	10	2.4 mg β-carotene	4.2	NA	NA	NA
Indonesia, 2003 [49, 50] Lind	Unselected infants[f]	Vitamin C Vitamin C + zinc	336	53.0	6	Daily	10	30 mg vitamin C	6.2	59.3	−0.37	−0.39
		Vitamin C + iron Vitamin C + iron + zinc	330	50.5	6	Daily	10	30 mg vitamin C, 10 mg iron	6.2	58.6	−0.32	−0.39

continued

TABLE 1. Selected characteristics of double-blind, randomized, controlled trials in prepubertal children and study subjects for each group comparison *(continued)*

Country, year [reference] author	Selection criteria for study population[a]	Group comparison[b]	Sample size[c]	% male	Supplementation scheme				Mean initial characteristics[c]			
					Duration (mo)	Frequency	Zinc dose (mg)	Other micronutrients[d]	Age (mo)	Serum zinc concentration (μg/dL)	HAZ	WAZ
Indonesia, 2007 [51] Fahmida	Unselected infants[f]	Vitamin A Vitamin A + zinc	391	49.9	6	Daily	10	100,000 IU vitamin A[e]	5.1	100.0	−0.99	−0.54
Jamaica, 1998 [52] Meeks Gardner	Preschoolchildren with HAZ < −2 and WAZ < median	MMN MMN + zinc	61	42.6	2.76	Daily	5	1,500 IU vitamin A, 0.5 mg vitamin B_1, 0.8 mg vitamin B_2, 7 mg vitamin B_3, 1 mg vitamin B_6, 30 mg vitamin C, 400 IU vitamin D	14.1	NA	−2.85	NA
Jamaica, 2005 [53] Meeks Gardner	Preschoolchildren with WAZ < −1.5	MMN MMN + zinc	114	33.2	6	Daily	10	1,500 IU vitamin A, 0.5 mg vitamin B_1, 0.8 mg vitamin B_2, 7 mg vitamin B_3, 1 mg vitamin B_6, 2 μg vitamin B_{12}, 1 mg folic acid, 30 mg vitamin C, 400 IU vitamin D, 8 mg iron	18.8	NA	−1.42	−2.16
Mexico, 1997 [82] Rosado [83] Allen [84] Munoz	Unselected preschoolchildren	Placebo Zinc	109	48.2	12	6/wk	20	None	28.7	89.8	−1.71	−1.40
		Iron Iron + zinc	108	45.0	12	6/wk	20	20 mg iron	28.2	103.7	−1.55	−1.40
Mexico, 2005 [85] Kordas [86] Rosado [87] Rico	Unselected children[l]	Placebo Zinc	252	56.8	6	5/wk	30	None	84.0	81.6	NA	NA
		Iron Iron + zinc	265	56.2	6	5/wk	30	30 mg iron	84.0	77.6	NA	NA
Mexico, 2006 [54] Long	Unselected infants	Placebo Zinc	364	49.5	12	Daily	20	None	9.9	NA	0.08	0.09
		Vitamin A Vitamin A + zinc	372	54.0	12	Daily	20	20,000 IU vitamin A for ≤ 1 yr of age; 45,000 IU for > 1 yr of age every 2 mo	9.7	NA	0.13	0.10

Nepal, 2006 [55, 56] Tielsch	Unselected infants and preschoolchildren	Vitamin A Vitamin A + zinc Vitamin A + folic acid + iron Vitamin A + folic acid + iron + zinc	13,385 17,079 	50.0 50.0 	13.7 13.7 	Daily Daily 	10[j] 10[j] 	200,000 IU vitamin A[j] every 6 mo 50 µg folic acid[j], 12.5 mg iron[j]; 200,000 IU vitamin A[j] every 6 mo 	12.4 12.4 	NA NA 	NA NA 	NA NA
Papua New Guinea, 2000 [88] Shankar	Unselected preschoolchildren	Placebo Zinc	274	47.0	10.58	6/wk	10	None	31.4	70.5	−1.90	NA
Peru, 2004a [89] Alarcon	Anemic preschoolchildren (hemoglobin 70–99.9 g/L)	Iron Iron + zinc	223	50.0	4.14	6/wk	7.3	3 mg/kg/day iron	17.4	NA	−1.04	−0.25
Peru, 2004b [57] Penny	Children with persistent diarrhea (> 14 days)	Vitamin C Vitamin C + zinc	159	50.3	6	Daily	10	50 mg vitamin C	18.9	70.3	−1.56	−1.13
Peru, 2007 [58] Brown	Infants with LAZ < −0.5 and WLZ > −3	MMN MMN + zinc	200	48.5	6	Daily	3	225 µg RE vitamin A, 0.5 mg vitamin B_1, 0.38 mg vitamin B_2, 3.8 mg vitamin B_3, 2.5 mg vitamin B_5, 0.5 mg vitamin B_6, 50 µg biotin, 20 mg vitamin C, 225 IU vitamin D, 3.8 mg vitamin E, 0.7 mg iron[m]	7.5	77.6	−1.19	−0.75
South Africa, 2005 [59] Bobat	HIV-positive preschoolchildren	MMN[n] MMN + zinc[n]	96	48.9	6	Daily	10	1,000 IU vitamin A, 1.5 mg vitamin B_1, 1.2 mg vitamin B_2, 10 mg vitamin B_3, 1 mg vitamin B_6, 50 mg vitamin C, 400 IU vitamin D	38.3	NA	−1.60	NA
Tanzania, 2006 [60, 61] Sazawal [62] Olney	Unselected infants and preschoolchildren	Vitamin A Vitamin A + zinc Vitamin A + folic acid + iron Vitamin A + folic acid + iron + zinc	42,546 16,070 	50.3 50.5 	12.7 12.7 	Daily Daily 	10[j] 10[j] 	200,000 IU vitamin A[j] every 6 mo 200,000 IU vitamin A[j] every 6 mo; 50 µg folic acid[j], 12.5 mg iron[j]	18.1 18.1 	NA NA 	−1.48 −1.45 	−1.28 −1.15

continued

TABLE 1. Selected characteristics of double-blind, randomized, controlled trials in prepubertal children and study subjects for each group comparison *(continued)*

Country, year [reference] author	Selection criteria for study population[a]	Group comparison[b]	Sample size[c]	% male	Supplementation scheme				Mean initial characteristics[c]			
					Duration (mo)	Frequency	Zinc dose (mg)	Other micronutrients[d]	Age (mo)	Serum zinc concentration (μg/dL)	HAZ	WAZ
Thailand, 1992 [90] Udomkesmalee [91] Kramer	Infants with serum retinol concentration < 1.05 μmol/L and serum zinc concentration < 12.2 μmol/L	Placebo Zinc	68	47.4	6	5/wk	25	None	110.5	86.3	NA	NA
		Vitamin A Vitamin A + zinc	65	69.5	6	5/wk	25	1,500 RE vitamin A	113.0	85.3	NA	NA
Thailand, 2006 [63] Wasantwisut	Unselected infants[f]	Vitamin A + vitamin C Vitamin A + vitamin C + zinc	304	51.5	6	Daily	10	1,500 RE vitamin A[e], 30 mg vitamin C	4.5	73.8	−0.69	−0.18
		Vitamin A + vitamin C + iron Vitamin A + vitamin C + iron + zinc	305	50.0	6	Daily	10	1,500 RE vitamin A[e], 30 mg vitamin C, 10 mg iron	4.5	71.0	−0.66	−0.12
Uganda, 1998 [92] Kikafunda	Unselected preschool and school-aged children	Placebo Zinc	153	54.1	8	3.75/wk	10	None	55.8	NA	−0.70	−0.41
USA, 1983 [64] Walravens	Preschoolchildren with HAZ < 10th percentile	Placebo Zinc	40	65.0	12	Daily	10	None	50.0	72.0	−2.07	−1.76
USA, 1989 [65] Walravens	Preschoolchildren with documented decline of ≥ 20 percentile in WAZ	Placebo Zinc	50	52.0	6	Daily	5.7	None	15.2	70.0	−1.35	−2.04
USA, 2006 [66] Heinig	Breastfed infants with birthweight > 2,500 g	Placebo Zinc	82	50.0	6	Daily	5	None	4.0	73.3	0.37	0.61

