PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

A Randomized Controlled Trial of Zinc as Adjuvant Therapy for Severe Pneumonia in Young Children

Sudha Basnet, Prakash S. Shrestha, Arun Sharma, Maria Mathisen, Renu Prasai, Nita Bhandari, Ramesh K. Adhikari, Halvor Sommerfelt, Palle Valentiner-Branth, Tor A. Strand and members of the Zinc Severe Pneumonia Study Group

Pediatrics 2012;129;701; originally published online March 5, 2012;
DOI: 10.1542/peds.2010-3091

A Randomized Controlled Trial of Zinc as Adjuvant Therapy for Severe Pneumonia in Young Children

AUTHORS: Sudha Basnet, MD,[a] Prakash S. Shrestha, MD,[a] Arun Sharma, MD,[a] Maria Mathisen, PhD,[b] Renu Prasai, DCH,[c] Nita Bhandari, PhD,[d] Ramesh K. Adhikari, MD,[a] Halvor Sommerfelt, PhD,[b,e] Palle Valentiner-Branth, PhD,[f] Tor A. Strand, PhD,[b,e,g] and members of the Zinc Severe Pneumonia Study Group

[a]Child Health Department, Institute of Medicine, Tribhuvan University, Kathmandu, Nepal; [b]Centre for International Health, University of Bergen, Bergen, Norway; [c]Kanti Children's Hospital, Kathmandu, Nepal; [d]Society for Applied Studies, New Delhi, India; [e]Division of Infectious Disease Control, Norwegian Institute of Public Health, Oslo, Norway; [f]Division of Epidemiology, Department of Epidemiology, Statens Serum Institut, Copenhagen, Denmark; and [g]Medical Microbiology, Innlandet Hospital Trust Lillehammer, Norway

KEY WORDS
zinc, pneumonia, young children, therapeutic, treatment failure

ABBREVIATIONS
CR—chest radiograph
LCI—lower chest indrawing
SpO_2—oxygen saturation
WHO—World Health Organization

Drs Basnet, Shrestha, Sharma, Adhikari, Sommerfelt, and Strand made primary contributions to the design, conduct, analysis, interpretation, and writing of this manuscript; Drs Prasai and Mathisen contributed to the field conduct, training and standardization, collection of biological specimen, and quality control of the trial; Dr Mathisen was also responsible for the virus analyses; Drs Bhandari and Valentiner-Branth contributed to the development and design of the trial and to the interpretation of the study results; Dr Strand had full access to all the data in the study and took the final decision to submit this report for publication.

This trial has been registered at www.clinicaltrials.gov (identifier NCT00252304).

www.pediatrics.org/cgi/doi/10.1542/peds.2010-3091

doi:10.1542/peds.2010-3091

Accepted for publication Nov 28, 2011

(Continued on last page)

WHAT'S KNOWN ON THIS SUBJECT: Pneumonia is still a significant problem in young children from developing countries where zinc deficiency is prevalent. Although zinc supplementation reduces the risk of childhood pneumonia, the effect of adjunct zinc on severe pneumonia is unclear with conflicting results.

WHAT THIS STUDY ADDS: The overall effect, if any, of zinc as adjuvant therapy for World Health Organization–defined severe pneumonia in young children is small.

abstract

FREE

BACKGROUND AND OBJECTIVE: Diarrhea and pneumonia are the leading causes of illness and death in children <5 years of age. Zinc supplementation is effective for treatment of acute diarrhea and can prevent pneumonia. In this trial, we measured the efficacy of zinc when given to children hospitalized and treated with antibiotics for severe pneumonia.

METHODS: We enrolled 610 children aged 2 to 35 months who presented with severe pneumonia defined by the World Health Organization as cough and/or difficult breathing combined with lower chest indrawing. All children received standard antibiotic treatment and were randomized to receive zinc (10 mg in 2- to 11-month-olds and 20 mg in older children) or placebo daily for up to 14 days. The primary outcome was time to cessation of severe pneumonia.

RESULTS: Zinc recipients recovered marginally faster, but this difference was not statistically significant (hazard ratio = 1.10, 95% CI 0.94–1.30). Similarly, the risk of treatment failure was slightly but not significantly lower in those who received zinc (risk ratio = 0.88 95% CI 0.71–1.10).

