Prevention of diarrhea and pneumonia by zinc supplementation in children in developing countries: Pooled analysis of randomized controlled trials

Zinc Investigators' Collaborative Group: Z. A. Bhutta, MBBS, PhD, R. E. Black, MD, MPH, K. H. Brown, MD, J. Meeks Gardner, PhD, S. Gore, PhD, A. Hidayat, MD, PhD, F. Khatun, PhD, R. Martorell, PhD, N. X. Ninh, MD, PhD, M. E. Penny, MBBS, J. L. Rosado, PhD, S. K. Roy, MD, MSc,PhD, M. Ruel, PhD, S. Sazawal, MBBS, MPH, PhD, and A. Shankar, DSc*

Objectives: This study assessed the effects of zinc supplementation in the prevention of diarrhea and pneumonia with the use of a pooled analysis of randomized controlled trials in children in developing countries.

Study design: Trials included were those that provided oral supplements containing at least one half of the United States Recommended Daily Allowance (RDA) of zinc in children <5 years old and evaluated the prevention of serious infectious morbidity through household visits. Analysis included 7 "continuous" trials providing 1 to 2 RDA of elemental zinc 5 to 7 times per week throughout the period of morbidity surveillance and 3 "short-course" trials providing 2 to 4 RDA daily for 2 weeks followed by 2 to 3 months of morbidity surveillance. The effects on diarrhea and pneumonia were analyzed overall and in subgroups defined by age, baseline plasma zinc concentration, nutritional status, and sex. The analysis used random effects hierarchical models to calculate odds ratios (OR) and 95% CIs.

Results: For the zinc-supplemented children compared with the control group in the continuous trials, the pooled ORs for diarrheal incidence and prevalence were 0.82 (95% CI 0.72 to 0.93) and 0.75 (95% CI 0.63 to 0.88), respectively. Zinc-supplemented children had an OR of 0.59 (95% CI 0.41 to 0.83) for pneumonia. No significant differences were seen in the effects of the zinc supplement between the subgroups examined for either diarrhea or pneumonia. In the short-course trials the OR for the effects of zinc on diarrheal incidence (OR 0.89, 95% CI 0.62 to 1.28) and prevalence (OR 0.66, 95% CI 0.52 to 0.83) and pneumonia incidence (OR 0.74, 95% CI 0.40 to 1.37) were similar to those in the continuous trials.

Conclusions: Zinc supplementation in children in developing countries is associated with substantial reductions in the rates of diarrhea and pneumonia, the 2 leading causes of death in these settings. (J Pediatr 1999;135:689-97)

From the Aga Khan University Medical Centre, Karachi, Pakistan; Johns Hopkins School of Public Health, Baltimore, Maryland; University of California, Davis, California; University of the West Indies, Mona, Jamaica; Medical Research Council Biostatistics Unit, Cambridge, United Kingdom; Trisakti University, Jakarta, Indonesia; Dhaka Medical College, Dhaka, Bangladesh; Emory University, Atlanta, Georgia; National Institute of Nutrition, Hanoi, Vietnam; Nutrition Research Institute, Lima, Peru; National Institute of Nutrition, Mexico City, Mexico; International Centre for Diarrhoeal Disease Research, Bangladesh, Dhaka, Bangladesh; Institute of Nutrition of Central America and Panama, Guatemala City, Guatemala; and All India Institute of Medical Sciences, New Delhi, India.

*Members of the group are listed in alphabetical order.

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Reprint requests: Robert Black, MD, MPH, Department of International Health, Johns Hopkins School of Public Health, 615 N Wolfe St, Baltimore, MD 21205.

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Zinc deficiency, a prevalent condition of young children in developing countries,[1] is associated with decreased immunocompetence[2] and increased rates of serious infectious diseases.[3,4] Recently, strong evidence for a causal relationship between zinc deficiency and childhood infections has come from

See related articles, p. 657, p. 661, and p. 683.