Vietnam, 1996 [67] Ninh	Preschoolchildren with WAZ < −2 and HAZ < −2	Placebo Zinc	146	50.0	5	Daily	10	None	17.6	NA	−2.91	−2.61
Vietnam, 2006 [68] Berger	Unselected infants[f]	Vitamin A Vitamin A + zinc	393	50.4	6	Daily	10	100,000 IU vitamin A[e]	5.8	94.8	−1.01	−0.56
		Vitamin A + iron Vitamin A + iron + zinc	391	47.7	6	Daily	10	100,000 IU vitamin A[e]; 10 mg iron	5.9	92.7	−1.06	−0.58
Zimbabwe, 1997 [10, 93] Friis	Unselected children	Placebo Zinc	313	46.0	12.2	3.5/wk	40	None	133.8	77.8	−1.18	−1.27

HAZ, height-for-age z-score; HIV, human immunodeficiency virus; LAZ, length-for-age z-score; LBW, low-birthweight; MMN, multiple micronutrients with at least four micronutrients; RE, retinol equivalent; SGA, small-for-gestational age; WAZ, weight-for-age z-score; WLZ, weight-for-length z-score; NA, not available

a. Only major selection criteria are listed here. A study population is considered "unselected" if the inclusion and exclusion criteria were such that almost all screened participants were eligible to participate in the study.

b. The study treatment groups included into a group comparison analysis differed only by the presence or absence of zinc in the supplement.

c. Total sample size and mean initial characteristics of both study groups combined, which were included into a group comparison.

d. All nutrients listed were provided to both study groups within a group comparison

e. Single-dose vitamin A was provided in all studies at baseline, except for Bangladesh 2001 [19, 20], in which it was provided at day 14.

f. Selected for breastfeeding, but more than 90% of the population was eligible for the study. The study population is therefore considered representative and defined as "unselected."

g. Iron supplementation after 4 months [27] and 5 months [29] of age.

h. No information on amount of micronutrients provided.

i. If a study included several zinc groups (different dosage or frequency), each groupwise comparison includes the placebo group and the respective zinc group.

j. Half the dose for children less than 12 months of age.

k. Half the dose for children less than 6 months of age.

l. Children with blood lead levels greater than 45 μg/dL and hemoglobin less than 90 g/L were excluded. However, 99.8% of the children screened were eligible and are therefore considered representative and defined as "unselected."

m. Children were also provided iron in iron-fortified cereal porridge separate from an aqueous multivitamin dose (containing zinc in the zinc group).

n. Most children received multivitamin supplement and cotrimoxazole.

Besides mean age, the magnitude of the effect of zinc supplementation on the incidence of diarrhea was negatively associated with the baseline anthropometric status of the study population (initial height, $p = .033$; initial weight, $p = .032$) and positively associated with the mean initial serum ferritin concentration ($p = .036$). However, there were no significant correlations between the daily zinc dose, inclusion of other micronutrients in the supplement preparation, or the duration of supplementation and the impact of supplementation on diarrhea incidence. We also examined whether methodologic issues, such as the duration of recall for illness reporting and whether the reports were based on specific signs of diarrhea or parental perceptions of illness, affected the conclusions. We found that there was no relation between the specific study methods and the effect size of the zinc response.

Data were available on the duration of diarrhea from just nine studies, which provided 13 groupwise comparisons among a total of 1,692 children. The mean age of the study participants ranged from 6 to 29 months. Unlike what has been reported previously from diarrhea treatment studies [100], there was no significant effect of preventive zinc supplementation on the duration of diarrhea in these community-based trials (effect size, 0.041; 95% CI, −0.216 to 0.299; $p = .73$, random-effects model).

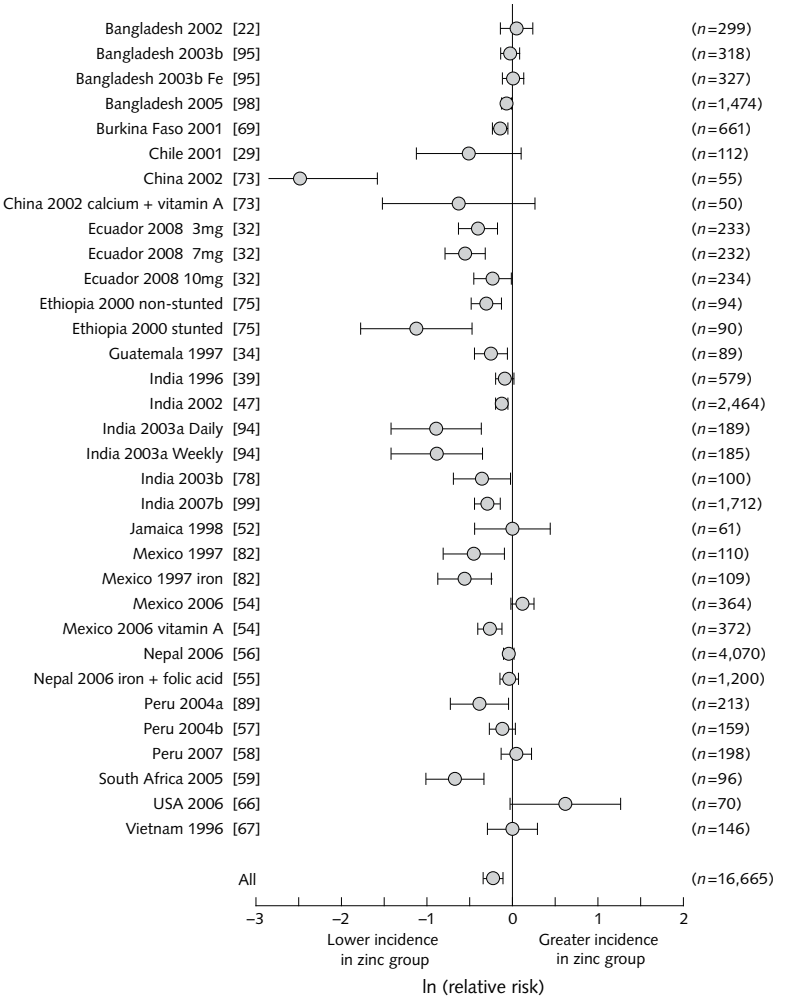

FIG. 2. Effect of zinc supplementation on diarrhea incidence from 24 intervention trials with 33 groupwise comparisons in which the supplements differed only by the presence or absence of zinc.

Respiratory disease morbidity. Analyses related to respiratory disease were restricted to studies that provided information on the incidence of ALRI, using either the World Health Organization (WHO) definition of ALRI, based on age-specific elevated respiratory rates [101], or clinical (auscultory or radiologic) evidence of pneumonia, as defined by the authors. When data were reported for elevated respiratory rates, both with and without associated severity signs, such as cough, difficulty breathing, fever, or lethargy, the illness rates based on the more severe degree of ALRI were used preferentially. Likewise, when information was available from both fieldworkers and physicians, illness rates based on the physicians' examinations were the ones included in the analysis. We also considered a second tier of studies that reported ALRI based on rapid breathing or difficulty breathing, as reported by the caregiver. Information was available from seven studies based on the former, objective criteria [32, 41, 45, 57–59, 98] and from five studies based on reported symptoms only [22, 54–56, 95].

