

# A randomized controlled trial of the effect of zinc as adjuvant therapy in children 2–35 mo of age with severe or nonsevere pneumonia in Bhaktapur, Nepal<sup>1–4</sup>

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## ABSTRACT

**Background:** Pneumonia is a leading cause of illness and death in young children. Interventions to improve case management of pneumonia are needed.

**Objective:** Our objective was to measure the effect of zinc supplementation in children with pneumonia in a population in which zinc deficiency is common.

**Design:** In a double-blind, placebo-controlled clinical trial, children aged 2–35 mo with severe ( $n = 149$ ) or nonsevere pneumonia ( $n = 2479$ ) defined according to criteria established by the World Health Organization were randomly assigned to receive zinc (10 mg for children aged 2–11 mo, 20 mg for children aged  $\geq 12$  mo) or placebo daily for 14 d adjuvant to antibiotics. The primary outcomes were treatment failure, defined as a need for change in antibiotics or hospitalization, and time to recovery from pneumonia.

**Results:** One of 5 children did not respond adequately to antibiotic treatment; the odds ratios between zinc and placebo groups for treatment failure were 0.95 (95% CI: 0.78, 1.2) for nonsevere pneumonia and 0.97 (95% CI: 0.42, 2.2) for severe pneumonia. There was no difference in time to recovery between zinc and placebo groups for nonsevere (median: 2 d; hazard ratio: 1.0; 95% CI: 0.96, 1.1) or severe pneumonia (median: 4 d; hazard ratio: 1.1; 95% CI: 0.79, 1.5). Regurgitation or vomiting  $\leq 15$  min after supplementation was observed more frequently among children in the zinc group than among those in the placebo group during the supplementation period (37% compared with 13%; odds ratio: 0.25; 95% CI: 0.20, 0.30).

**Conclusion:** Adjuvant treatment with zinc neither reduced the risk of treatment failure nor accelerated recovery in episodes of nonsevere or severe pneumonia. This trial was registered at clinicaltrials.gov as NCT00148733. *Am J Clin Nutr* doi: 10.3945/ajcn.2009.28907.

## INTRODUCTION

Pneumonia is the leading cause of illness and death in young children (1). Routine zinc administration lowers the risk of acute lower respiratory illnesses and clinical pneumonia in children from low-income countries (2). However, therapeutic trials of zinc given to hospitalized patients with severe pneumonia have yielded inconsistent results, ranging from a positive effect (3) to no overall effect (4–7). In 2 of the studies that reported no overall effect of zinc, subgroup analyses showed a negative effect in children with severe pneumonia of suspected bacterial etiology

(8) and a positive effect of zinc in boys and in children with fever (4).

A recent Cochrane review of 18 trials of therapeutic oral zinc for diarrhea showed that time to recovery was reduced by  $\approx 12$  h in children aged between 6 mo and 5 y with acute or persistent diarrhea (9). Since May 2004 the World Health Organization (WHO) and UNICEF have promoted zinc treatment as part of the case management of acute diarrhea for children  $< 5$  y of age (10). The recommended duration of zinc supplementation is 10–14 d. When zinc has been given for a period of  $\geq 14$  d, the preventive effect of zinc on childhood infections has been shown to last for up to 6 mo after zinc was given (11, 12). In view of these existing recommendations and findings, the chosen intervention period was 14 d for the present trial.

The WHO-recommended systematic case management approach has greatly reduced the mortality of children with pneumonia (13). It was concluded in a recent review that the results of previously conducted trials on zinc as an adjunct for childhood pneumonia are mixed (14), and that future studies should use the WHO case management approach to avoid misclassification of outcomes and to make comparisons between trials easier. Pneumonia definitions used in the Integrated Management of Childhood Illness (IMCI) have been validated in

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studies carried out by the WHO, and it was concluded that these definitions had an 80% sensitivity and an 80% specificity (15).

To make our findings easily comparable with those of other trials, we used IMCI pneumonia definitions and case management strategies in the present trial in Bhaktapur, Nepal, which is a site at which an earlier trial had shown a substantial beneficial effect of zinc on the outcome of acute diarrhea (16) and where zinc deficiency is common (17).

## SUBJECTS AND METHODS

This was a double-blind, randomized, placebo-controlled trial in children designed to measure the efficacy of daily zinc administration for 14 d on the recovery from severe or nonsevere pneumonia defined according to criteria established by the WHO. The trial had ethical clearance from the ethics board of the Institute of Medicine, Tribhuvan University in Katmandu, Nepal, and the Regional Committee for Medical and Health Research Ethics, Norway. The implementation of all aspects of the project was in agreement with the International Ethical Guidelines for Research Involving Human Subjects as stated in the latest version of the Helsinki Declaration. Informed written consent was obtained from at least one of the parents. A witnessed verbal informed consent was obtained from those who were illiterate.

