Efficacy of zinc given as an adjunct in the treatment of severe and very severe pneumonia in hospitalized children 2–24 mo of age: a randomized, double-blind, placebo-controlled trial1–3


ABSTRACT
Background: Pneumonia is a leading cause of death; in India, an estimated 370,000 children die of pneumonia each year. Zinc has multiple influences on the immune response to infections. Zinc supplementation has been shown to prevent diarrhea and pneumonia in children. However, zinc’s therapeutic effect on respiratory infections is less clear.

Objective: We evaluated the role of zinc as an adjunct to antibiotics in children with pneumonia.

Design: In this randomized, double-blind, placebo-controlled trial, we enrolled 550 children aged 2–24 mo with severe or very severe pneumonia. Within each hospital and pneumonia-severity stratum, children were randomly assigned to receive zinc (20 mg elemental zinc/d) or a placebo in addition to antibiotics and supportive care.

Results: The time to recovery from severe or very severe pneumonia was similar in both groups (HR: 0.98; 95% CI: 0.82, 1.17). In the stratified analysis, zinc was shown to be efficacious in reducing the time to recovery in children with very severe pneumonia (HR: 1.52; 95% CI: 1.03, 2.23); however, the effect was no longer statistically significant after adjustment for recovery and severity (10–12), whereas other studies suggest that zinc has no treatment benefit (13, 14). Additional information is needed to determine whether zinc has a role in the treatment of children hospitalized for pneumonia before policy recommendations can be made. In addition, the earlier studies did not evaluate the effect of zinc in a subgroup of children with very severe pneumonia. It is possible that zinc supplementation only has an effect on very severe pneumonia but not on milder forms.

INTRODUCTION
Pneumonia is a leading cause of death in young children and causes ~18% of all deaths in children <5 y of age (1). In India, which has the single highest burden of pneumonia globally, an estimated 370,000 children die of pneumonia each year. Community-based standardized case management has been a hallmark of strategies to reduce pneumonia mortality; it is estimated that such an approach may reduce the mortality rate by ~70% (2).

Zinc deficiency has been well characterized in Indian children and other low- and middle-income countries (3–5). Zinc plays an important role in the immune system; it is essential for the normal function and development of innate and adaptive immune systems (6). In clinical trials, zinc supplementation has provided a cost-effective approach to decreasing morbidity, mortality, and the economic burden associated with childhood diseases in low- and middle-income countries. A recent meta-analysis showed a 19% reduction in pneumonia morbidity and 13% reduction in incidence of diarrhea in children who received preventative zinc supplementation (7). Zinc is currently recommended by the WHO as an adjunct therapy for treating diarrhea (8, 9).

However, zinc’s therapeutic effect on respiratory infections is less clear. Studies that examined the clinical effects of zinc for treating pneumonia in children have shown conflicting results, with some studies that showed a beneficial effect on the duration of recovery and severity (10–12), whereas other studies suggest that zinc has no treatment benefit (13, 14). Additional information is needed to determine whether zinc has a role in the treatment of children hospitalized for pneumonia before policy recommendations can be made. In addition, the earlier studies did not evaluate the effect of zinc in a subgroup of children with very severe pneumonia. It is possible that zinc supplementation only has an effect on very severe pneumonia but not on milder forms.

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forms of pneumonia. We conducted a randomized, double-blind, controlled trial to evaluate the efficacy of daily orally administered zinc given in addition to standard antimicrobial therapy in the treatment of severe and very severe pneumonia.

**SUBJECTS AND METHODS**

**Study design**

This randomized, double-blind, placebo-controlled trial was undertaken from February 2007 to March 2010 at the following 3 tertiary hospitals in New Delhi, India: the Kalawati Saran Children’s Hospital, the Deen Dayal Upadhyay Hospital, and the All India Institute of Medical Sciences. The study protocol was approved by the respective institutional ethics committees as well as the Ethics Review Committee of WHO, the Institutional Review Board of the Johns Hopkins Bloomberg School of Public Health, and the Health Ministry Screening Committee of the Ministry of Health And Family Welfare, Government of India.