The combined set of studies yielded a total of 16 treatment comparisons from 12 studies with a total of 12,144 subjects. The children's mean initial age ranged from 0.9 to 49 months. Zinc supplements were compared with placebo in six treatment group comparisons. Three comparisons were of MMN, with and without zinc, one of vitamin C, with or without zinc, and six of vitamin A with other micronutrients, such as iron, iron and folic acid, or vitamin B_2, with and without zinc. Overall, there was a significant 15% reduction in ALRI (relative risk, 0.85; 95% CI, 0.75 to 0.97; $p = .017$,

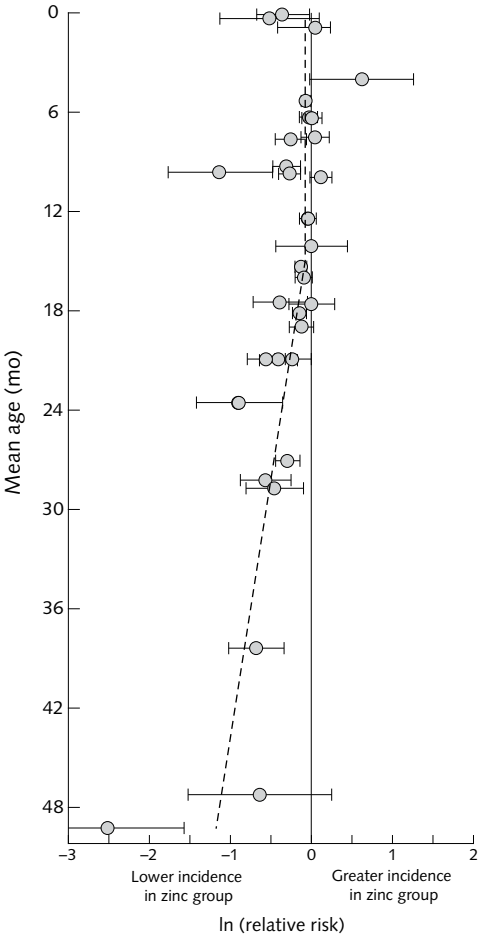

FIG. 3. Effect of zinc supplementation on diarrhea incidence, according to mean initial age of study subjects in each trial. The curve represents ln(risk ratio) = − 0.081 for age less than 15 months, − .081 − .032*(age − 15) for age greater than 15 months

random-effects model) (**fig. 4**). There was significant heterogeneity among studies ($p = .008$). The two factors that were significantly associated with the magnitude of reduction of relative risk of ALRI following zinc supplementation were the initial height-for-age z-score (HAZ) ($p = .010$) and the quality of ALRI diagnosis ($p = .024$). Specifically, studies that enrolled children who initially were more stunted found a greater impact of zinc supplements on ALRI reduction, as did those studies that relied on more rigorous diagnostic criteria. The relative risk for those studies that diagnosed ALRI based on counting respiratory rate or a physician's examination was 21% less in the zinc group than in the comparison group (relative risk, 0.79; 95% CI, 0.67 to 0.94; $p = .013$, random-effects model). In contrast, the studies that based the diagnosis only on reported rapid breathing or difficulty breathing (without a physician's examination) found no significant difference between the group that received zinc and the comparison group (relative risk, 0.99; 95% CI, 0.91 to 1.08; $p = .78$, random-effects model). When both factors (initial HAZ and diagnostic rigor) were included in the explanatory models, only HAZ remained statistically significant.

Malaria morbidity. The effects of zinc supplementation on the risk of malaria were examined in the first technical document prepared by the International Zinc Nutrition Consultative Group (IZiNCG) [102]. At that time, the results of just three intervention trials were available, two of which found 32% (Gambia 1993 [11]) and 38% (Papua New Guinea 2000 [88]) reductions in clinic visits for malaria, and one of which found no impact on the incidence of cases detected by daily home visits (Burkina Faso 2001 [69]). The former IZiNCG review concluded that zinc supplementation may ameliorate the severity of malaria infections, hence reducing the number of clinic visits, possibly without affecting the overall incidence of infections. However, the number of available trials was too small to allow definitive conclusions to be drawn.

Since then, only two new relevant studies have become available, neither of which fulfilled the inclusion criteria for the present review. A study in the Peruvian Amazon enrolled children from 0.5 to 15 years of age, some of whom exceeded the age range established for the present review [8]. Children who received either zinc or zinc plus iron had ~15% fewer episodes of *Plasmodium vivax* infections, as assessed by twice-weekly home visits, compared with the placebo group, although the results were not statistically significant ($p > .36$). However, there was a significant interaction between age group and treatment group, such that, among children less than 5 years of age, those who received zinc without iron had an incidence rate ratio (IRR) of 0.43 (95% CI, 0.17 to 1.10; $p = .079$), and those who received zinc with iron had an IRR of 0.30 (95% CI, 0.12 to 0.80; $p = .016$), compared with the placebo group. However, among children aged 5 years or older, there was no significant effect of zinc alone or zinc plus iron. In another study recently completed in Burkina Faso, children were randomly assigned to receive either daily zinc supplements plus a single large dose of vitamin A or placebo supplements [103]. There was a 22% lower rate of fever in the supplemented group, as diagnosed during daily home visits, and a 30% reduction in malaria incidence, as determined during clinic visits. However, because of the intervention design, which included both zinc and vitamin A, it was not possible to determine whether the results were uniquely attributable to the zinc supplements.

In summary, there is still insufficient evidence to allow definitive conclusions to be drawn regarding the effect of zinc supplementation on the risk of malaria, although the weight of currently available information suggests that zinc may reduce the incidence of malaria,

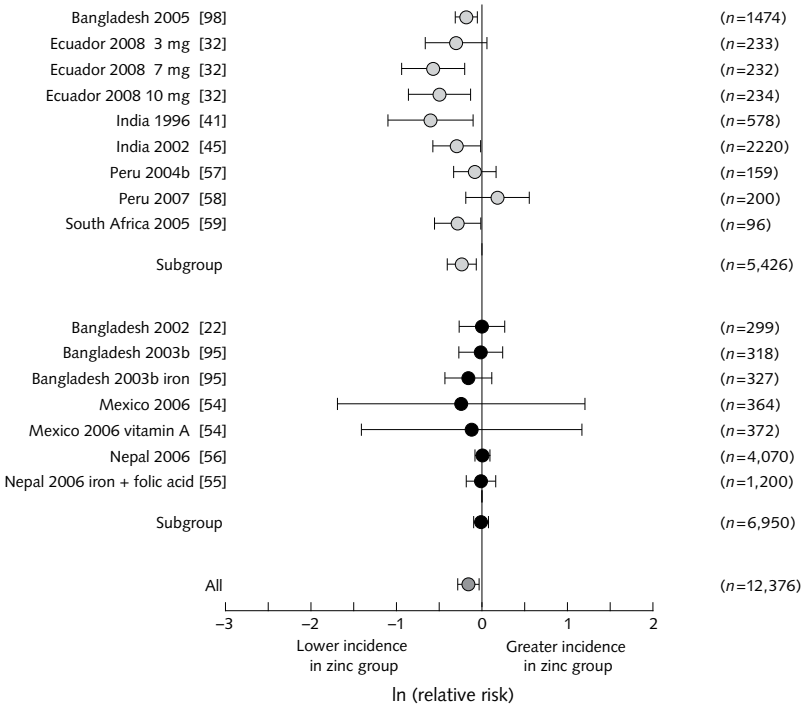

FIG. 4. Effect of zinc supplementation on the incidence of acute lower respiratory tract infection (ALRI)[a] from 12 intervention trials with 16 groupwise comparisons in which the supplements differed only by the presence or absence of zinc.

a. Gray circles indicate studies in which ALRI was diagnosed by fieldworkers or physicians by using objective clinical signs; black circles indicate studies in which the diagnosis was based on caregiver reports of elevated respiratory rate or difficulty breathing

especially that of more severe cases that result in clinic attendance.