CONCLUSIONS: Adjunct treatment with zinc reduced the time to cessation of severe pneumonia and the risk of treatment failure only marginally, if at all, in hospitalized children. *Pediatrics* 2012;129:701–708

The estimated number of deaths globally in children aged <5 years was 8.8 million in 2008.[1] Pneumonia and diarrhea combined are responsible for ~45% of these deaths.[2] It is estimated that zinc deficiency in association with diarrhea, pneumonia, and malaria contributes to 4.4% of deaths and 3.8% of lost disability adjusted life years among children aged 6 to 59 months in Africa, Latin America, and Asia.[3] In a meta-analysis of clinical trials evaluating the preventive role of zinc, daily supplementation led to 14% and 8% reductions in the risk of diarrhea and pneumonia, respectively.[4] The World Health Organization (WHO) now recommends zinc for the treatment of children with diarrhea[5] because there is sufficient evidence demonstrating that supplementation reduces the severity and duration of the episode.[6] The benefit of zinc in the treatment of pneumonia is, however, unclear. Although zinc as adjuvant therapy for hospitalized children with pneumonia was found to be beneficial in 1 clinical trial in Bangladesh,[7] other trials in India[8] and Australia[9] found no effect. In developing countries, the estimated incidence of clinical pneumonia in children aged <5 years is 0.29 episodes per child year.[10] Despite a declining trend, the incidence of pneumonia in Nepal is 0.13 episodes per child per year with severe pneumonia accounting for 1.2% of the all cases of acute respiratory infections.[11] We have previously shown that zinc deficiency is common in children[12] and in women of reproductive age[13] in the Kathmandu valley. In a large community-based trial in Bhaktapur, Nepal, zinc administration did not reduce time till recovery or risk of treatment failure in children with pneumonia.[14] Whether zinc administration has a beneficial effect when given to children hospitalized with severe pneumonia needs to be clarified. We therefore undertook a clinical trial to assess the efficacy of zinc as adjuvant therapy to standard antibiotic treatment in reducing the time to cessation and the risk of treatment failure of a severe pneumonia episode.

METHODS

This was a double-blind, randomized, placebo-controlled trial in young children designed to measure the impact of daily zinc administration for up to 14 days on time to cessation of severe pneumonia. An important secondary outcome was the risk of treatment failure. Clearances were obtained from the ethical board of the Institute of Medicine, Tribhuvan University, and Nepal Health Research Council, Kathmandu.

Sample Size Calculation

The study was based on the hypothesis that zinc sulfate given as adjuvant therapy to standard antibiotic treatment would result in a reduction of the median duration of hospital stay by 1 day. In a similar study in Bangladesh,[7] the median time to resolution from severe pneumonia was 3 days in the zinc and 4 days in the placebo group. With a minimal detectable hazard ratio of 1.30 for time to cessation of severe pneumonia, we estimated a total sample size of 500 children. Calculations were done with 80% power and an α error of 5%. Assuming up to 20% loss to follow-up, we enrolled 610 children.

Enrollment, Baseline Clinical Workup, and Initiation of Antibiotic Therapy

Children aged 2 to 35 months presenting to the Kanti Children's hospital emergency or outpatient departments with complaints of cough lasting <14 days and/or difficult breathing of <72 hours duration with lower chest indrawing (LCI) were screened for enrollment by trained physicians. The Integrated Management of Childhood Illnesses algorithm was used to define severe pneumonia.[15] Eligible children were initially assessed for hypoxemia by using a pulse oximeter (Nellcor Puritan Bennett NPB-40, Pleasanton, CA) with a pediatric sensor (Nellcor Pedichek D-YSPD) and presence of wheezing. Oxygen saturation (SpO_2) was recorded twice after stabilization of the reading for 1 minute. The higher of the 2 readings was used. For children with SpO_2 of <90%, oxygen was provided before further evaluation. Children with wheezing were given up to 3 doses of nebulized Salbutamol 15 minutes apart, reassessed, and excluded if LCI disappeared.[16] A history of the child's illness was taken and physical examination carried out by using a standardized form. Children were weighed by using an Electronic Scale 890 (SECA, Hamburg, Germany) that measures to the nearest 100 g. Height was measured by using a standard wooden height measuring board, and recumbent length in children <2 years was measured by using an infantometer, both to the nearest 0.1 cm. Stunting defined as length-for-age ≤2 *z* score and wasting as weight-for-length ≤2 *z* score were calculated by using the 2006 WHO Child Growth Standards.[17] We measured hemoglobin concentrations by using Hemocue (Ångelholm, Sweden). A chest radiograph (CR) taken in all children was interpreted by a radiologist blinded to clinical data by using the WHO standardized tool for interpretation of CRs and findings classified as endpoint consolidation, other infiltrates, or normal.[18] Children with recurrent wheezing (defined as >3 episodes over the past 6 months and on treatment with bronchodilators), disappearance of LCI after nebulized salbutamol, severe wasting,[19] severe anemia (hemoglobin <7 g/dL), heart disease, documented tuberculosis, or concomitant diarrhea with dehydration and those with severe illness requiring special care or surgical intervention were excluded. Informed consent was obtained for eligible children.