### Sample size calculations

Sample sizes were calculated for 90% power and 5% 2-sided type I error. Sample size calculations were based on estimates from a previous study in Pakistan that used the same definition of pneumonia (18). Hence, we expected that 20% of the children with nonsevere pneumonia would experience treatment failure. Assuming a 25% reduction in the proportion with treatment failure among the zinc-supplemented children, we aimed to enroll 1250 children in each group. For the analysis of time to recovery from the enrollment episode, a relative hazard ratio of 1.25 required a group size of 426, with the same assumptions for power and type I error.

### Inclusion and exclusion criteria, definitions, and randomization

Children aged 2–35 mo with cough or difficulty breathing were screened by a physician in our study clinic at Siddhi Memorial Hospital and fulfilled the inclusion criteria if they had severe or nonsevere pneumonia according to WHO definitions (19) and if  $\geq 6$  mo had lapsed from a previous enrollment. Nonsevere pneumonia was defined as fast breathing without lower chest indrawing (LCI). A child had fast breathing if the lower of 2 counts of respiratory rate was  $\geq 50$  breaths/min in children aged 2–11 mo and  $\geq 40$  breaths/min in children aged  $\geq 12$  mo. Severe pneumonia was defined as LCI but without general danger signs (ie, inability to drink/breastfeed, persistent vomiting, convulsions, lethargy, or unconsciousness) (19).

In a child with wheezing, two 2.5-mg doses of nebulized salbutamol were given 15 min apart, and the child was reassessed after 30 min to establish whether he or she still fulfilled the inclusion criteria.

Exclusion criteria were as follows: nonconsent, not planning to live in the area for the next 6 mo, requiring special care for very severe disease (ie, with any general danger sign), severe mal-

nutrition (defined as being  $<70\%$  of the median weight for height according to National Center for Health Statistics standards), presence of congenital heart disease, documented tuberculosis, documentation of any oral antibiotic treatment in the past 48 h, cough for  $>14$  d, severe anemia (defined as hemoglobin  $<7$  g/dL), or dysentery.

To enhance baseline comparability between children receiving zinc and children receiving placebo, randomization was stratified on age  $<1$  y and from  $\geq 1$  y as well as on severe and nonsevere pneumonia. Children were allocated to either of the intervention groups by being randomly assigned to blocks of 16. For each enrollment, the child was given a unique serial number and a package with the intervention or placebo with the corresponding number. The randomization list that linked the serial numbers to the treatment groups was generated offsite by using Stata (Stata Corporation, College Station, TX) by a scientist who was otherwise not involved in the study. The scientist sent this list to the manufacturer of the placebo and zinc tablets that labeled the packages. The list was not available for any of those involved in the study until all participants had been enrolled and completed follow-up, data cleaning and management were finished, and the plan of analysis had been prepared. Children who were enrolled more than once received a new serial number and were thus re-randomly assigned.

### Interventions, blinding, cointerventions, and outcome definitions

The supplement consisted of dispersible tablets containing 10 mg zinc sulfate or placebo (Nutriset, Malaunay, France). The dosage used was 10 mg for children aged 2–11 mo and 20 mg for children aged  $\geq 12$  mo. Tablets of both groups were similar in packaging, appearance, taste, and inactive ingredients. The first dose of supplement was administered at the clinic. Fieldworkers observed and recorded side effects such as regurgitation or vomiting during the first 15 min after administration. Subsequent doses were given daily by a fieldworker at home, except on public holidays when the supplement was given by the caretaker, usually the mother.

The children received antibiotic treatment according to WHO standard case management guidelines for pneumonia (19) with oral co-trimoxazole in a dose of 4 mg trimetoprim/kg bodyweight and 20 mg sulfamethoxazole/kg bodyweight twice daily for 5 d. A fieldworker examined each child daily at home until recovery from the pneumonia episode. At each home visit, details of illness characteristics, including respiratory rate, presence of LCI, danger signs, and axillary temperature, were recorded. Recovery from nonsevere pneumonia was defined as the first of 2 consecutive days with normal respiratory rate. The child was referred to the clinic if fast breathing persisted 72 h after enrollment. If the physician at the clinic confirmed that the child still had nonsevere pneumonia according to WHO criteria, treatment was changed to amoxicillin (15 mg/kg 3 times daily) for 5 d. If the child developed LCI (ie, severe pneumonia) or danger signs, the child was hospitalized, and the condition was treated with administration of parenteral antibiotics. Parents were advised to bring their child to the clinic whenever required. Similarly, fieldworkers were instructed to refer the child to the clinic whenever they believed a medical evaluation of the child was necessary. According to the protocol, a change to second-line antibiotics should be made at

day 3 if the respiratory rate was still elevated. However, if the physician considered such an action to be necessary due to a worsening of the child's clinical condition despite compliance with first-line antibiotic treatment, antibiotics were changed earlier. Treatment failure was defined as antibiotic change or hospitalization due to pneumonia  $\leq 3$  d after enrollment.