Mortality. Thirteen pertinent groupwise comparisons of mortality outcomes were available from 10 studies. Seven of these studies were carried out in unselected study populations [45, 48, 55, 56, 60, 61, 69, 88, 98], one included only low-birthweight infants [12], one included only SGA infants [43], and one enrolled only children with human immunodeficiency virus (HIV) infection [59]. Three of the group comparisons completed among unselected children were from large-scale studies carried out in Tanzania 2006 (n = 16,070 [60]), Nepal 2006 (n = 17,079 [55]), and India 2007a (n = 78,346 [48]), in which zinc plus iron and folic acid was compared with iron and folic acid only, and two were from the same studies in Tanzania 2006 (n = 42,546 [61]) and Nepal 2006 (n = 25,018 [56]), in which zinc was compared with placebo. Four smaller studies also compared mortality outcomes following supplementation with zinc or placebo (Bangladesh 2005, n = 1,474 [98]; India 2002, n = 2,482 [45]; Papua New Guinea 2000, n = 274 [88]; Burkina Faso 2001, n = 685 [69]) in unselected children. These latter studies were not originally designed with sufficient statistical power to detect small differences in mortality outcomes, so the results may be susceptible to publication or reporting bias. Some of the studies also provided a single high-dose vitamin A supplement at baseline [45] or every 6 months during the study period [55, 56, 60, 61]. Although the distribution of high-dose vitamin A supplements was not reported in the other studies [48, 69, 88, 98], children may have received such supplements as part of ongoing national programs.

Overall, there were 1,407 deaths among the 100,081 children in the control groups (1.41%) and 1,328 deaths among the 101,535 children in the zinc-supplemented groups (1.31%). The estimated relative risk of mortality was 0.94 (95% CI, 0.86 to 1.02; p = .11, random-effects model) (**fig. 5**). There was significant heterogeneity in the results (p = .005), but the number of studies was too small to explore systematically the specific sources of heterogeneity.

Because of the heterogeneity among studies and the fact that the results are dominated by the larger trials in Nepal 2006 [55, 56], Tanzania 2006 [60, 61], and India 2007a [48] (with five groupwise comparisons), we reexamined the outcomes for specific age subgroups presented within these three larger trials and whether or not iron and folic acid were provided

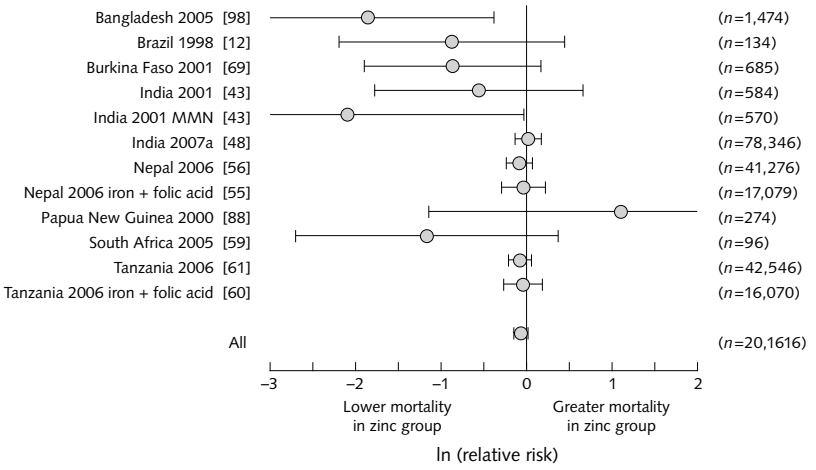

FIG. 5. Effect of zinc supplementation on childhood mortality from 10 intervention trials[a] with 13 groupwise comparisons in which the supplements differed only by the presence or absence of zinc.

a. The figure does not include the study by Bhandari et al. [45] (India, 2002; n = 2,482) because this study had no deaths in the zinc-supplemented group

along with zinc. The authors of these trials graciously provided the results of their respective studies disaggregated by age group (< 12 months or ≥ 12 months) for the comparisons of zinc versus placebo and zinc plus iron and folic acid versus iron and folic acid. We modeled the mortality data using mixed models with log relative risk as the outcome variable, with possible explanatory variables age group (as defined above), iron and folic acid treatment, study (a random effect), and their interactions. Notably, there was a significant (p = .04) interaction between age and supplementation with iron and folic acid, such that when zinc supplements were compared with placebo, there was a significantly lower mortality rate among the older children who did not receive iron and folic acid as compared with the other three groups. When iron and folic acid were provided along with zinc, there was no significant effect of zinc on mortality in either age group. The combined results are summarized in **table 2** by age group and treatment group.

In summary, when the results of these studies are combined, zinc supplementation reduced mortality of children 12 months of age or older by ~18% but had no effect on younger children. However, when iron and folic acid were provided in addition to zinc, the impact of zinc among older children was no longer evident. The remaining studies either enrolled only younger children or did not present the results disaggregated by age, so it is not possible to explore this issue further with the available information.

Among the studies of selected study populations, two enrolled low-birthweight [12] or SGA infants [43]. In the study Brazil 1998, low-birthweight infants received zinc or placebo [12], whereas the study India 2001

TABLE 2. Effect of supplementation with zinc only or zinc plus iron and folic acid on risk of death among children < 12 months or ≥ 12 months of age: Combined analyses of results from three large-scale trials (with five groupwise comparisons) [48, 55, 56, 60, 61]

Age group (mo)	Group comparison[a]	Sample size	Child-yr	Deaths	Mortality rate per 1,000 child-yr	Relative risk	95% CI	p
< 12	Zinc	27,440	15,328	385	25.1	1.05	0.91–1.21	.52
	Placebo	26,974	14,951	360	24.1			
≥ 12	Zinc	14,802	43,595	332	7.6	0.82	0.70–0.96	.013
	Placebo	14,606	43,343	406	9.4			
< 12	Folic acid + iron + zinc	32,859	23,410	349	14.9	0.97	0.82–1.15	.72
	Folic acid + iron	32,456	23,205	352	15.2			
≥ 12	Folic acid + iron + zinc	38,441	34,681	242	7.0	1.05	0.90–1.24	.52
	Folic acid + iron	37,721	33,977	230	6.8			

a. Refers to comparisons of treatment groups that differed only by the presence or absence of zinc. (i.e., zinc versus placebo or zinc plus iron and folic acid versus iron plus folic acid).

included two group comparisons in which SGA infants received vitamin B_2 with and without zinc or MMN with or without zinc [43]. Although the sample sizes were relatively small, both studies found 52% to 68% lower mortality rates among children who received zinc (Brazil 1998, $p = .33$; India 2001, $p = .04$). These results are consistent with the analyses by birthweight in Nepal 2006, where infants with birthweight less than 2,000 g who received zinc had a relative risk of mortality that was nearly half that of their counterparts who did not receive zinc (relative risk, 0.56; 95% CI, 0.30 to 1.04; $p = .06$). These combined sets of results indicate that providing preventive zinc supplementation in settings where there is an elevated risk of zinc deficiency would reduce mortality among children greater than 1 year of age and possibly among low-birthweight infants. However, additional studies are needed to confirm these two sets of results.