OR Odds ratio
WHO World Health Organization

Table I. Characteristics of trials evaluating the preventive effects of supplementation with zinc on diarrhea, pneumonia, or both

Trial	No. of children		Total child-years		Enrollment	
	Zinc group	Control group	Zinc group	Control group	Age (mo)	Other criteria
Continuous supplementation						
India[8,9]	286	293	122.9	124.8	6-35	Recovered from acute diarrhea
Mexico[6]	97	97	116.0	117.1	18-36	—
Papua New Guinea[18]	136	138	75.3	80.7	6-60	—
Peru[19]	80	79	36.1	37.4	6-35	Recovered from persistent diarrhea
Vietnam[5]	73	73	30.8	30.8	4-36	Weight/age & height/age <–2z
Guatemala[7]	45	44	23.2	22.9	6-9	—
Jamaica[20]	31	30	7.1	6.2	6-24	Weight/height <–2z
Short-course supplementation						
Bangladesh[21]	77	75	12.8	13.5	3-24	Recovered from persistent diarrhea
Pakistan[22]	41	40	10.8	10.6	6-36	Recovered from persistent diarrhea
Bangladesh[23]	32	33	0.6	0.7	3-24	Recovered from acute diarrhea

randomized controlled trials of zinc supplementation in poor but not severely malnourished children in several developing countries.[5-9] These trials have demonstrated that zinc supplementation can substantially reduce the incidence of acute lower respiratory infections and diarrhea.

Trials of zinc supplementation reported to date have varied with regard to the magnitude of the effect demonstrated and the presence of a differential effect by sex, age, nutritional status, or baseline plasma zinc concentration. Most trials have had insufficient power to examine effects on infrequent outcomes such as pneumonia, dysentery, or persistent diarrhea. Furthermore, published trials have used a variety of subgroup and outcome definitions, making summarization of effects difficult, and some trials remain unpublished, which could lead to a biased interpretation of possible benefits. To provide a complete and accurate summary of the effects of zinc supplementation on childhood infectious diseases, we formed a group of investigators and advisors to conduct a pooled analysis of original data from all identified published and unpublished trials. We attempted to overcome problems of the comparability of trials and the validity of subgroup analysis by defining outcomes and subgroups in advance. We present the results of pooled analyses with data conforming to these definitions from 10 trials in 9 developing countries.

METHODS

Analysis coordinators (REB and SS) identified published randomized controlled trials from systematic searches of bibliographic databases including MEDLINE, SCI-SCIMATE, CURRENT CONTENTS, and references from papers. Other trials were identified through contacts with possible funding agencies and with investigators in the field of micronutrition. Investigators of all identified trials agreed to join a Zinc Investigators' Collaborative Group, which also included 2 external advisors selected by the World Health Organization Program on Child Health and Development and 1 selected by the coordinators of the pooled analyses.

An initial meeting with some of the trial investigators and correspondence with the others resulted in consensus on inclusion criteria, subgroup and outcome definitions, and procedures for the pooled analyses. For trials meeting inclusion criteria, all but 1 of the investigators provided the necessary data and descriptive information for their studies. A preliminary analysis was performed, and the Zinc Investigators' Collaborative Group met to determine whether more analyses were needed and to decide on the conclusions and implications. Final analyses and manuscripts were approved by all investigators who had trials included.

Supplement		Supplement schedule and duration
Zinc	Control	
10 mg as gluconate	Both groups Vitamin A,B,D,E	Daily for 26 weeks
20 mg as methionate (half with iron)	Placebo (half with iron)	5 times per week for 54 weeks
10 mg as gluconate	Placebo	6 times per week for 46 weeks
10 mg as gluconate	Placebo	Daily for 26 weeks
10 mg as sulfate	Placebo	Daily for 22 weeks
10 mg as sulfate	Placebo	Daily for 28 weeks
5 mg as sulfate	Both groups Vitamin A, B, C, D	Daily for 12 weeks
20 mg as acetate	Both groups Vitamin A, B, D, E	Daily for 2 weeks
20 mg as sulfate	Both groups Vitamin A, B, C, D	Daily for 2 weeks
20 mg as acetate	Both groups Vitamin A, B, D, E	Daily for 2 weeks

The pooled analyses included randomized controlled trials providing supplements containing at least one half of the United States Recommended Daily Allowance of zinc in children.[10] This Recommended Daily Allowance for infants is 5 mg elemental zinc/d, and for children 1 to 4 years old it is 10 mg/d. For developing countries where the bioavailability of zinc in the diet is often much lower than that in the United States, it may be useful to relate the doses given to the lower limits of safe population mean intakes of dietary zinc recently published by WHO.[11] In settings with low dietary availability, children from the second 6 months of life to age 3 years are said to need to consume 8.0 mg/d of zinc to meet their basal physiologic requirements. Zinc must have been the only micronutrient that differed between experimental and control groups, but trials that gave other minerals or vitamins to both groups were acceptable. For a trial to be included, the supplement should have been given for at least 2 weeks, and the surveillance for outcomes by household visits should have been done for at least 4 weeks. Studies using a factorial design had the 2 zinc- and 2 non-zinc-containing cells combined for the analysis to isolate the effect of zinc and to avoid double counting of trials.