Children with severe pneumonia were hospitalized at Siddhi Memorial Hospital (Siddhi Memorial Hospital, Bhaktapur, Nepal) and received benzylpenicillin (50,000 units/kg intravenously every 6 h) for 3 d. Children were examined at 12-h intervals by a physician, and details of illness characteristics, including respiratory rate, presence of LCI, danger signs, axillary temperature, oxygen saturation, and auscultatory findings, were recorded. The day of recovery from severe pneumonia was defined as the beginning of the first 24-h period without LCI, without grunting and with no nasal flaring. After recovery, treatment was changed to oral amoxicillin ( $15 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{dose}^{-1}$ , 3 times daily) for a total of 5 more days. If the child did not improve on benzylpenicillin after 48 h, treatment was changed to chloramphenicol (25 mg/kg intravenously every 8 h) until recovery and continued with chloramphenicol orally for a total course of 10 d. The child would normally be discharged after recovery from severe pneumonia and followed up with daily home visits by a fieldworker, who monitored the clinical condition of the child and registered the date of recovery from nonsevere pneumonia.

Diarrhea was managed according to WHO guidelines (19). Children  $\geq 6$  mo of age and with hemoglobin concentrations between 7 and 10 mg/dL received supplementation with 3 mg elemental iron/kg daily for 1 mo after the end of the 14-d intervention period to avoid interaction with zinc (20).

### Data collection

At enrollment, children were weighed (UNICEF Electronic Scale 890; SECA, Hamburg, Germany), and length to the nearest 0.1 cm was measured (as height in children aged  $\geq 2$  y and as recumbent length in children aged  $< 2$  y). The child's respiratory rate was assessed according to WHO guidelines (19) by counting twice for 1 min with the use of a UNICEF timer. The lower of the 2 counts represented the child's respiratory rate. All enrolled children had a capillary or venous blood sample collected to measure hemoglobin (Hemocue, Vedbæk, Denmark) and C-reactive protein (CRP; Quikread CRP; Orion Diagnostica, Hellebæk, Denmark) by using a rapid test with a measurement range of  $< 8$ , 8–160, and  $> 160$  mg/L.

Oxygen saturation was measured on a finger or a toe with a pulse oxymeter (Siemens MicO2; Siemens Medical Systems Inc, Danvers, MA) and by using a pediatric sensor (Nellcor, Pleasanton, CA). After stabilization of the reading for 1 min, oxygen saturation was recorded twice, and the average of the 2 readings was used.

Nasopharyngeal aspirates were examined for 7 different RNA viruses by using a commercially available multiplex reverse transcriptase polymerase chain reaction assay (Hexaplex Plus; Prodesse Inc, Waukesha, WI) (21). Plasma zinc concentration was determined by inductively coupled plasma mass spectrometry (PlasmaQuad 3; VG Elemental, Cheshire, United Kingdom).

### Data management and analysis

Fieldworker candidates participated in a weeklong course in the Integrated Management of Childhood Illness training program given by Nepalese pediatricians as facilitators at Kanti Hospital, Kathmandu. The fieldworkers were trained in refresher sessions at Kanti Hospital and in our outpatient study clinic in Bhaktapur in detecting LCI, counting respiratory rate, and measuring axillary temperature, length, height, and weight; physicians were trained in detecting LCI, counting respiratory rate, and in the detection of wheezing and crepitations. Furthermore, throughout the entire study period, in 5% of all home visits, supervisors or study physicians supervised the fieldworkers or undertook independent visits and completed the same questionnaires in addition to a separate form on fieldworker performance.

The data were double-entered with the use of Microsoft VisualFoxPro databases (Microsoft Corp, Redmond, WA) with computerized logic, range, and consistency checks. Length-for-age and weight-for-length  $z$  scores were calculated by using the 2006 WHO Child Growth Standards (22).

Statistical analyses were undertaken by using the statistical data management package Stata, version 10 (Stata Corp), and SAS, version 9.1 (SAS Institute, Cary, NC). All analyses were conducted in an intention-to-treat basis. The identity of the intervention groups was revealed to the investigators only after the statistical analyses were completed. Mann-Whitney Wilcoxon's rank-sum test was used to compare continuous variables, and chi-square analysis or Fisher's exact test for contingency data were used, as appropriate, to assess treatment group differences at baseline. Comparison of the number of days from enrollment until recovery and length of hospital stay was undertaken by using Cox proportional hazards models, whereas comparisons of dichotomous outcomes such as treatment failures were assessed in logistic regression models. We coded the outcomes and interventions so that HRs  $< 1$  and odds ratios (ORs)  $> 1$  would represent a beneficial effect of zinc administration. We adjusted the CIs for repeated enrolments by using the cluster option in Stata and thus allowed for possible dependence of observations in a child that was enrolled more than once. Student's  $t$  test was used to compare change in plasma zinc between the 2 groups.