Physical growth. Information on change in height was available from 37 studies, which contained 47 groupwise comparisons. The mean initial HAZ ranged from −2.9 [67] to 0.36 [66], and the mean initial age ranged from less than 1 month [12] to 134 months [10]. There was a significantly greater change in height among children who received zinc supplements, with an overall effect size of 0.170 (95% CI, 0.075 to 0.264; $p = .001$, random-effects model) (**fig. 6**). There was significant heterogeneity among studies ($p < .0001$). The effect size for change in height was negatively correlated with concurrent administration of iron ($p = .04$) and vitamin A supplements ($p = .04$). Unlike the results of a previous meta-analysis of the effect of zinc supplementation on children's growth [1], which found a positive response to zinc only among those studies that enrolled children whose initial mean HAZ was less than approximately −1.5 z, there was no correlation between mean initial HAZ and effect size in the present analysis, even when the analysis was restricted to the subset of studies that

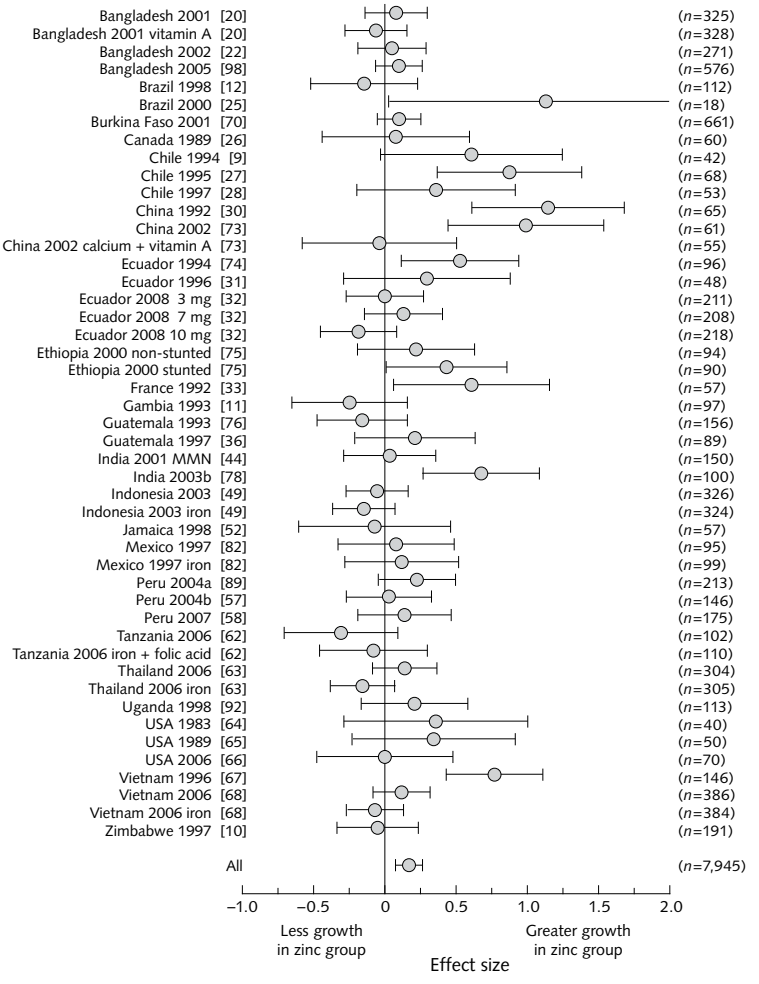

FIG. 6. Effect of zinc supplementation on change in height in prepubertal children from 37 controlled supplementation trials with 47 groupwise comparisons in which the supplements differed only by the presence or absence of zinc.

lasted at least 6 months or to those studies that enrolled children with a mean initial age less than 3 years. This difference from the earlier meta-analysis may be due to the exclusion of studies of hospitalized, severely malnourished children from the present analysis.

Thirty-five studies presented sufficient information to permit assessment of the effect of zinc supplementation on the change in weight from baseline to the end of the intervention. These studies provided 45 groupwise comparisons, and the mean initial weight-for-age z-score (WAZ) ranged from −2.61 [67] to 0.76 [33]. Zinc supplementation had a significant positive overall impact on change in weight, with a mean effect size of 0.119 (95% CI, 0.048 to 0.190; $p = .002$, random-effects model) (**fig. 7**). There was significant heterogeneity among studies ($p < .001$). The effect size for change in weight was negatively correlated with concurrent administration of iron supplements ($p = .002$), but not with any other characteristics of the studies or study subjects.

Twenty-two studies, with 30 groupwise comparisons, provided information on the effect of zinc supplementation on change in weight-for-height z-score (WHZ). There was a small, marginally significant, positive effect of zinc on change in WHZ (**fig. 8**). The estimated effect size was 0.062 (95% CI, 0.000 to 0.123; $p = .049$, random-effects model), and there was no significant heterogeneity among studies ($p = .28$).

There were 11 studies and 14 groupwise comparisons of the effect of zinc supplementation on change in mid-upper-arm circumference. Zinc supplementation did not have a significant effect on change in mid-upper-arm circumference (data not presented here).

In summary, zinc supplementation produced a small, but highly statistically significant, positive impact on children's linear growth and weight gain and a marginal effect on weight-for-height. There was significant heterogeneity in the results of studies of growth velocity,

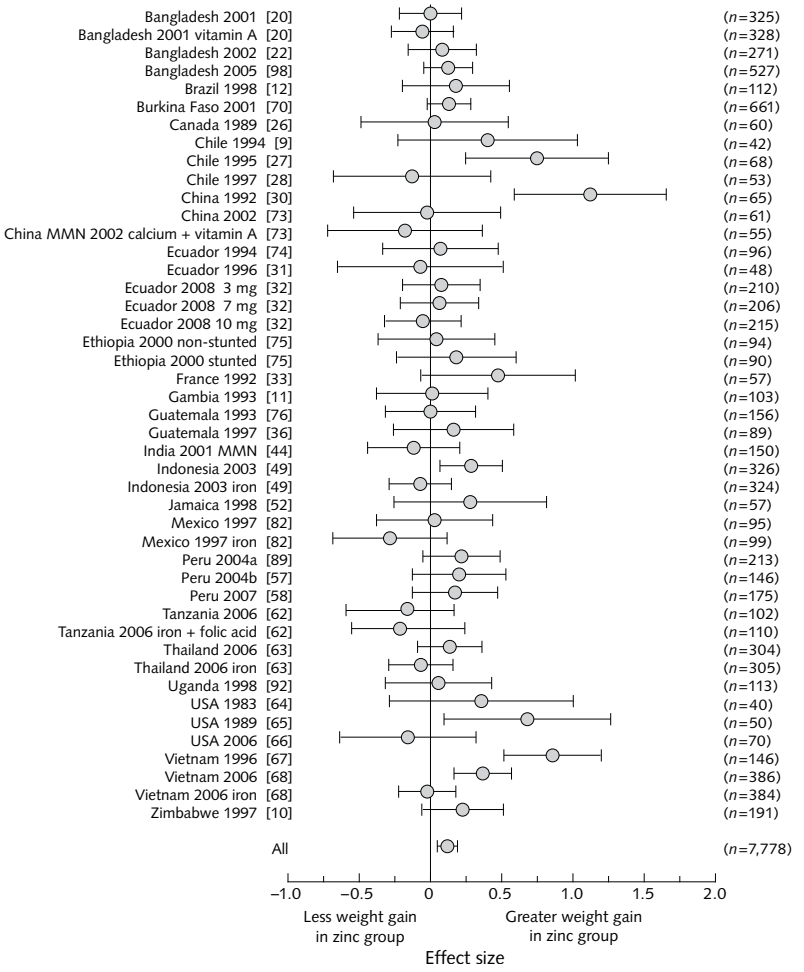

FIG. 7. Effect of zinc supplementation on change in weight in prepubertal children from 35 supplementation trials with 45 groupwise comparisons in which the supplements differed only by the presence or absence of zinc.