Trials were determined to be of 2 types: those in which supplements were provided for the entire period of morbidity surveillance (referred to as "continuous" supplementation trials) and those in which supplements were given for a short period (2 weeks) and morbidity surveillance was done for a subsequent period (referred to as "short-course" trials). The 2 types of trials were analyzed separately. Subgroups for the analysis defined *a priori* were age (<12 months or ≥12 months), plasma zinc concentration (<60 μg/dL or ≥60 μg/dL), weight for height (<−2z or ≥−2z compared with the National Center for Health Statistics reference),[12] and sex.

The trial outcomes included disease incidence and prevalence (the number of new episodes of the illness and of days with the illness, respectively, per total days of observation). Investigators provided data conforming to the agreed outcome definitions. A day of diarrhea was defined as a 24-hour period with 3 or 4 (depending on the original study) unformed stools. An episode of diarrhea was defined as at least 1 day of diarrhea, with the final day of the episode being the last day meeting the diarrhea definition followed by at least 48 hours without diarrhea. An episode of dysentery was defined as an illness meeting the definition of diarrhea in which blood was observed in the stools. An episode of persistent diarrhea was defined as a diarrheal illness that lasted ≥14 days.

An episode of pneumonia was defined in several ways, because trials varied in the clinical data collected. Any of the following were considered acceptable: (1) reported cough or difficult breathing, respiratory rate above the WHO-defined[13] age-specific values (>50/min in 2- to 11-month-olds and >40/min in 12- to 59-month-olds) and either documented fever of >101°F or chest indrawing,[13] (2) a diagnosis of pneumonia based on chest examination by a physician, or (3) a diagnosis of pneumonia based on a chest radiograph. Insufficient data were collected in the trials to permit determination of the duration of pneumonia episodes, so prevalence could not be assessed. Only 1 trial had data on malaria, precluding a pooled analysis for this outcome.

A detailed methodological assessment and scoring system with a maximum of 100 points was developed and studies independently scored by authors REB and SS; any disagreements were resolved by further review of the methods and consensus. At a meeting of the Zinc Investigators' Collaborative Group, the methodological scores were reviewed by the trial's principal investigators, and errors or inconsistencies were corrected.

Table II. Background characteristics and plasma zinc concentrations before and after zinc supplementation in preventive zinc trials

	Preventive zinc trials						
	Percentage			Plasma zinc concentration (μg/dL)			
				Zinc group		Control group	
Trial	Illiterate mothers	Height/age <−2z	Weight/height <−2z	Before	After	Before	After
Continuous supplementation							
India[8,9]	81	67	21	64.6 ± 1.0	87.6 ± 2.4	65.0 ± 1.4	63.8 ± 0.9
Mexico[6]	0	34	1	97.4 ± 3.0	114.6 ± 3.6	95.8 ± 3.0	96.6 ± 3.0
Papua New Guinea[18]	NA	45	10	66.9 ± 1.6	70.7 ± 1.8	75.9 ± 2.7	74.4 ± 2.3
Peru[19]	3	32	2	70.4 ± 1.4	97.5 ± 4.1	70.2 ± 1.7	76.9 ± 2.5
Vietnam[5]	3	100	NA	NA	NA	NA	NA
Guatemala[7]	58	56	0	NA	NA	NA	NA
Jamaica[20]	NA	90	26	NA	NA	NA	NA
Short-course supplementation							
Bangladesh[21]	40	34	42	87.6 ± 3.5	88.9 ± 3.8	87.6 ± 3.2	77.9 ± 3.3
Pakistan[22]	83	87	35	78.0 ± 5.2	85.6 ± 5.1	70.3 ± 3.2	74.8 ± 3.9
Bangladesh[23]	51	52	46	73.0 ± 2.8	89.0 ± 5.0	82.2 ± 4.5	80.2 ± 4.0

NA. Not available.