**Patient eligibility and assessment**

We screened children aged 2 (60 d)–24 mo who presented to the emergency department of study hospitals with a cough for <30 d or difficult breathing for ≥7 d for clinical symptoms and signs of severe or very severe pneumonia. Definitions of severe pneumonia and very severe pneumonia were adapted from the WHO criteria (15). Children were categorized as having severe pneumonia if they had fast breathing (≥50 breaths/min in children <12 mo of age or ≥40 breaths/min in children ≥12 mo of age), chest indrawing, and crepitations on chest auscultation. Children who had signs of pneumonia (fast breathing and crepitations with or without chest indrawing) and cyanosis or any general danger sign (lethargy, inability to drink, or convulsions) were categorized as having very severe pneumonia. Children were excluded if they presented with a need for mechanical ventilation or inotropic medications, had major congenital anomalies, inborn errors of metabolism, chronic disorders such as renal failure, preexisting seizure disorders, surgical or other conditions that interfered with oral feeding, HIV infection, were born to mothers with documented HIV infection, had active measles, severe malnutrition that required separate medical attention, or had any other serious underlying medical condition. Children who had received intravenous antimicrobials >48 h for the current illness or zinc supplementation in the past 3 mo were also excluded. Children who presented with clinical signs of wheezing were treated with 3 nebulizations of salbutamol at 20-min intervals. At the end of this therapy, if the signs of severe or very severe pneumonia persisted irrespective of wheeze, the child was eligible for enrollment. Study physicians obtained written (or a thumb print from individuals who were illiterate) informed consent from the parent or guardian of eligible patients in the presence of a witness.

**Random assignment, masking, and intervention**

Immediately after informed consent was obtained, children were stratified by pneumonia severity (severe or very severe pneumonia, as previously defined). A scientist, who was otherwise not involved in the study, generated allocation sequences with STATA software (version 9.0; StataCorp) so that, within each hospital and pneumonia severity, patients were randomly assigned equally in permuted blocks of 6 to receive zinc or a placebo. Dispersible tablets that were identical in color, taste, and appearance and packed in identical looking blister strips with or without zinc sulfate (10 mg elemental zinc; Nutriset) were provided by the WHO. Each strip was labeled with a unique serial number according to the randomization list. A zip-lock bag that held 3 such blister strips coded with the same unique serial number was assigned for each subject. Information regarding random assignment was not available to any of the investigators until the data had been obtained, entered, and locked. Participants and investigators were masked to treatment allocation. We maintained masking during data analysis by coding the treatment allocation with 2 letters.

After random assignment, study physicians gave each child one tablet of zinc (10 mg elemental zinc) or a placebo dissolved in 3 mL distilled water every 12 h until recovery (ie, the end of a 24-h period without any clinical signs of severe or very severe pneumonia) or the completion of 14 d, whichever was earlier. Administration was repeated ≤3 times in children who vomited within 15 min of dose administration. The day of randomization and initial dose administration was designated as day 1.

**Clinical monitoring and antibiotic therapy**

Study physicians examined patients for signs of severe and very severe pneumonia and other relevant clinical features every 6 h (or more often if clinically indicated) until recovery or day 14. The respiratory rate count was repeated if it was ≥50 breaths/min in children <12 mo of age or ≥40 breaths/min in children ≥12 mo of age and recorded. If the discrepancy between the 2 counts was >5 breaths/min, a third count was done, and the average of the 2 closest counts was recorded as the respiratory rate. Study staff recorded nude weights at random assignment and every 24 h until recovery or day 14. The site supervisor, who was a pediatrician, supervised the monitoring and was responsible for overseeing at least one daily assessment done by each study physician.