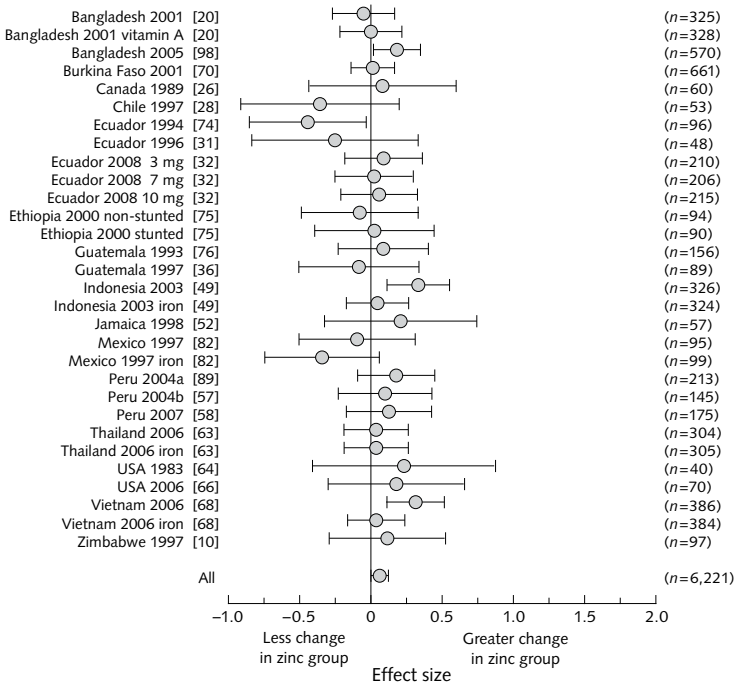

FIG. 8. Effect of zinc supplementation on change in weight-for-height z-score (WHZ) in prepubertal children from 22 controlled supplementation trials with 30 groupwise comparisons in which the supplements differed only by the presence or absence of zinc.

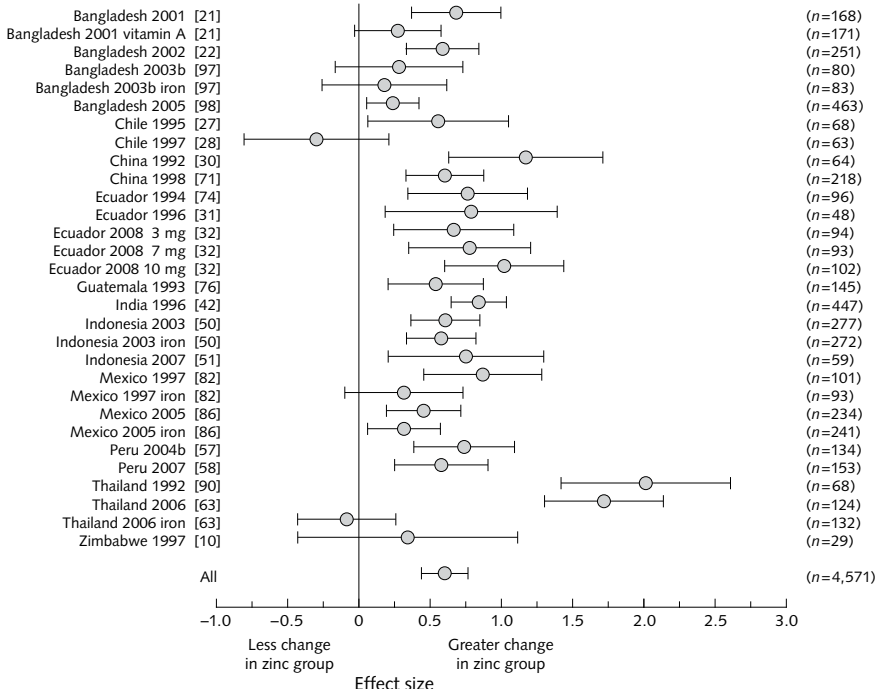

FIG. 9. Effect of zinc supplementation on change in serum or plasma zinc concentration in children from 22 controlled supplementation trials with 30 groupwise comparisons in which the supplements differed only by the presence or absence of zinc.

but the source of heterogeneity generally could not be identified, except for a negative association with concurrent supplementation of either iron or vitamin A for change in height and a negative association with concurrent iron supplementation for change in weight. There was no overall effect of zinc supplementation on mid-upper-arm circumference measurements.

Serum or plasma zinc concentration. Information on the change in serum or plasma zinc concentration was available from 22 intervention trials consisting of 30 groupwise comparisons (**fig. 9**). As in previous meta-analyses [1, 104], there was a consistent, moderately large, statistically significant positive effect of zinc supplementation on the change in serum zinc concentration, with an overall effect size of 0.602 (95% CI, 0.439 to 0.766; $p < .0001$, random-effects model). The daily zinc dose equivalents ranged from 2.9 to 21.4 mg of zinc/day, and the studies lasted from 2 weeks to 14 months. There was significant heterogeneity of results ($p < .001$), but the source of heterogeneity could not be identified.

Mental and motor development. The available studies that reported on children's developmental outcomes in relation to zinc supplementation varied greatly with regard to their developmental assessment methods. For the present analyses, we only considered studies that reported information on the mental development index (MDI) or psychomotor development index (PDI), using the Bayley Scales. Most studies did not present intraindividual changes in developmental scores during the course of the intervention, so only final values could be compared. Final MDI and PDI values were reported from seven studies that provided nine groupwise comparisons. The study duration ranged from 1.9 to 12 months, and just two studies lasted more than 6 months. Two comparisons evaluated the impact of zinc supplementation versus placebo [13, 23], and the others provided additional micronutrients, such as iron [29, 49, 96] or vitamin A [46, 96], to both groups. None of the studies found a significant positive effect of zinc on final MDI (**fig. 10**). The overall estimated effect size was 0.021 (95% CI, –0.133 to 0.175; $p = .76$, random-effects model). There was marginally significant heterogeneity among studies ($p = .065$), and there was a significant association between effect size for final MDI and the percentage of males enrolled in the individual studies ($p = .024$).

As with MDI, there was no significant overall impact of zinc supplementation on final PDI (**fig. 11**). The estimated effect size was 0.025 (95% CI, –0.149 to 0.198,

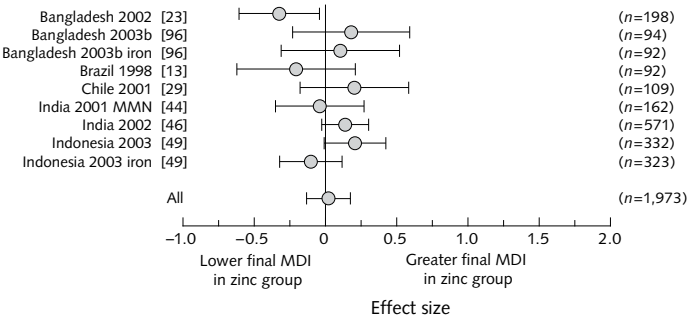

FIG. 10. Effect of zinc supplementation on final mental development index (MDI) among infants and young children from seven intervention trials with nine groupwise comparisons in which the supplements differed only by the presence or absence of zinc.

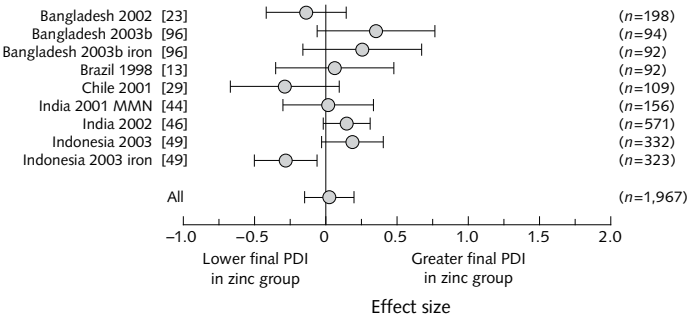

FIG. 11. Effect of zinc supplementation on final psychomotor development index (PDI) in infants and young children from seven zinc supplementation trials with nine groupwise comparisons in which the supplements only by the presence or absence of zinc.