### RESULTS

From 1 January 2004 to 30 June 2007 we screened 8651 children aged 2–35 mo with cough and/or difficult breathing; 3180 (37%) had WHO-defined pneumonia. Of these children, 552 (17%) were not eligible to be randomly assigned mainly because of intake of antibiotics during the previous 48 h or because the parents did not give consent. Of the remaining 2628 cases, 149 had severe pneumonia and 2479 had nonsevere pneumonia. In the severe pneumonia group, 111 were infants and 38 were  $\geq 12$  mo of age (ie, toddlers). The corresponding numbers in the nonsevere pneumonia group were 1097 infants and 1382 children aged  $\geq 12$  mo. The children were followed up until recovery or until they dropped out of the study. The number of dropouts in the zinc and placebo groups was 14 and 15, respectively. There were 4 trial deviations, 1 in the zinc group and 3 in the placebo group: 2 children reported cough for  $> 14$  d, 1 child received the wrong supplement, and 1 child had severe

anemia, and these children were excluded from the analysis (**Figure 1**). A total of 2201 episodes were first-time enrollments, 396 were second-time enrollments, and 31 were third-time enrollments.

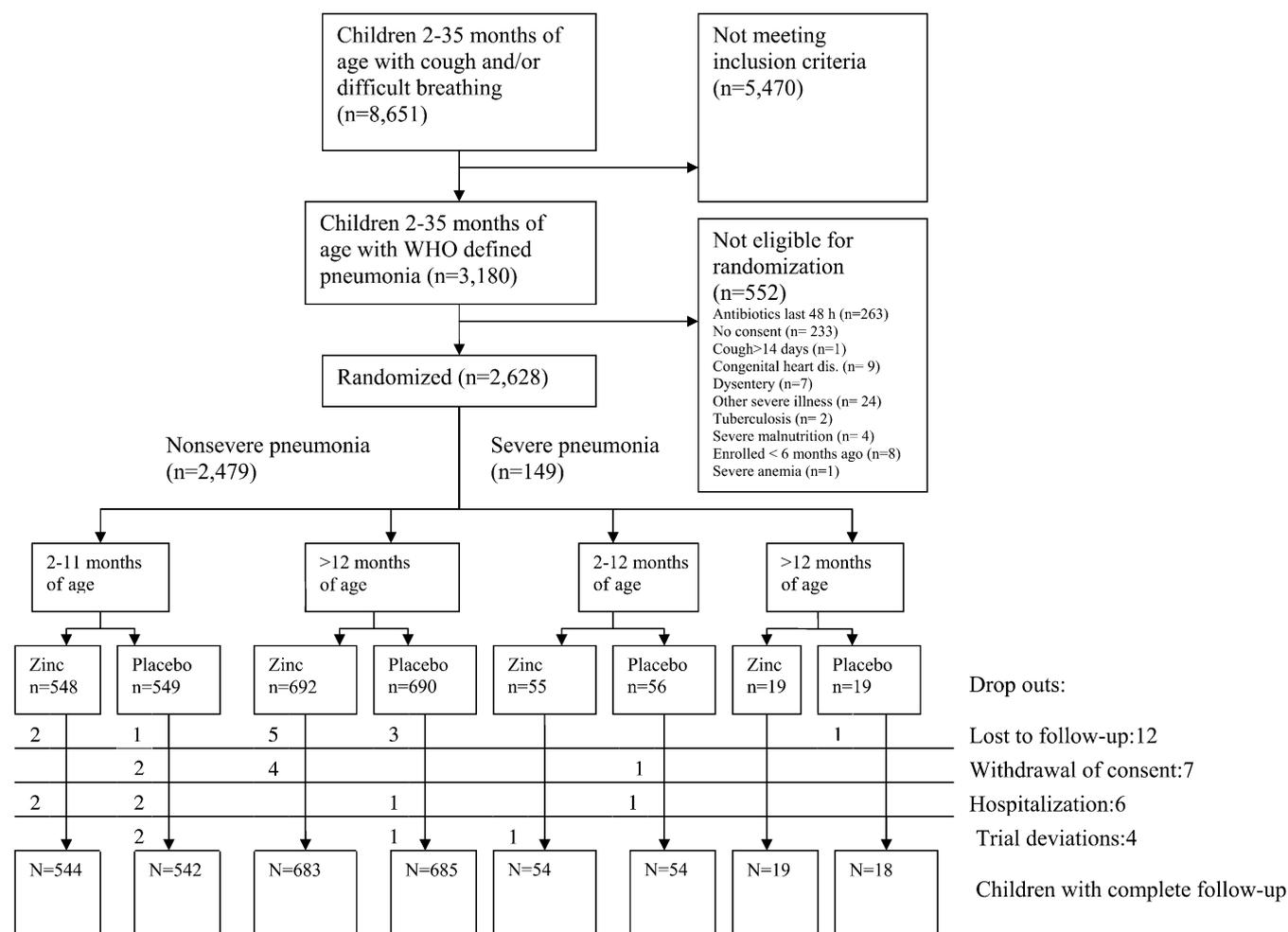
Baseline characteristics of the nonsevere pneumonia group, including those associated with severity of the episode, such as CRP concentration and oxygen saturation, were evenly distributed between randomization groups in the 2 age strata, with the exception of the proportion of illiterate fathers in children aged 2–11 mo (**Table 1**). Overall, wheezing was found in 39% and crepitations in 28% of cases. In one-third of cases, wheezing disappeared after nebulization treatment with salbutamol, with no difference between the 2 treatment arms.