Table III. Effect of zinc supplementation on the incidence of persistent diarrhea, dysentery, and pneumonia

	Odds ratio (95% CI)		
Trial	Persistent diarrhea	Dysentery	Pneumonia
India[8,9,24]	0.79 (0.57-1.09)	0.86 (0.63-1.16)	0.57 (0.34-0.93)
Mexico[6]	0.77 (0.16-3.30)	—	—
Peru[19]	1.24 (0.38-4.15)	0.90 (0.53-1.52)	0.85 (0.35-2.04)
Vietnam[5]	0.44 (0.10-1.54)	0.81 (0.21-2.94)	0.56 (0.39-0.80)
Guatemala[7]	0.25 (0.08-0.68)	—	—
Jamaica[20]	—	—	0.12 (0.00-13.58)
Pooled estimate	0.67 (0.42-1.06)	0.87 (0.64-1.19)	0.59 (0.41-0.83)

The analysis was performed with the Confidence Profile Method,[14] (FAST*PRO Software version 1.8).[15] With the use of Bayesian methods, we estimated a joint posterior probability distribution for the parameter of interest with a random effects hierarchical model.[14,16] From these joint distributions, odds ratios and CIs were calculated for each study and in each stratum. Finally, summary effects and 95% CI were estimated. We used a random effects model because it does not require homogeneity of effects across studies. It assumes random variability among studies and takes this into account for estimations of CI. This method is a more conservative method than a fixed effects model.[17]

RESULTS

Seven continuous and 3 short-course supplementation trials were included in the 2 sets of pooled analyses (Table I). All of these trials were in apparently healthy children, although 2 trials recruited children who had recently recovered from diarrhea, and 2 others recruited children with growth retardation in the community. The 3 short-course trials began as therapeutic trials of zinc during an episode of acute or persistent diarrhea, giving the supplement for a fixed period of 2 weeks. Apparently healthy children who recovered from the diarrheal episode within the 2 weeks of supplementation had effects on morbidity assessed by surveillance for a subsequent 2 to 3 months without further supplementation. One of these trials had substantial attrition resulting in limited data but was included because it met all criteria including attempted surveillance for 2 months.

The study populations varied substantially in background characteristics including nutritional status, with the children in the short-course trials being less well nourished than those in the continuous trials (Table II). In the trials that assessed plasma zinc concentration before and after the supplementation period, zinc-supplemented children generally had an increase in plasma zinc, whereas the control group had no change or even a decrease (Table II).

All of the continuous supplementation trials had point estimates for effects (OR) on incidence and prevalence that were <1, indicating a lower rate in the zinc-supplemented group than in the control group. In 5 of the 7 trials the upper limit of the 95% CI was <1 for both outcomes (Fig 1). The pooled OR for the effect of zinc supplementation on diarrheal incidence was 0.82 (95% CI 0.72 to 0.93) and on prevalence was 0.75 (95% CI 0.63 to 0.88).

Five continuous supplementation trials had persistent diarrhea, and 3 had dysentery outcome data available (Table III). The pooled OR for persistent diarrhea was 0.67 and for dysentery 0.87. The upper limit of the 95% CI crossed 1 in both analyses, which may have been related to the limited data resulting from relative infrequency of these outcomes. Four trials had data on pneumonia resulting in a pooled OR of 0.59 (95% CI 0.41 to 0.83) for zinc supplementation.

In the continuous supplementation trials, the analysis of effects on diarrheal or pneumonia incidence did not reveal significant differences between any of the specific subgroups examined (Fig 2). The provision of vitamins along with the zinc supplement among the limited data available did not appear to change the effects of zinc supplementation. For diarrhea the pooled estimates for 2 trials that included use of multivitamins were not significantly different from pooled estimates of the 5 trials that did not include use of multivitamins. In a similar manner, the pooled estimates for pneumonia of the 2 trials that included vitamins were not significantly different from the 2 that did not.