Literate parents signed the consent form after they had read a written statement in the local Nepali language. For parents who were unable to read or write, verbal informed consent was obtained in the presence of a witness. After obtaining consent, blood was collected for investigations, and the first dose of intravenous antibiotics was administered. This was followed by collection of nasopharyngeal aspirate for identification of 7 respiratory viruses. Details of the sampling technique and the results of these analyses have been described in a separate publication[20]

Randomization, Intervention, and Blinding

The intervention was dispersible tablets containing 10 mg of elemental zinc sulfate or placebo, manufactured and packed by Nutriset (Malaunay, France) in a blister pack with 15 tablets. Tablets of both groups were identical in packaging, appearance, and inactive ingredients with no indication of group identity and content. For each child in the study, there were 3 blister packs with zinc or placebo tablets labeled with a serial number to match the child study identification number. The randomization list linking the treatment groups to these identification numbers was generated by and kept with a person not otherwise involved in the study. Children were allocated to either of the 2 intervention groups by randomization in blocks of 16 in a 1:1 ratio. Randomization was stratified on age $<$12 months or $\geq$12 completed months and on wheezing status before nebulization. Study physicians selected blister packs with the lowest number from a box specifying the stratum to which each child belonged. Children $<$12 months were given 1 tablet and children $\geq$12 months were given 2 tablets dissolved in 5 mL of clean water or breast milk. The first dose was dispensed by the study physician and subsequently by trained study assistants who were not otherwise involved in patient care. The zinc or placebo dispersions were given as a single daily dose until discharge or for a maximum of 14 days. All children were observed for vomiting. For children who vomited within the first 15 minutes, a repeat dose was given. Children who vomited the second time were given the required amount in 2 divided doses over a 24-hour period from the next day onward.

Outcome Definitions

The primary outcome, time to cessation of severe pneumonia, was defined as the period starting from enrollment to the beginning of a 24-hour consecutive period of absence of LCI, hypoxia, and any danger signs. We used WHO guidelines to define hypoxia (SpO_2 of $<$90%) and danger signs such as inability to breastfeed or drink, vomiting everything consumed, convulsions, lethargy, or unconsciousness.[19] The secondary outcome, treatment failure, was defined as a requirement for change in antibiotics, development of complications, such as empyema or pneumothorax requiring surgical intervention, or admission to the ICU for ventilator or inotropic support.

Cointerventions

Enrolled children were admitted to the hospital and monitored by study physicians at ~8 hourly intervals until discharge. Benzyl penicillin (50 000 U/kg intravenously every 6 hours) and gentamicin (7.5 mg/kg intravenously once daily) were given until clinical improvement, defined as absence of danger signs, of hypoxia for 24 consecutive hours and of LCI for a 48-hour period. Patients were then discharged with advice to continue oral amoxicillin to complete treatment of a total duration of 10 days.

Antibiotics were changed to cefotaxime in children with failure to improve, defined as persistence of LCI or of any danger signs present at enrollment despite 48 hours of treatment or appearance of new danger signs or hypoxia with deterioration of patient's clinical status anytime after initiation of treatment. A decision to change antibiotics was made only after consultation with senior pediatricians involved in the study. For children unable to eat/drink or breastfeed, intravenous fluids based on daily requirements were initiated.[19] Humidified oxygen was given to children with documented hypoxia. During each physician visit, oxygen saturation was documented after a washout period of 5 minutes and oxygen discontinued when they were no longer hypoxic. The absence of hypoxia was confirmed after a second reading taken 30 minutes later.

Study physicians were trained to assess and manage children with severe pneumonia, and their performance was monitored each day by experienced pediatricians, who were also the investigators for this study. Standardization exercises were conducted before the start of the trial. Each physician was assigned to record axillary temperature, count respiratory rate, observe for LCI, and listen for wheezing and crepitations in at least 10 children. Their findings were matched against those of an experienced pediatrician until the desired agreement was reached.

Data Management and Analysis

The completed forms with patient data were collected by the study assistants on a daily basis. All forms were checked manually by 1 of the clinical supervisors before data entry, which was done within 48 hours. The data were double entered into a database (Visual FoxPro 6.0, Microsoft Corp, Redmond, WA) with inbuilt logic, range, and consistency checks. Statistical analyses were undertaken by using Stata, version 10 (Stata Corp, College Station, TX). Data cleaning,

definition of outcome variables, exclusion of cases as well as programming of scripts in the statistical packages were done before the analysis files were merged with the randomization lists. We used Cox proportional hazards regression models to compare the time to cessation of severe pneumonia between the treatment groups, the effect estimates expressed as hazard ratios. Treatment failure, risk of prolonged illness and vomiting after the first dose of the intervention was compared by using generalized linear regression models with log link functions and binomial distributions, yielding relative risks. We coded the outcomes and interventions so that hazard ratios >1 and relative risks <1 would represent a beneficial effect of zinc. Differences were considered significant when a two-sided *P* value was <.05.