Baseline characteristics of the severe pneumonia group were also fairly evenly distributed in the 2 age strata, with the exception of the proportion of boys, stunting, having an illiterate father or mother, and crepitations (**Table 1**). Overall, in children with severe pneumonia, the proportion of children with crepitations and wheezing after nebulization were very high at 63% and 77%, respectively.

Because the efficacy of zinc was similar in the 2 age strata with nonsevere pneumonia, the data were pooled. There was no difference in time to recovery between the zinc and placebo groups

(HR: 1.0; 95% CI: 0.96, 1.1) (**Table 2**). Adjustment for skewed baseline variables, such as having an illiterate father, did not alter our results (data not shown). Furthermore, there was no difference in the risk of treatment failure between the zinc group (23% in infants, 20% in toddlers) and the placebo group (22% in infants, 19% in toddlers) (OR: 0.95; 95% CI: 0.78, 1.2). During the 14-d period of the zinc/placebo intervention, the proportion of nonsevere pneumonia cases who needed a change to second-line antibiotics was 29% in the zinc and 27% in the placebo group (and within the first 3 d, these proportions were 21% and 20%, respectively). During the 14-d supplementation period, the proportion of children who were hospitalized due to pneumonia was comparable between the zinc group (2.5%) and the placebo group (1.7%) (OR: 1.5; 95% CI: 0.85, 2.6).

For the severe pneumonia stratum, the median time to recovery from severe pneumonia (ie, the beginning of a 24-h period without LCI) was 2 d for infants and 1 d for toddlers (**Table 3**). Because the efficacy of zinc was similar in both age strata, the data were pooled, and there was no difference in time to recovery between the zinc and placebo groups (HR: 1.1; 95% CI: 0.77, 1.5). Overall, the median duration of hospitalization was 3 d (interquartile range: 3–4 d), and this did also not differ between the zinc and placebo groups (HR: 1.1; 95% CI: 0.77, 1.5).



**FIGURE 1.** Consort flowchart of a randomized, placebo-controlled trial of zinc as adjunct therapy for pneumonia in children 2–35 mo of age in Bhaktapur, Nepal. WHO, World Health Organization.

**TABLE 1**Enrollment characteristics of children 2–35 mo of age with nonsevere or severe pneumonia in a trial evaluating the effect of zinc in Bhaktapur, Nepal<sup>1</sup>