The methodologic score of the trials ranged from 76 to 95 out of a possible 100, but all studies were judged to be of acceptable quality. Overall the interaction with methodologic score was not statistically significant for any of the outcomes, but a negative correlation was seen between the score and effect size for diarrheal prevalence (Pearson r = −0.768, $P = .04$). Within the range of zinc doses used in the supplements (approximately 0.7 to 1.8 mg zinc/kg), no significant correlation was seen between dose and effect size for diarrheal incidence (Pearson r = 0.655, $P = .11$), diarrheal prevalence (Pearson r = 0.298, $P = .52$), or pneumonia incidence (Pearson r = −0.340, $P = .66$).

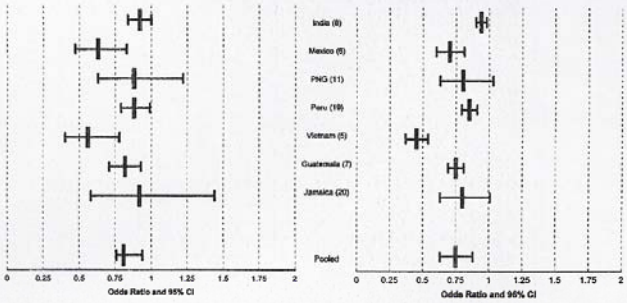

Fig 1. Effect of zinc supplementation on incidence and prevalence of diarrhea.

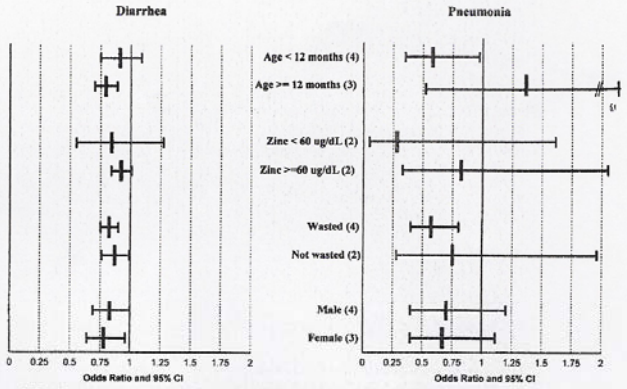

Fig 2. Effect of zinc supplementation on diarrhea and pneumonia in subgroups.

All of the short-course trials had diarrheal incidence and prevalence data, and 2 had pneumonia data. The ORs for diarrheal incidence and prevalence were 0.89 (95% CI 0.62 to 1.28) and 0.66 (95% CI 0.52 to 0.83), respectively. The OR for pneumonia incidence was 0.74 (95% CI 0.40 to 1.37). The point estimates of the effects in the short-course trials were not significantly different from those in the continuous supplementation trials, but the confidence intervals in these trials were wide because of the limited data available (Fig 3).

DISCUSSION

The pooled analysis of the trials of continuous zinc supplementation demonstrated effects on diarrheal inci-

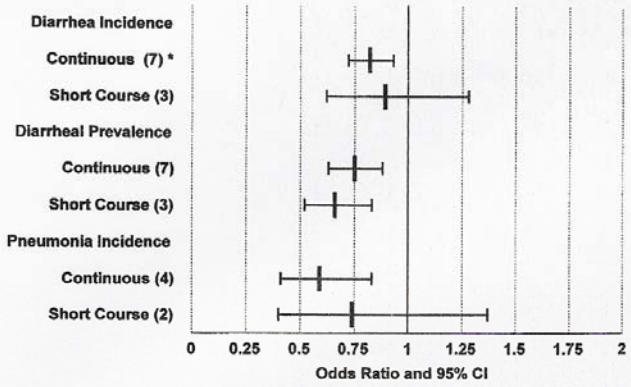

Fig 3. Preventive effect of zinc supplementation on diarrheal incidence and prevalence and pneumonia incidence with continuous or short-course supplementation.

dence and prevalence that were substantial and consistent among children in 7 developing countries. Data from 1 trial in 6- to 48-month-old Bangladeshi children that used 20 mg zinc as acetate were not available; however, it was reported previously that the zinc-supplemented group in this trial had 13% less diarrhea than the control group, which was not a statistically significant difference (D. Mahalanabis, personal communication). The addition of this trial to the pooled analysis would have resulted in only a very small change in the estimate of the effect of zinc on diarrheal incidence.