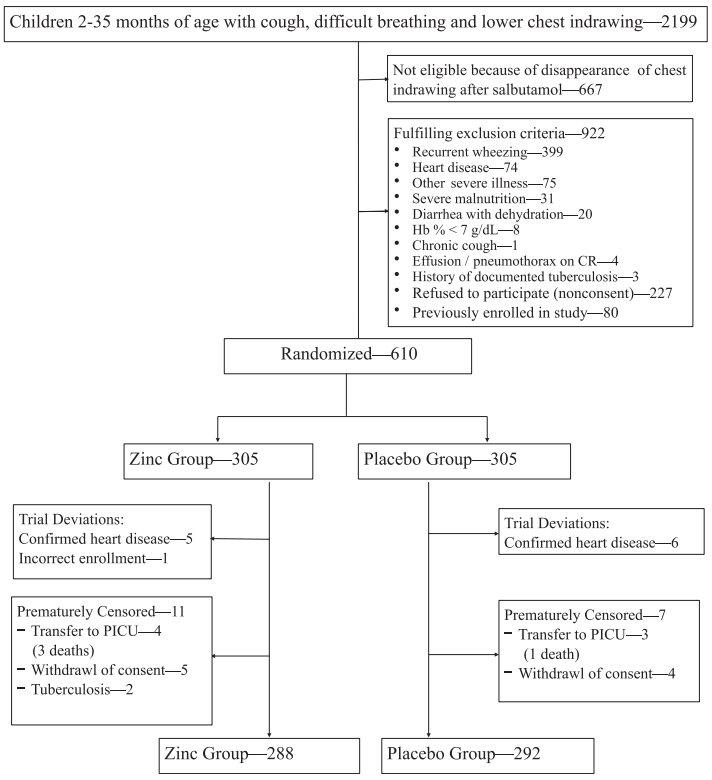

FIGURE 1
Trial profile of a randomized, placebo-controlled trial of zinc as adjunct therapy for severe pneumonia in children aged 2 to 35 months of age in Kanti Children's Hospital, Kathmandu, Nepal.

RESULTS

From January 8, 2006, to June 30, 2008, we screened 2199 children meeting inclusion criteria. There were 1589 (72%) who were not eligible for randomization, of whom 1282 (58%) fulfilled the predefined exclusion criteria (Fig 1), 227 (10%) did not consent, and 80 (4%) had been previously enrolled. After enrollment and randomization of the remaining 610 children, we discovered that 11 with heart disease 1 with cough duration >14 days had been included. These trial deviates were evenly distributed between the study arms (Fig 1) and were excluded from the analysis. Of the remaining 598 children, 299 were randomized to receive zinc and 299 to receive placebo. In the zinc group, 199 of the 245 (81%) infants and 45 of the 54 (83%) older children had wheezing. In the placebo group, 208 of the 248 (84%) infants compared with 40 of the 51 (78%) older children presented with wheezing. Eleven children were lost to follow-up in the zinc arm and 7 in the placebo arm (Fig 1). The remaining 580 (288 in the zinc and 292 in placebo arms) stayed in the study until recovery from severe pneumonia.

Viruses were isolated from nasopharyngeal aspirates in 29% with details described elsewhere.[20] Among 533 CRs available for interpretation, 520 films were of adequate quality. Endpoint consolidation was identified in 126 (24%), 196 (38%) had other infiltrates, and 198 (38%) were normal. Most baseline characteristics were evenly distributed between groups (Tables 1 and 2).

Analyses were done by intention to treat. The time until cessation of severe pneumonia was slightly shorter among the zinc recipients, with a hazard ratio of 1.10, 95% confidence interval 0.94 to 1.30; $P = .22$ (Table 3). We explored whether the effect of zinc was different in subgroups on the basis of age, gender, presence of fever, hypoxia, wheezing, crepitations, virus isolated in nasopharyngeal aspirate, endpoint consolidation on CR, wasting, and stunting. In the subgroup consisting of children with endpoint consolidation, zinc recipients recovered significantly faster than those in the placebo group (Fig 2). The effect of zinc, however, was not significantly different between those with and without radiographic pneumonia, that is, the interaction was not statistically significant. We also compared the proportion of children with severe pneumonia at 72, 96, or 120 hours after admission between the study groups. These comparisons were also in favor of zinc, but none reached statistical significance (Table 3). The risk of treatment failure was lower among the zinc recipients; however, this was also not statistically significant (risk ratio: 0.88; 95% confidence interval: 0.71–1.10). Adjusting for potential confounders altered the results

TABLE 1 Baseline Demographic Characteristics of Children aged 2 to 35 Months in a Clinical Trial Evaluating Efficacy of Zinc as Adjuvant Therapy for Severe Pneumonia

Characteristic	Zinc Group		Placebo Group	
	n	Value	*n*	Value
Mean age in months (SD)	299	7.8 (6.0)	299	7.1 (5.6)
Age groups (months)				
2–6, *n* (%)	299	167 (55.9)	299	185 (61.7)
7–11, *n* (%)	299	78 (26.1)	299	63 (21.1)
12–23, *n* (%)	299	45 (15.1)	299	45 (15.0)
24–35, *n* (%)	299	9 (3.0)	299	6 (2.0)
Male subjects, *n* (%)	299	177 (59.2)	299	190 (63.6)
Mean age of mother, y (SD)	292	24.7 (4.2)	294	24.1 (4.1)
Illiterate[a] mother (%)	292	79 (27.1)	294	75 (25.5)
Illiterate[a] father (%)	293	20 (6.8)	295	18 (6.1)
Unemployed[b] mother (%)	290	205 (70.7)	294	213 (72.5)
Unemployed[b] father (%)	289	10 (3.5)	291	9 (3.1)
Child still breastfeeding	299	283 (94.6)	299	288 (96.3)

[a] No schooling with inability to read part or whole of a sentence.