Variable	Nonsevere pneumonia				Severe pneumonia			
	2–11 mo of age		≥12 mo of age		2–11 mo of age		≥12 mo of age	
	Zinc (n = 548)	Placebo (n = 549)	Zinc (n = 692)	Placebo (n = 690)	Zinc (n = 55)	Placebo (n = 56)	Zinc (n = 19)	Placebo (n = 19)
Age (mo)	6 (4–8) <sup>2</sup>	6 (4–8)	18 (14–24)	18 (14–24)	4 (3–6)	4 (3–6)	16 (14–26)	16 (13–22)
Boys [n (%)]	309 (56)	312 (57)	387 (56)	377 (55)	32 (58)	36 (64)	8 (42)	13 (68)
Breastfed [n (%)]	539 (98)	540 (98)	544 (79)	525 (76)	52 (95)	53 (95)	15 (79)	16 (84)
Duration of cough before enrollment (d)	3 (2–4)	3 (2–4)	3 (2–3)	3 (2–4)	3 (2–4)	3 (2–5)	3 (2–3)	2 (2–3)
Wheezing at first examination [n (%)]	237 (43)	212 (39)	254 (37)	266 (39)	49 (89)	49 (88)	16 (84)	16 (84)
Wheezing persisted after nebulizer [n (%)]	162 (30)	150 (27)	154 (22)	170 (25)	41 (75)	43 (77)	16 (84)	14 (74)
Crepitations [n (%)]	118 (22)	120 (22)	218 (32)	227 (33)	30 (55)	38 (68)	17 (89)	9 (47) <sup>3</sup>
CRP concentration (mg/L)	13 (<8–26)	14 (<8–26)	18 (8–32)	15 (8–29)	27 (<8–46)	21 (10–33)	17 (9–50)	14 (8–33)
Oxygen saturation (%)	94 (92–96)	94 (92–97)	94 (92–96)	94 (92–96)	92 (86–95)	92 (86–95)	92 (87–93)	91 (88–94)
Virus detected [n (%)]	181 (39)	165 (36)	251 (43)	232 (40)	19 (39)	24 (51)	8 (44)	8 (44)
Length-for-age less than –2Z (stunted) [n (%)]	54 (10)	50 (9.1)	240 (35)	259 (38)	9 (16)	4 (7.1)	7 (37)	12 (63)
Weight-for-length less than –2Z (wasted) [n (%)]	14 (2.6)	21 (3.8)	42 (6.1)	32 (4.6)	2 (3.6)	4 (7.1)	2 (11)	2 (11)
Illiterate father [n (%)]	33 (6.0)	20 (3.6)	40 (5.8)	49 (7.1)	2 (3.6)	4 (7.0)	1 (5.3)	3 (16)
Illiterate mother [n (%)]	132 (24)	136 (25)	203 (29)	197 (29)	17 (31)	12 (21)	4 (21)	11 (58) <sup>3</sup>
Serum zinc (μmol/L)	8.8 ± 2.1 <sup>4</sup>	8.9 ± 2.4	9.0 ± 2.4	8.8 ± 2.4	8.1 ± 2.9	8.9 ± 2.2	13 ± 13	7.9 ± 1.5

<sup>1</sup> CRP, C-reactive protein (CRP range: <8, 8–160, and >160 mg/L); –2Z, –2 z scores. Mann-Whitney Wilcoxon's rank-sum test was used to compare medians (and means). Chi-square or Fischer's test was used to compare proportions.

<sup>2</sup> Median; interquartile range in parentheses (all such values).

<sup>3</sup> Significantly different between groups,  $P < 0.05$ .

<sup>4</sup> Mean ± SD (all such values).

The time from enrollment with severe pneumonia to recovery from nonsevere pneumonia (ie, not having an elevated respiratory rate) was 4 d in the zinc group compared with 3 d in the placebo group for the infants, and 5 compared with 4 d for the toddlers in the zinc and placebo groups, respectively. Because the efficacy of zinc was similar in the 2 age strata, the data were pooled; the HR was 1.1 (95% CI: 0.77, 1.2), thus showing

no significant difference in the time to recovery between the zinc and placebo groups. Adjustment for the skewed baseline variables (proportion of boys, stunting, having an illiterate father or mother, and crepitations) did not change our results, with the exception that there was some confounding of time to recovery from severe pneumonia in toddlers (adjusted HR: 1.3; 95% CI: 0.57, 3.0). Treatment failure, defined as still having LCI after 48

**TABLE 2**

Main outcomes in a trial evaluating the effect of zinc as adjuvant treatment of nonsevere pneumonia in children 2–35 mo of age in Bhaktapur, Nepal

Variable	Nonsevere pneumonia			
	2–11 mo of age		≥12 mo of age	
	Zinc (n = 544)	Placebo (n = 542)	Zinc (n = 683)	Placebo (n = 685)
Median time to recovery (d)	2 (1–4) <sup>1</sup>	2 (1–4)	2 (1–4)	2 (1–4)
Hazard ratio for time to recovery (95% CI) <sup>2</sup>	1.1 (0.95, 1.2)		1.0 (0.92, 1.1)	
Hazard ratio for time to recovery (95% CI), pooled age strata <sup>2</sup>	1.0 (0.96, 1.1)			
Treatment failures [n (%)]	126 (23)	122 (22)	139 (20)	130 (19)
Odds ratio for treatment failure (95% CI) <sup>3</sup>	0.97 (0.73, 1.29)		0.92 (0.71, 1.20)	
Odds ratio for treatment failure (95% CI), pooled age strata <sup>3</sup>	0.95 (0.78, 1.2)			

<sup>1</sup> Median; interquartile range in parentheses (all such values).

<sup>2</sup> Derived by using a Cox proportional hazards model.

<sup>3</sup> Derived by using a logistic regression model.