Children were treated according to a standardized protocol adapted from the Indian Academy of Pediatrics guidelines (16) in accordance with the standard of care that was being provided at the hospitals. Oxygen saturation was measured by using a pulse oximeter at admission and every 6 h thereafter. Oxygen was administered to children with a saturation <90%. Breathing was continued in children who were able to feed. Children with severe pneumonia who came directly to our study sites were treated with recommended doses of intravenous ampicillin and an aminoglycoside (intravenous gentamicin or amikacin). Children with very severe pneumonia were given a third-generation cefalosporin. Children who had been initiated on antibiotics before presenting to study sites were given a third-generation cefalosporin if diagnosed with severe pneumonia and vancomycin along with ceftriaxone-sulbactam or piperacillin-tazobactam if diagnosed with very severe pneumonia. Anti-staphylococcal antibiotics were administered if there was clinical suspicion of staphylococcal infection. Children who had not recovered by the end of 14 d were no longer monitored by the study staff but were managed by hospital physicians.
**Clinical outcomes**

The primary outcome was the time to recovery, which was calculated as the time from random assignment until recovery. Recovery was defined as the end of a 24-h period without any clinical signs of severe or very severe pneumonia (as previously defined).

The secondary outcome was treatment failure. Treatment failure was a composite outcome, which was defined as a need to change antimicrobial therapy in ≤7 d of random assignment or a need for intensive care (mechanical ventilation or vasoactive drug infusion or both) or withholding of the intervention for worsening in clinical condition or death at any time within 14 d of random assignment, or a failure to recover by day 14. The decision to change antimicrobials was made by 2 senior pediatricians (site investigators) on the basis of a priori guidelines stated in the study protocol (ie, persistence of chest indrawing or any initially identified danger sign ≥48 h of random assignment or worsening of clinical features that defined severe or very severe pneumonia at any time after random assignment).

**Laboratory procedures**

Study physicians obtained blood specimens at random assignment, 48 h, and recovery. Hemoglobin, total and differential leukocyte counts, a blood culture, serum zinc, and C-reactive protein (CRP) were determined at random assignment at each clinical site. Chest X-rays were done in the emergency room. Blood cultures were processed in the microbiology laboratory at the All India Institute of Medical Sciences by using the fully automated microbiology growth and detection system, BACTEC (model PEDS PLUS/F; Becton Dickinson), and antibiotic sensitivity was determined using the Kirby-Bauer disc diffusion technique (17). Serum for the zinc concentration was obtained at 48 h and recovery, whereas serum was taken at recovery for the CRP concentration. The serum was stored at −20°C. The laboratory at the All India Institute of Medical Sciences measured serum concentrations of zinc with a flame furnace atomic absorption spectrophotometer (GBC Avanta) as per standard procedures (18) and CRP concentrations by using a commercial ELISA (Biocheck).

**Quality assurance and monitoring of adverse serious events**

Before study initiation, study procedures were standardized to consistently identify primary and secondary outcomes. Site supervisors (trained pediatricians) received standard training with print and video material on patient assessment and outcomes according to a standard protocol to ensure uniformity across study sites. Regular standardization exercises for clinical outcomes and laboratory procedures were conducted among the research team members to minimize intraobserver and interobserver variability within and across the 3 hospitals. Particular emphasis was given to counting the respiratory rate, identifying chest indrawing, and auscultating the chest for crepitations. An independent data safety monitoring board was constituted before initiation of enrollment; the board was comprised of a biostatistician and 3 clinicians experienced in research who were not affiliated with study hospitals. The board reviewed each serious adverse event (death or need for intensive care) and met every 3 mo to ensure that the study was done according to the protocol.