[b] No work/housework.

TABLE 2 Baseline Clinical Characteristics of Children Aged 2 to 35 Months Enrolled in a Clinical Trial on the Efficacy of Zinc as Adjuvant Therapy for Severe Pneumonia

Characteristic	Zinc		Placebo	
	n	Value	*n*	Value
Mean duration of cough in days (SD)	299	4.0 (2.0)	299	4.2 (2.2)
Mean duration of difficulty breathing in hours (SD)	299	30.2 (20.2)	299	29.6 (18.3)
Mean duration of fever in days (SD)	264	3.5 (2.0)	279	3.5 (2.1)
Wt for length/height ≤2 *z* score[a] (%)	296	86 (29.1)	298	71 (23.8)
Length/height for age ≤2 *z* score[a] (%)	299	28 (9.4)	299	22 (7.4)
Mean hemoglobin in g/dL (SD)	299	11.0 (1.4)	299	10.9 (1.4)
Mean axillary temperature in °C (SD)	299	37.7 (0.8)	299	37.7 (0.9)
Febrile[b] (%)	299	46 (15.4)	299	46 (15.4)
Mean respiratory rate in breaths per minute (SD)				
2–11 mo	245	64 (12)	248	65 (12)
12–35 mo	54	60 (13)	51	63 (10)
Mean oxygen saturation (SD)	299	86 (8)	299	87 (9)
Oxygen saturation (%)				
<90%	299	186 (62.2)	299	187 (62.5)
<93%	299	255 (85.3)	299	249 (83.3)
Wheezing (%)	299	244 (81.6)	299	248 (82.9)
Crepitations (%)	299	273 (91.3)	299	276 (92.3)
Endpoint consolidation on CR	258	60 (23.3)	262	66 (25.2)
Symptoms of severe pneumonia				
Child unable to drink/breastfeed (%)	299	30 (10.0)	299	24 (8.0)
History of convulsions (%)	299	1 (0.3)	299	2 (0.7)
Vomiting everything child eats (%)	294	9 (3.1)	292	5 (1.7)
Child unconscious/lethargic (%)	299	25 (8.4)	299	30 (10.0)
Signs of severe pneumonia				
Nasal flaring (%)	298	116 (38.9)	299	116 (38.8)
Grunting (%)	299	60 (20.1)	299	71 (23.8)
Head nodding (%)	299	65 (21.7)	299	73 (24.4)
Central cyanosis (%)	299	1 (0.3)	299	2 (0.7)

[a] Derived by using the recent WHO Child Growth Standards.[17]

[b] Defined as axillary temperature of >38.5°C.

only marginally. The proportion of children who vomited after the first dose of supplement was higher (14%) in the zinc than in the placebo group (9%; $P = .052$).

DISCUSSION

This study on zinc as adjunct therapy in children with severe pneumonia shows a modest but not statistically significant effect of daily zinc administration in reducing time to cessation of severe pneumonia defined as a 24-hour consecutive period of absence of LCI, hypoxia, and any other danger sign.

In a study undertaken in Bangladesh,[7] children who received zinc recovered faster, and fewer had treatment failure and duration of severe pneumonia lasting >72, 96, or 120 hours. The results from our trial were in the same direction but smaller. Another trial in South India[8] failed to show any beneficial effect of zinc on duration of illness in young children with severe pneumonia. In another study from Kolkatta, India,[21] although zinc was efficacious in boys, the overall effect as well as the interaction between gender and zinc administration was not statistically significant. All these studies, like our study, were double-blind randomized controlled trials assessing the efficacy of zinc in children with severe pneumonia. Inherent differences in the populations studied and differences in the illness characteristics including preenrollment duration and definition of recovery would explain the discrepancy between studies.

In the current trial, the proportion of children with wheezing was 82% compared with 37% in the Bangladeshi[7] and 62.5% in the South Indian trial.[8] Because children with reactive airway disease would meet criteria for inclusion in our study, we excluded children with a history of recurrent wheezing and enrolled others only if LCI persisted after salbutamol administration. Brooks et al reported that in children without wheezing, administration of zinc resulted in earlier resolution of clinical signs.[7] The effect of zinc was not modified by wheezing status in our subgroup analysis (Fig 2), a finding similar to that reported from South India.[8] However, because there were only 106 children without wheezing, we had insufficient power to detect an effect of zinc in this subgroup.