**TABLE 3**

Main outcomes in a trial evaluating the effect of zinc as adjuvant treatment of severe pneumonia in children 2–35 mo of age in Bhaktapur, Nepal

Variable	Severe pneumonia			
	2–11 mo of age		≥12 mo of age	
	Zinc <i>n</i> = 54	Placebo <i>n</i> = 54	Zinc <i>n</i> = 19	Placebo <i>n</i> = 18
Time to recovery from severe pneumonia (d)	2 (1–3) <sup>1</sup>	2 (1–3)	1 (1–1)	1 (1–2)
Hazard ratio for recovery from severe pneumonia (95% CI) <sup>2</sup>	1.1 (0.75, 1.7)		0.99 (0.52, 1.9)	
Hazard ratio for recovery from severe pneumonia (95% CI), pooled age strata <sup>2</sup>	1.1 (0.77, 1.5)			
Time to recovery (d)	4 (2–7)	3 (2–6)	5 (2–6)	4 (2–6)
Hazard ratio for time to recovery (95% CI) <sup>2</sup>	1.1 (0.75, 1.6)		0.95 (0.49, 1.8)	
Hazard ratio for time to recovery (95% CI), pooled age strata <sup>2</sup>	1.1 (0.77, 1.2)			
Time to discharge from hospital (d)	3 (3–4)	3 (3–4)	3 (3–4)	3 (3–4)
Hazard ratio for time to discharge from hospital (95% CI) <sup>2</sup>	1.1 (0.72, 1.5)		1.2 (0.63, 2.3)	
Hazard ratio for time to discharge from hospital (95% CI), pooled age strata <sup>2</sup>	1.1 (0.77, 1.5)			
Treatment failure [ <i>n</i> (%)]	12 (22)	14 (26)	2 (10)	0 (0)
Odds ratio for treatment failure (95% CI) <sup>3</sup>	0.86 (0.35, 2.1)		Not calculated	
Odds ratio for treatment failure (95% CI), pooled age strata <sup>3</sup>	0.97 (0.42, 2.2)			

<sup>1</sup> Median; interquartile range in parentheses (all such values).<sup>2</sup> Derived by using a Cox proportional hazards model.<sup>3</sup> Derived by using a logistic regression model.

h of antibiotic treatment, was more common in infants (24%) than in toddlers (5%). Overall, the proportion of cases with treatment failure was 19%. There was no difference in the risk of treatment failure between zinc and placebo groups (OR: 0.97; 95% CI: 0.42, 2.2).

The proportion of cases with observed regurgitation or vomiting ≤15 min after receiving supplementation on the day of enrollment and during the whole supplementation period was substantially higher in cases receiving zinc than in those receiving placebo (Table 4). Similarly, in the morbidity interviews, vomiting during the first 24 h was more frequently reported in the zinc group than in the placebo group. The children receiving zinc had substantially higher plasma zinc concentrations 14 d after enrollment than did those in the placebo group.

## DISCUSSION

As a potential strategy for improving the management of pneumonia in developing countries, we measured the efficacy of zinc as adjuvant treatment of pneumonia. The present large clinical trial was conducted at a study site where a beneficial effect of zinc on the recovery from diarrhea was documented previously (16) and zinc deficiency is prevalent (17).

Overall, the compliance was very high. Only on 22 d (10 in the placebo compared with 12 in the zinc group) was it reported that the child did not receive the tablet dispersion. Good compliance was also confirmed by the expected rise in plasma zinc.

Zinc doses administered in this trial were comparable to those recommended by the WHO for case management of acute diarrhea (10), and we expected that any potential effect of zinc on

**TABLE 4**

Effect size of the intervention on regurgitation or vomiting and serum zinc in a trial evaluating the effect of zinc as adjuvant treatment of severe or nonsevere pneumonia in children 2–35 mo of age in Bhaktapur, Nepal

Variable	Zinc	Placebo	Strength of association
Observed regurgitation or vomiting after supplementation on day 1 [ <i>n</i> (%)] <sup>1</sup>	182 (13.9)	53 (4.0)	0.26 (0.19, 0.36) <sup>2</sup>
Observed regurgitation or vomiting during the 14 d of supplementation [ <i>n</i> (%)] <sup>1</sup>	484 (37)	166 (13)	0.25 (0.20, 0.30) <sup>2</sup>
Reported any cause vomiting during first 24 h after enrollment in children with nonsevere pneumonia [ <i>n</i> (%)] <sup>1</sup>	541 (42)	423 (33)	0.68 (0.58, 0.80) <sup>2</sup>
Change in plasma zinc concentration from enrollment to after 14 d of supplementation (μmol/L) <sup>3</sup>	5.9 ± 6.7 [89] <sup>4</sup>	0.5 ± 3.1 [90] <sup>4</sup>	5.4 (3.9, 6.9) <sup>5</sup>

<sup>1</sup> Derived by using a logistic regression model.<sup>2</sup> Odds ratio; 95% CI in parentheses.<sup>3</sup> Derived by using Student's *t* test.<sup>4</sup> Mean ± SD; *n* in brackets.<sup>5</sup> Mean difference; 95% CI in parentheses.

therapy for lower respiratory infections could be shown with this dosage. In the trial, we found an increased risk of regurgitation and vomiting among the zinc recipients similar to what was shown in trials of zinc supplementation in acute diarrhea (9, 16).