The greater overall reduction of diarrheal prevalence (25%) than of incidence (18%) is probably because zinc supplementation also reduces the duration of episodes, as has been demonstrated in therapeutic trials of zinc in both acute[25,28] and persistent diarrhea.[22,29-31] The effect of zinc supplementation on prevention of diarrhea compares very favorably with other potential interventions to reduce diarrheal prevalence in children in developing countries. A WHO-sponsored review of preventive interventions estimated that high-quality improvement of water and sanitation together would reduce childhood diarrhea by 27%.[32] A meta-analysis of vitamin A trials in developing countries reported that no consistent decrease occurred in the occurrence of diarrhea, although there was a substantial reduction of diarrheal mortality.[33]

These zinc trials showed a large effect on pneumonia, reducing its incidence by 41%. The use of strict definitions of pneumonia, with emphasis on clinical documentation of key signs[13] or radiographic diagnosis, avoids misclassification and leads to greater confidence in the findings. This effect is greater than that estimated for any other intervention to prevent pneumonia, although the size of the effect is what might be anticipated from the elimination of malnutrition as a risk factor.[34]

The effect of zinc supplementation was consistent in the selected age, plasma zinc, nutritional status, and sex subgroups examined; however, limited data in some subgroups reduced the power of these analyses. Definitive answers will come from randomized trials with stratification to assess effects in particular subgroups. Nevertheless, these results suggest that the benefits of zinc supplementation are not limited to selected groups and that interventions should include all economically disadvantaged children in developing countries with likely childhood zinc deficiency and high rates of infectious morbidity. Given the current limitations of zinc status determination with plasma or other biologic samples,[35,36] it would be helpful to have simple dietary assessment methods that could be used to decide which populations would benefit from interventions to improve zinc nutriture.[1]

Because zinc, unlike vitamin A, is not stored in the body after a large oral dose, it has been thought that adequate zinc must be available in the daily diet.[36] Although this is clearly desirable, the results of the short-course trials suggest that a period of consumption of adequate zinc may have more prolonged functional benefits. Further evidence for this comes from a placebo-controlled, masked, but not randomized trial in Brazilian infants with low birth weight who received 5 mg zinc/d for the first 8 weeks of life.[37] Zinc-supplemented infants had 48% less diarrhea than a control group during their initial 26 weeks of life ($P < .001$). It is also conceivable that children consuming a diet marginal in zinc could maintain more normal zinc status for some time after their zinc nutriture is restored by a period of supplementation.

Zinc deficiency impairs many cellular and humoral immune functions including lymphocyte number and function,[2] and supplementation of children in developing countries has resulted in improved delayed cutaneous hypersensitivity and an increase in CD4 (helper) lymphocytes.[38,39] The diverse study populations were likely to have had some level of zinc deficiency as a result of consumption of diets with low zinc content and bioavailability.[40] Deficient zinc status of these populations is suggested by the low plasma zinc levels at baseline. It is most likely that the effects of the zinc supplements were due to correction of this deficiency and

restoration of immune functions.[41] On the other hand, the possibility of a pharmacologic effect of zinc cannot be eliminated. Oral zinc in very high doses (660 mg/d for 1 month) given to adults in Belgium who were presumably replete in zinc resulted in increased in vitro lymphocyte response to mitogens.[42] This possible effect has not been studied with more physiologic doses of zinc or in children.

The availability of 10 randomized controlled trials of zinc supplementation in the prevention of childhood diarrhea and pneumonia in developing countries enabled these pooled analyses. In these trials intensive community-based surveillance for morbidity outcomes provided an extensive set of data reflecting the true rates of serious infectious diseases. It is highly unlikely that trials were overlooked. Furthermore the trial that could not be included had results similar to those of the pooled analysis. The pooled analysis approach used has a number of strengths compared with a usual literature review or even a meta-analysis with trial publications as the main source of information.[17,43] The involvement of investigators from all trials meeting inclusion criteria including unpublished trials avoided publication bias and permitted standardization of subgroups and outcomes and inclusion of information not presented in publications. A review of methodologic characteristics allowed a rigorous selection of those studies having the essential features of randomized controlled trials. The availability of original data from the trials permitted the use of optimal statistical methods, and the advisors provided valuable analytic advice and independent perspective. The primary limitation was that the trials did not provide as much data on some less frequent infections such as pneumonia as they did on diarrhea. It is also regrettable that there have been no trials in the Middle East or Sub-Saharan Africa. Zinc deficiency has been found to be prevalent in these areas.[44-47]