TABLE 3 Primary and Secondary Outcomes in a Randomized, Placebo-Controlled Trial on Oral Zinc as Adjunct Therapy for Severe Pneumonia in Children 2 to 35 Months of Age

	Zinc Group		Placebo Group		Hazard Ratio[a] (95% CI)	*P*
	n	Value (IQR)	*n*	Value (IQR)		
Median time to cessation of severe pneumonia in hours	288	49 (33, 77)	292	49 (29, 91)	1.10 (0.94 – 1.30)	.22
Proportion with duration of severe pneumonia in hours					Risk Ratio[b] (95% CI)	
>72	295	83 (28)	297	104 (35)	0.80 (0.63–1.02)	.07
>96	294	56 (19)	296	64 (22)	0.88 (0.64–1.21)	.44
>120	293	31 (11)	294	46 (16)	0.67 (0.44–1.03)	.07
Proportion with treatment failure	296	98 (33)	298	111 (37)	0.88 (0.71–1.10)	.29
Proportion with vomiting after supplement[c]	299	41 (14)	299	26 (9)	1.57 (0.99–2.50)	.05

IQR, interquartile range.

[a] Hazard ratio for time until cessation of severe pneumonia was estimated by using Cox proportional hazards models. A value of >1 indicates beneficial effect of zinc.

[b] From generalized linear models with a log link function and binomial distribution.

[c] After the first dose.

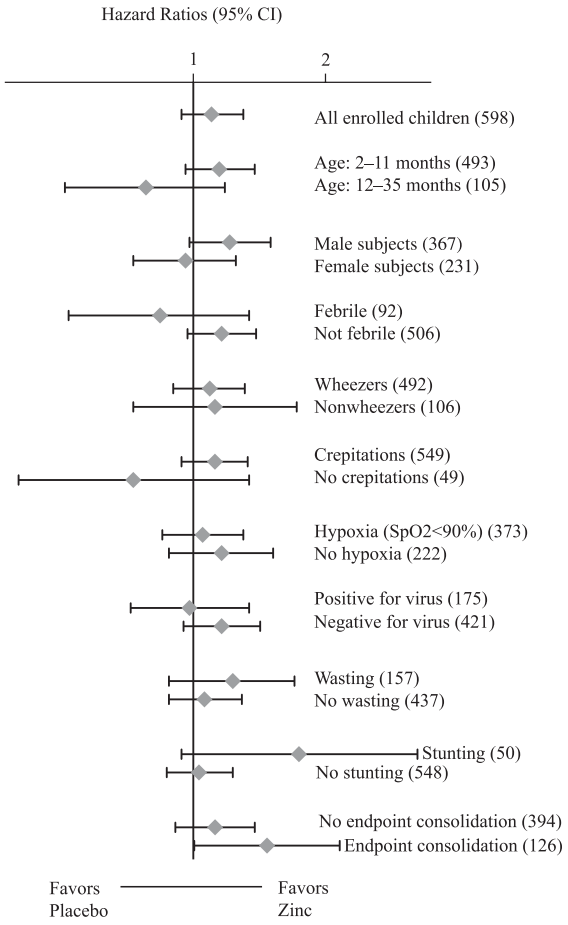

FIGURE 2

The efficacy of oral zinc given during an episode of severe pneumonia in Nepalese children aged 2 to 35 months in selected subgroups. Hazard ratios for time until cessation of severe pneumonia were estimated by using Cox proportional hazards models. A value >1 indicates beneficial effect of zinc. Weight for length/height ≤2 *z* score by using WHO child growth standards. Length/height for age ≤2 *z* score by using WHO child growth standards.

This study enrolled 610 children and to our knowledge is the largest trial conducted to date on zinc given during severe pneumonia. The study was conducted in an area where zinc deficiency is common[12,13] and in a country where pneumonia in young children is a significant health problem.[11] The study site is the only government hospital and referral center for children living in as well as outside Kathmandu. We had study physicians who were well trained and dedicated only to this trial. Daily doses of supplement were provided by study assistants and not the physicians recruited for the study. Limiting duration of difficulty breathing to ≤72 hours ensured that we enrolled children with an acute episode of pneumonia. We used objective outcomes for defining resolution, disappearance of LCI and SpO_2 ≥90%, which are replicable findings. In a review assessing the precision of clinical signs in the diagnosis of pneumonia, Margolis et al concluded that there is better agreement among observers for a clinical sign that can be observed, such as respiratory effort retractions (κ = 0.48), than for an auscultatory sign, such as presence of adventitious sounds (κ = 0.3).[22]

The high proportion of children with wheezing is a limitation of this study, a finding likely due to use of WHO criteria in defining severe pneumonia. This definition has high specificity for severe lower respiratory tract infection but does not define the etiology.[23] Severe pneumonia includes a wide spectrum of causes and predisposing factors that may respond differently to zinc administration. Furthermore, this heterogeneity can also result in poor specificity of the outcomes, which again may dilute

a measureable effect of zinc. Using CRs to improve the diagnosis enabled us to identify only 24% with radiographic pneumonia. It is also noteworthy that there was significant beneficial effect of zinc in this subgroup. Future studies are needed exploring the role of zinc in severe pneumonia in which children with wheezing are excluded and CR, microbiologic, and inflammatory markers are used in an attempt to arrive at a more specific diagnosis.[24]

CONCLUSIONS

This trial yielded a small but not statistically significant efficacy estimate for zinc in the resolution of severe pneumonia in hospitalized 2- to 35-month-old children. All study participants received optimized antibiotic and other therapies, an aspect that needs to be taken into account when the results from this trial as well as those of other completed, ongoing, and planned studies are interpreted and summarized to determine the role of zinc in the treatment of severe pneumonia.