To avoid including children with reactive airway disease but without lower respiratory tract infection, children who presented with wheeze were treated with salbutamol. However, because wheezing is a part of the symptoms of lower respiratory tract infections (23), we included children who continued to have fast breathing after such nebulization.

To address the possibility that zinc may have an effect only in more severe episodes than those defined by the standard WHO diagnostic criteria, we also restricted our analyses to subgroups of nonsevere pneumonia that fulfilled the following criteria: oxygen saturation <93%; respiratory rates >10 breaths/min higher than WHO cutoffs; CRP concentration of  $\geq 40$  mg/L, which may be an indication of bacterial pneumonia (8); axillary temperature of  $\geq 38.5^\circ\text{C}$ ; no RNA virus detected by polymerase chain reaction in nasopharyngeal aspirate (21); and absence of wheezing or presence of crepitations. However, apart from a longer duration of the episode of pneumonia among toddlers with crepitations, we did not observe a statistically significant effect of zinc compared with placebo in the other subgroups (data not shown).

The 14-d course of zinc neither decreased the risk of treatment failure nor the time to recovery from pneumonia. Theoretically, the failure to observe an effect of zinc could have been due to lack of specificity of our ability to determine the outcome. Other factors, however, were strongly associated with these outcomes; CRP concentrations  $\geq 80$  mg/L and wheezing were associated with increased risk of treatment failure and longer time to recovery, whereas increasing age and current breastfeeding were associated with shorter duration and lower risk of treatment failure (data not shown). These observations lend credibility to our capacity to adequately identify cessation of pneumonia.

Treatment failures in response to oral co-trimoxazole for nonsevere pneumonia have been assessed in previous trials. Two large multicenter trials in Pakistan found 19% treatment failures at day 3, which is comparable to our findings (24, 25).

The required sample size for a comparison in time to recovery between zinc and placebo recipients with the use of a Cox proportional hazards model was much higher than the 149 participants who were enrolled in the severe pneumonia stratum. The fact that we did not include children who had received any antibiotics in the previous 48 h may have resulted in a bias toward milder cases. In fact, in the present trial, we found that children with severe pneumonia were more likely to have received antibiotics in the previous 48 h compared with children with nonsevere pneumonia (19% compared with 8%, respectively).

Zinc plays a role in the development and maintenance of host defense against infections (26). The acute phase response that follows infection is characterized by a decrease in serum zinc concentrations (27). It has been hypothesized that preventing this decline by supplementing zinc would lead to a better clearing of the infection by some (3), whereas others have claimed that this may exaggerate the acute phase response as indicated by, for example, elevated body temperature (28). The convincing studies of the effect of zinc in diarrhea led us to assume that zinc would also have a beneficial effect as adjunct therapy for pneumonia. However, although the lower respiratory tract is often referred to as part of the common mucosal immune system, it is very dif-

ferent from the gut because, under normal circumstances, it is sterile below the larynx. Damage inflicted by infection to the lower respiratory tract occurs not only through evasion of the immune system and direct pathogen-induced host cell killing but also through “collateral/bystander effects” damage due to the robust host response. Indeed, the same host defense mechanisms that eradicate infection cause tissue damage and may be the major cause of damage found in a pathogenic insult (29). Thus, in acute lower respiratory infections it may be beneficial to actually lower inflammatory signals (26). This is demonstrated by studies showing that a significant reduction, but no elimination of T cells, does not impede pathogen clearance or the deposition of sufficient immune memory to rapidly blunt subsequent encounters (30).

Despite substantial increases in plasma zinc concentrations reflecting good compliance, we have shown with very high precision that zinc neither had a beneficial effect in the adjunct treatment of community acquired nonsevere childhood pneumonia nor, albeit with much lower precision, in severe pneumonia. Zinc was associated with mild side effects, such as an increased risk of regurgitation and vomiting, especially during the first day of supplementation, as shown previously in this study site and elsewhere. On the basis of this large study conducted in a population with subclinical zinc deficiency, we believe that zinc has no place in the case management of nonsevere pneumonia. Further large studies are needed to assess whether zinc may have an effect in severe pneumonia or in severe bacterial infection.

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