$p = 0.75$, random-effects model). There was significant heterogeneity among studies ($p = .013$), but there were no significant correlations between study or subject characteristics and effect size.

Section 2

Are there adverse effects of preventive zinc supplementation?

Conclusions

According to the previous studies that have been used to define the safe upper level of zinc intake [105], the first signs of excessive intake are perturbations of copper and iron metabolism, resulting in impaired status of these nutrients. Thus, we have reviewed available studies that examined the impact of zinc supplementation on indicators of iron and copper status. There are no overall adverse effects of zinc supplementation on concentrations of hemoglobin, serum ferritin, and serum copper.

Detailed review of evidence

A number of studies have examined the effects of zinc supplementation on iron absorption and vice versa, either by using isotopic tracers during short-term studies to assess mineral absorption or by assessing biochemical and functional responses following longer-term supplementation. The tracer studies indicate that each mineral may interfere to some extent with absorption of the other, but only when they are provided simultaneously in aqueous solutions and in disproportionate molar doses [106]. However, there is no evidence of interference when they are delivered in near isomolar amounts or with food [107]. Some longer-term studies also suggest that when given together each mineral may reduce the magnitude of the response observed with single-nutrient supplementation [50, 68, 79], although nutritional status is still enhanced to a considerable extent despite the nutrient–nutrient interactions [108]. Less information is available with regard to interactions between zinc and copper, but some studies have found a negative effect of large-dose zinc supplementation on indicators of copper status in adults [109, 110].

Because some studies have noted negative effects of zinc supplementation on the absorption or status of other minerals, we completed a systematic analysis of the overall impact of preventive zinc supplementation trials on indicators of children's iron status (namely, hemoglobin and serum ferritin concentrations) and copper status (serum copper concentration). Studies were identified by using the same strategy described above in Section 1.

Hemoglobin and iron status. A total of 11 studies, which included 19 groupwise comparisons, provided information on the change in hemoglobin concentration following zinc supplementation. The daily dose equivalents for those 19 sets of observations ranged from 2.9 to 21.4 mg of zinc/day. Iron supplements were also provided in eight of these groupwise comparisons [50, 58, 62, 63, 83, 86, 89, 97]. Considering all of the available information, there is no overall effect of zinc supplementation on change in hemoglobin concentration (**fig. 12**). The estimated mean effect size was

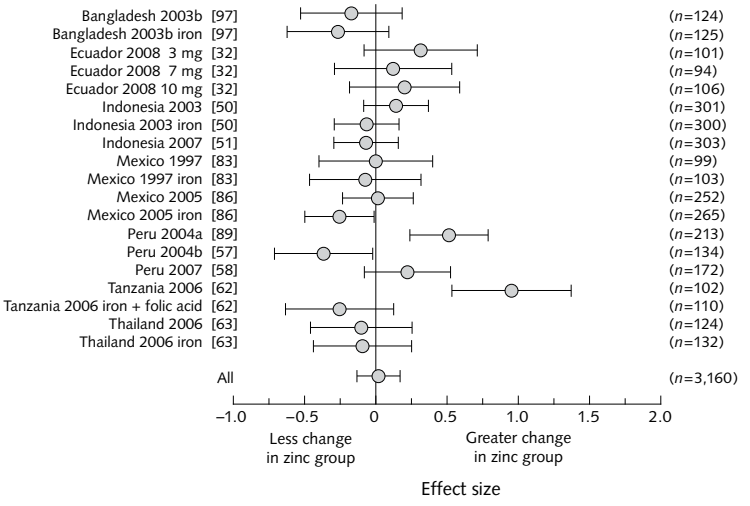

FIG. 12. Effect of zinc supplementation on change in hemoglobin concentration among children from 11 controlled zinc supplementation trials with 19 groupwise comparisons in which the supplements differed only by the presence or absence of zinc.

0.019 (95% CI, −0.132 to 0.170; $p = .80$, random-effects model). There was significant heterogeneity among studies ($p < .0001$), but no particular characteristics of the studies or the study subjects were associated with the magnitude of hemoglobin response. In particular, neither the daily zinc dose nor the presence of iron in the supplement was correlated with effect size of the change in hemoglobin concentration due to zinc.

Similarly, there was no overall effect of zinc supplementation on the change in serum or plasma ferritin concentration among the 17 available groupwise comparisons derived from 10 studies (**fig. 13**), 7 of which also provided iron [50, 58, 63, 83, 86, 89, 97]. The estimated effect size was 0.051 (95% CI, −0.150 to 0.252; $p = 0.60$, random-effects model). There was significant heterogeneity among comparisons ($p < .0001$); the magnitude of the change in serum ferritin concentration in relation to zinc supplementation was negatively correlated with the presence of iron in the supplement ($p = .024$), the mean initial hemoglobin concentration ($p = .018$), and the mean initial ferritin concentration ($p = .019$).

Copper status. Four studies involving eight groupwise comparisons supplied results on the change in serum copper concentration following zinc supplementation (**fig. 14**). There was no overall effect of zinc supplementation on the change in serum copper concentration. The estimated effect size was −0.041 (95% CI, −0.213 to 0.131; $p = .59$, random-effects model), and the daily zinc dose was not correlated with the change in serum copper concentration. However, it should be recognized that serum copper concentration is a relatively insensitive biomarker of copper status [111]. It is possible that more subtle changes in copper metabolism may have occurred, although such changes, if they did occur, would be unlikely to have any functional significance.

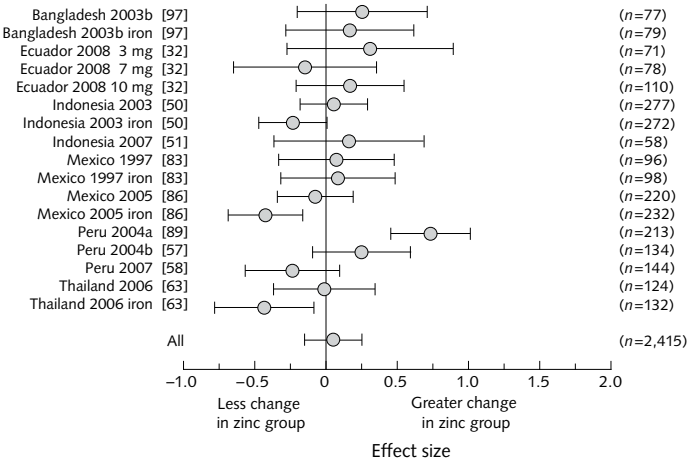

FIG. 13. Effect of zinc supplementation on change in serum or plasma ferritin concentration in children from 10 controlled zinc supplementation trials including 17 groupwise comparisons in which the supplements differed only by the presence or absence of zinc.

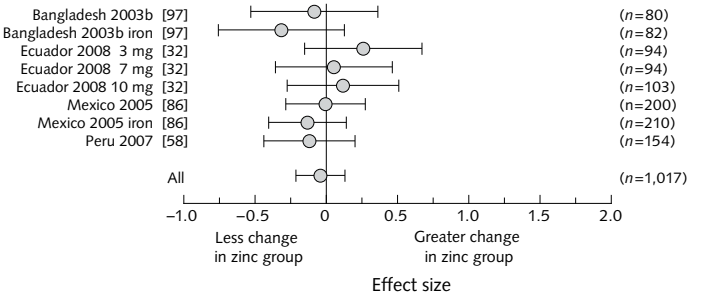

FIG. 14. Effect of zinc supplementation on change in serum copper concentration in children from four controlled zinc supplementation trials with eight groupwise comparisons in which the supplements differed only by the presence or absence of zinc.

Section 3

What are the opportunities to link preventive zinc supplementation programs to existing health and nutrition programs, and what technical, social, behavioral, and programmatic challenges must be confronted?