The substantial benefits of zinc supplementation for prevention of diarrhea and pneumonia, the 2 leading causes of death in children in developing countries, suggest that this could be an important means to improve child survival. Assessment of the effect of zinc supplementation on child mortality is a priority. There is preliminary evidence for such an effect, because a randomized controlled trial in Indian term small-for-gestational age infants found a reduction by two thirds in mortality during the study period of 1 to 8 months of age attributable to supplementation with 5 mg zinc daily.[48]

The development of effective and feasible interventions to improve the zinc status of developing country populations is essential. One such intervention, zinc fortification of bread, has been shown in a controlled trial lasting 3 months to reduce diarrhea, respiratory illnesses, and skin infections by 56% ($P < .05$) in Turkish schoolchildren.[49] Dietary diversification,[50] enhancement of bioavailable zinc in foods by genetic engineering and plant breeding,[51] and periodic supplementation[52] are other possible intervention strategies that should be evaluated in developing countries.

Robert E Black and Sunil Sazawal organized and conducted the pooled analysis and wrote the draft manuscript. Zulfiqar Bhutta, Julie Meeks Gardner, Ngugen Ninh, Mary Penny, Jorge Rosado, Swapan Roy, Marie Ruel, Sunil Sazawal, and Anu Shankar were principal investigators of zinc prevention trials. Adi Hidayat and Farida Khatun, as principal investigators of zinc therapy trials, participated in the ZINC Group. Kenneth Brown, Sheila Gore, and Reynaldo Martorell served as advisors. All assisted with editing the manuscript.

Other investigators in prevention trials:

India (R. E. Black, M. K. Bhan, S. Jalla, A. Sinha, N. Bhandari), Mexico (P. López, E. Muñoz, H. Martínez, L. H. Allen), Papua New Guinea (B. Genton, M. Baisor, J. Paino, S. Tamja, S. Arnold, L. Wu, J. Tielsch, K. West, M. Alpers), Peru (R. M. Matin, A. Duran, J. M. Peerson, C. F. Lanata, B. Lönnerdal, R. E. Black, K. H. Brown), Vietnam (J. P. Thissen, L. Collettte, G. G. Gerard, H. H. Khoi, J. M. Ketelslegers), Guatemala (J. A. Rivera, M.C. Santizo, B. Lönnerdal, K. H. Brown), Jamaica (M. M. Witter, D. D. Ramdath), Bangladesh (A. M. Tomkins, R. Haider, S. M. Akramuzzaman, R. H. Behrens, D. Mahalanabis, G. Fuchs), Pakistan (S. Q. Nizami, S. K. Niazi, A. Issani).

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50 Years Ago in The Journal of Pediatrics

MEASLES IN THE NEPHROTIC SYNDROME

Rosenblum AH, Lander HB, Fisher RM. J Pediatr 1949;35:574-85

Rosenblum et al contributed 6 cases to the growing body of literature documenting rather soundly that dramatic remissions of nephrotic syndrome frequently occur in the week after onset of natural measles. The observation had been suggested by others, but measles epidemics in the Chicago area in the winters of 1947 and 1948 permitted physicians at the Cook County Hospital to collect data from a series of patients. They showed that children with lipoid nephrosis, and additionally some with more complex nephropathies, had dramatic diuresis. They also observed life-threatening measles in one patient and cautioned against purposefully exposing children with nephrotic syndrome to individuals with contagious cases.

The authors' observations were subsequently verified by others. Other infectious diseases, notably viral diseases such as varicella, also led to remissions, but none as dramatically as measles.

The authors speculate that protein (ie, gammaglobulin) synthesis in response to measles might be responsible for improvement by ameliorating the effect of hypoalbuminemia. We now know that the immune-modulating, immunosuppressive effect of measles is almost certainly the mechanism. We are currently in a more advantageous position to help our patients: we have measles vaccine to prevent that serious disease and corticosteroid therapy to hasten remission of nephrotic syndrome.

Sarah S. Long, MD
Section of Infectious Diseases
St. Christopher's Hospital for Children
Philadelphia, PA 19134-1095