ACKNOWLEDGMENTS

The Zinc Severe Pneumonia Study Group is: Rameswar Man Shrestha, MD; Uday Raj Upadhaya, DCH; Chandeshwar Mahaseth, MRCP; Rojen Sundar Shrestha, DCH; Puja Shrestha, MBBS; Geetika KC, MBBS; Yagya Ratna Shakya, MBBS; Ujma Shrestha, MBBS.

We thank all the children and their families who took part in the study. We are indebted to field assistants Mahesh Kumar Thapa and Ram Krishna Khatri and the study physicians for their contribution to the study as well as other staff of the Child Health Research Project. We thank the director of the Kanti Children Hospital and staff of the Emergency, Observation, Acute Respiratory Illness/Oral Rehydration Therapy, Medical, Paying and Special Cabin wards for their invaluable support. We also thank the head of the Department of Child Health, Professor Pushpa Raj Sharma, and other faculty members for their support, the Department of Microbiology, Tribhuvan University Teaching Hospital, Kathmandu, for providing the laboratory facilities and Dr Dhiraj Man Shrestha for interpretation of chest radiographs. We thank Solfrid Vikøren for excellent administrative support and Hans Steinsland for generating the randomization list and maintaining it until the end of the study.

REFERENCES

1. Black RE, Cousens S, Johnson HL, et al; Child Health Epidemiology Reference Group of WHO and UNICEF. Global, regional, and national causes of child mortality in 2008: a systematic analysis. *Lancet*. 2010;375(9730):1969–1987
2. Rudan I, El Arifeen S, Black RE, Campbell H. Childhood pneumonia and diarrhoea: setting our priorities right. *Lancet Infect Dis*. 2007;7(1):56–61
3. Fischer Walker CL, Ezzati M, Black RE. Global and regional child mortality and burden of disease attributable to zinc deficiency. *Eur J Clin Nutr*. 2009;63(5):591–597
4. Aggarwal R, Sentz J, Miller MA. Role of zinc administration in prevention of childhood diarrhea and respiratory illnesses: a meta-analysis. *Pediatrics*. 2007;119(6):1120–1130
5. World Health Organization; United Nations Children's Fund; Johns Hopkins Bloomberg School of Public Health; USAID. *Implementing the New Recommendations on the Clinical Management of Diarrhea: Guidelines for Policy Makers and Programme Managers*. Geneva, Switzerland: World Health Organization; 2006
6. Fontaine O. Effect of zinc supplementation on clinical course of acute diarrhea. *J Health Popul Nutr*. 2001;19(4):338–346
7. Brooks WA, Yunus M, Santosham M, et al. Zinc for severe pneumonia in very young children: double-blind placebo-controlled trial. *Lancet*. 2004;363(9422):1683–1688
8. Bose A, Coles CL, Gunavathi JH, et al. Efficacy of zinc in the treatment of severe pneumonia in hospitalized children <2 y old. *Am J Clin Nutr*. 2006;83(5):1089–1096, quiz 1207
9. Chang AB, Torzillo PJ, Boyce NC, et al. Zinc and vitamin A supplementation in Indigenous Australian children hospitalised with lower respiratory tract infection: a randomised controlled trial. *Med J Aust*. 2006;184(3):107–112
10. Rudan I, Boschi-Pinto C, Biloglav Z, Mulholland K, Campbell H. Epidemiology and etiology of childhood pneumonia. *Bull World Health Organ*. 2008;86(5):408–416
11. Ghimire M, Pradhan YV, Maskey MH. Community-based interventions for diarrheal diseases and acute respiratory infections in Nepal. *Bull World Health Organ*. 2010;88:216–221
12. Strand TA, Adhikari RK, Chandyo RK, Sharma PR, Sommerfelt H. Predictors of plasma zinc concentrations in children with acute diarrhea. *Am J Clin Nutr*. 2004;79(3):451–456
13. Chandyo RK, Strand TA, Mathisen M, et al. Zinc deficiency is common among healthy women of reproductive age in Bhaktapur, Nepal. *J Nutr*. 2009;139(3):594–597
14. Valentiner-Branth P, Shrestha PS, Chandyo RK, et al. 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. *Am J Clin Nutr*. 2010;91:1667–1674
15. World Health Organization; United Nations Children's Fund. Model IMCI Handbook: Integrated Management of Childhood Illness. *WHO/FCH/CAH/00.12*. Geneva, Switzerland: Division of Child and Adolescent Health and Development, World Health Organization; 2005
16. Hazir T, Qazi S, Nisar YB, et al. Assessment and management of children aged 1–59 months presenting with wheeze, fast breathing, and/or lower LCI; results of a multicentre descriptive study in Pakistan. *Arch Dis Child*. 2004;89:1049–1054.
17. World Health Organization Multicentre Growth Reference Study Group. *WHO Child Growth Standards: Length/Height-for-Age, Weight-for-Age, Weight-for-Length, Weight-for-Height and Body Mass Index-for-Age: Methods and Development*. Geneva, Switzerland: World Health Organization; 2006
18. World Health Organization Pneumonia Vaccine Trial Investigator's Group. *Standardization of Interpretation of Chest Radiographs for the Diagnosis of Pneumonia in Children*. WHO/V&B/ 01.35. Geneva, Switzerland: World Health Organization; 2001
19. World Health Organization. Pocket Book of Hospital Care for Children: Guidelines for