Available evidence regarding the impact of preventive zinc supplementation of infants and children on morbidity (diarrhea, ALRI, and perhaps malaria), mortality in children greater than 12 months of age and possibly SGA infants, and physical growth argues for the need to develop programs to prevent zinc deficiency in those countries where an elevated risk of zinc deficiency has been identified. There is no evidence of adverse effects of preventive zinc supplementation on markers of iron and copper status, indicating that zinc supplements can be delivered safely, either alone or with other micronutrients. The challenges for scaling up zinc supplementation programs are similar to those faced by other programs that attempt to procure and distribute nutritional supplements or medicines, as discussed below.

It has been stated previously that zinc needs to be provided on a daily basis for an extended period of time [102], although one study found equivalent beneficial effects when supplemental zinc was provided weekly [94]. In either case, the likely need for frequent administration of zinc supplements presents a number of programmatic challenges related to product delivery over an extended period of time and ensuring compliance. The most common, currently existing supplementation program requiring daily dosing and high compliance is iron and folic acid supplementation for pregnant and lactating women. The main operational constraints to successful delivery of such supplements have been described elsewhere [112] and include procurement and distribution of supplements, limited access to and poor utilization of health services by the target population, inadequate training and motivation of frontline health workers, inadequate counseling of target recipients or their caregivers, and low compliance of the intended beneficiaries. These are common obstacles that will need to be addressed by any supplementation program, including programs that distribute potential products such as tablets, powders, and pastes, as discussed below. In addition, there are generic issues of introduction of any new product, which include the regulatory environment, quality assurance and control, costs, supply chain and storage, product acceptability and packaging [113, 114].

The following section examines existing delivery platforms that can be tapped for distribution of zinc supplements and discusses issues that need to be addressed to deliver preventive zinc supplements successfully, either alone or in multiple-micronutrient products.

Twice-yearly vitamin A supplementation (VAS). Globally, the most successful micronutrient supplementation program for children less than 5 years of age is VAS, which is increasingly integrated into twice-yearly events for child survival (combining such interventions as deworming, vaccinations, distribution of insecticide-treated bednets, etc.) [115]. It is estimated that 79% of children 6 to 59 months of age in sub-Saharan Africa and 71% of children 6 to 59 months of age in South Asia received at least one dose of vitamin A in 2005 [116]. A recent publication that describes the progress and future directions of twice-yearly VAS in West and Central Africa [117] documents the success of such programs and calls for institutionalizing the child health day approach to deliver VAS and other low-cost, high-impact services for child survival and development. VAS programs have been very effective in reaching children 12 to 59 months of age, although they have been somewhat less successful in reaching infants 6 to 11 months of age [118]. This platform probably offers the most promising avenue for rapid scale-up of delivery of preventive zinc products, but a number of issues must be addressed:

- What duration of dosing will caregivers be able to administer correctly if the supplement supply is delivered only once every 6 months?
- What combination of zinc dose and duration of supplementation will result in optimal improvement in zinc status when delivered at 6-month intervals?
- What is the optimal presentation of the product (supplement, powder, paste) to maximize compliance and minimize costs and logistical burden?
- Can existing twice-yearly VAS programs support the additional input and logistical costs of adding preventive zinc supplementation?
- What communication strategies are required during twice-yearly events and as follow-up to these events to support optimal compliance by caregivers?
- Twice-yearly VAS programs only need to address coverage, since doses are consumed at delivery. Compliance will be essential for effective preventive zinc programs. How will programs be able to monitor and evaluate compliance?
- What is the effectiveness of these programs?

Growth monitoring and promotion (GMP). GMP programs could be ideal platforms for delivering preventive zinc supplements, because such programs provide frequent contacts with young children, thereby allowing for delivery of zinc-containing products, counseling on their use, and monitoring of compliance. A recent review of GMP programs concluded that these programs should "maximize their potential, strengthen the nutrition counseling elements, [and] combine growth monitoring with other health interventions" [119]. Preventive zinc supplementation is certainly one such health intervention that could easily meld with GMP activities. A particular advantage of such programs is

that they provide routine contacts that can be exploited to ensure delivery of supplements over an extended period and to promote compliance.

Community-based or community-directed distribution programs. Various community-based distribution systems exist in which the supply system is an extension of the health services. In these systems, either health workers visit communities to renew and supervise distribution of supplies or community distributors report to the health center to renew stocks. For example, community-directed treatment with ivermectin (CDTI) is active in 26 countries in sub-Saharan Africa to control onchocerciasis. Community-directed distributors are chosen by the community to provide once-yearly treatment. The scope of CDTI is being expanded to include elimination of lymphatic filariasis and delivery of other services [120, 121]. Another example is provided by traditional birth attendants, who have been trained to deliver a variety of services, including distribution of iron and folic acid tablets to pregnant and lactating women [122]. The issues of integrating preventive zinc products are similar to those described for GMP programs, particularly if the program has ongoing contact with the intended beneficiaries. For programs such as CDTI that only have intermittent contact operations, research is needed to see whether these systems can be expanded to deliver products on an ongoing basis.

Social marketing. This strategy is increasingly used to deliver products through commercial channels or messages to intended beneficiaries. A 1992 review defines social marketing as "a broader, systematic approach to developing strategies to define acceptable concepts, behaviors, or products, to promote them, and in the case of products, to distribute and price them for the market. A complete social marketing strategy not only develops and promotes a good 'product,' but also achieves and maintains political support and trains and motivates program implementers" [123]. Prices are often subsidized or programs have cross-subsidies to enhance reach to low-socioeconomic groups. In addition to issues cited for other delivery strategies, a specific issue is the extent to which such approaches reach the poorest and most remote beneficiaries and how well relevant messages on dosing issues can be communicated.

Point-of-use fortificants. There has been rapid development of point-of-use fortificants, including powders (often called "Sprinkles"), dispersible or crushable tablets, and lipid-based nutrient supplements, which are designed to address deficiencies in MMN and sometimes essential fatty acids and proteins [124]. The programmatic issues of their delivery are not substantially different from delivery of a supplement, and it is assumed that the above-mentioned platforms could be used. These products have the added advantage of favoring a delivery strategy that copromotes the product and optimal infant and young child feeding practices. An issue specific to zinc is determining the level of zinc necessary in the context of specific diets to result in adequate improvement in zinc status [125]. If such products are to include iron, there are several other issues that need to be addressed to ensure safety [126], although a full review of these issues is beyond the scope of this paper

Reaching low-birthweight infants. Low-birthweight infants have multiple special nutritional needs. They have a greater risk of breastfeeding difficulties and have an elevated risk of iron deficiency [127, 128]. Thus, programs to address the special health and nutritional needs of low-birthweight infants would have a scope far broader than just preventive zinc supplementation, although preventive zinc supplementation should be included as a key component. Although birthweight is often measured in clinical settings, this information is seldom used to provide a special package of interventions to meet the needs of low-birthweight infants. Issues that would have to be addressed in designing a strategy to target these infants would include:

» Systematic identification of low-birthweight infants (ensuring accurate weighing at delivery for births attended by trained personnel; integrating weighing at the first contact for other infants, for example, through the expanded program on immunization, etc.);
» Definition of the minimum package of low-birthweight infant care;
» Identifying community and health service contacts that can be mobilized to deliver the package;
» Monitoring and evaluation of delivery of and compliance with the package.

In summary, the available evidence on the impact of preventive zinc supplementation supports the need for intervention programs to enhance zinc status. There are a number of available opportunities to deliver preventive zinc supplementation as one component of programs to prevent MMN deficiencies and to address other nutrition and health needs of infants and children. Efforts are needed to test these delivery mechanisms and evaluate their potential for providing cost-effective preventive zinc supplementation to high-risk target groups on a large scale.

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