the Management of Common Illnesses With Limited Resources. Geneva, Switzerland: World Health Organization; 2005

20. Mathisen M, Basnet S, Sharma A, et al. RNA viruses in young Nepalese children hospitalized with severe pneumonia. *Pediatr Infect Dis J.* 2011;30:1032–1036
21. Mahalanabis D, Lahiri M, Paul D, et al. Randomized, double-blind, placebo-controlled clinical trial of the efficacy of treatment with zinc or vitamin A in infants and young children with severe acute lower respiratory infection. *Am J Clin Nutr.* 2004;79(3):430–436
22. Margolis P, Gadomski A. The rational clinical examination. Does this infant have pneumonia? *JAMA.* 1998;279(4):308–313
23. Puumalainen T, Quiambao B, Abucejo-Ladesma E, et al; ARIVAC Research Consortium. Clinical case review: a method to improve identification of true clinical and radiographic pneumonia in children meeting the World Health Organization definition for pneumonia. *BMC Infect Dis.* 2008; 8:95
24. Das RR. Differential effects of zinc in severe pneumonia in children. *Indian J Pediatr.* 2011;78:1159–1160

THE LASTING IMPACT OF A GOOD TEACHER: *How important is a good teacher? That question has been the subject of intense debate over the past several years. Although most people agree that a good primary school teacher is incredibly valuable, how to define a good teacher is quite difficult, and defining a poor teacher is even more challenging. One controversial way to assess the quality of a teacher is through use of value-added ratings. Most simply, value-added ratings compare the test scores of students for a teacher in one year to test scores of previous years and are also compared to students of other teachers. Previous research has shown that the positive effect of a single teacher on the subsequent scores of students fades within a few years. As reported in* The New York Times *(Education: January 6, 2012), a large study that looked at 2.5 million students for more than 20 years, concluded that good teachers have a lasting impact not just on student test scores but on many other measures including adult income. The researchers used value-added ratings to characterize elementary and primary school teachers as good, average, or poor. Students of teachers characterized as good had lower teenage-pregnancy rates, were more likely to attend college, and had greater adult earnings. The impact of a single teacher on a single student is quite small. For example, having a single good teacher rather than all average teachers between fourth and eighth grade may result in a net increase in adult lifetime income of only $4,600. However, if the results of an entire class are aggregated over time, the total effect becomes quite large. Importantly, the difference between poor and average was just as large and strong as the difference between good and average. The implications are that given the challenge of finding, hiring, and training good teachers, weeding out poor teachers may be more valuable. Of course, the use of value-added ratings is quite controversial. Some school officials argue that teachers may be unfairly singled out for dismissal or that if high value-added ratings become critical to job security, teachers may begin teaching to the test. Regardless, the data shows that having either good or poor primary or elementary school teachers has a lasting impact on student lives. This is just one way to identify those teachers.*

Noted by WVR, MD

(Continued from first page)

Address correspondence to Tor A. Strand, PhD, Medical Microbiology, Innlandet Hospital Trust, Anders Sandvigsgate 17, 2629 Lillehammer, Norway. E-mail: tors@me.com

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: *The authors have indicated they have no financial relationships relevant to this article to disclose.*

FUNDING: Supported by a grant from the European Commission (EU-INCO-DC contract INCO-FP6-003740); by funding from the Meltzer Foundation in Bergen, Norway; by the Danish Council of Developmental Research (project 91128); and by the Research Council of Norway (projects 151054 and 172226). The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

A Randomized Controlled Trial of Zinc as Adjuvant Therapy for Severe Pneumonia in Young Children

Sudha Basnet, Prakash S. Shrestha, Arun Sharma, Maria Mathisen, Renu Prasai, Nita Bhandari, Ramesh K. Adhikari, Halvor Sommerfelt, Palle Valentiner-Branth, Tor A. Strand and members of the Zinc Severe Pneumonia Study Group

Pediatrics 2012;129;701; originally published online March 5, 2012;
DOI: 10.1542/peds.2010-3091