**Sample-size estimation**

On the basis of unpublished data from one of the participating hospitals, the total time (±SD) taken to recover from severe pneumonia or very severe pneumonia in children <2 y old and receiving standard care was estimated at 96 ± 48 h and 144 ± 60 h, respectively. With the use of this assumption, a total sample size of 492 children [292 children with severe pneumonia (146 children in each group) and 200 children with very severe pneumonia (100 children in each group)] was calculated to detect a 20% reduction in the total time taken to recover from severe or very severe pneumonia by administering zinc. With assumption of a 10% loss to follow-up, this sample size provided a power of 90% and 95% confidence. Because of the difficulty of enrolling children in the very severe pneumonia category, the total enrollment limit was increased from 492 to 550 to recruit children in the very severe pneumonia stratum.

**Data management and statistical analysis**

Site supervisors checked all completed case-report forms twice before they were sent for interactive double data with Microsoft Access software (version 2007; Microsoft Corp) with in-built logic, range, and consistency checks. With STATA software (version 11.0; StataCorp), all analyses were done on an intention-to-treat basis. We used time-to-event analyses for the primary outcome that censored children in whom recovery could not be documented because of withdrawal of consent for continuation in the study. Subjects who did not recover by day 14 (336 h) were censored at that time. Children who died during the study period of 14 d were censored at 337 h (ie, 1 h longer than the maximum time of observation). Irrespective of whether treatment failure had occurred, a Cox proportional hazards regression model compared the time until recovery between study groups; an HR >1 indicated a beneficial effect of zinc. We calculated the proportion of treatment failures in the 2 trial arms and the corresponding RR and risk difference. We compared the change in serum zinc concentration from baseline to recovery between the 2 intervention groups by using Student’s t test. Serum zinc at recovery was compared between the 2 groups by using the Mann-Whitney U test.

We performed a predefined subgroup analysis on severity groups by using time-to-event analyses to determine whether the baseline severity of pneumonia modified the effect of treatment with zinc. Interactions were assessed in Cox-proportional hazard models to determine whether the severity of pneumonia modified the effects of treatment with zinc.

**RESULTS**

**Enrolled patients**

A total of 10,066 children between the ages 2 and 24 mo were identified with difficult breathing for ≤7 d or cough for <30 d or both. Of these children, 3164 subjects had signs of severe or very severe pneumonia. On additional evaluation, 2284 children were not eligible for the study for reasons described in Figure 1. The remaining 880 children were approached for enrollment...
(Figure 1), of which consent was refused for 330 children. Of the 550 enrolled patients, 274 and 276 children were assigned to receive zinc and a placebo, respectively. Overall, 4.9% of children (zinc: 12 subjects; placebo: 15 subjects) were lost to follow-up, 1.5% of children (zinc: 4 subjects; placebo: 4 subjects) died during the course of the study, and 2.18% of children (zinc: 6 subjects; placebo: 6 subjects) did not recover by day 14. There was one protocol deviate in the placebo group who inadvertently received one dose that was assigned for another patient and also received antibiotics that were different from what was defined in the protocol.

The 2 groups had comparable baseline characteristics (Table 1): 82.4% of children were <12 mo of age, and 67.3% of children were boys. Nearly one-quarter (22.9%) of children had a weight-for-age z score less than −3, and a large number (75%) of children were anemic (hemoglobin concentration <11 g/dL). A total of 430 enrolled children (78.2%) were diagnosed with severe pneumonia, whereas 120 enrolled children (21.8%) were categorized as having very severe pneumonia. The median duration of symptoms before admission into the study was 3.2 d (IQR: 3, 5 d). Illness severity, as determined by clinical characteristics and laboratory markers of inflammation, was similar in the 2 groups. Median (IQR) concentration of CRP was 9.41 mg/L (2.32, 24.51 mg/L) in the zinc group and 8.46 mg/L (2.17, 19.64 mg/L) in the placebo group. The baseline serum zinc concentration was similar in both zinc and placebo groups at 9.3 and 9.2 μmol/L, respectively. More than 50% of the patients had serum zinc concentrations less than 9.2 μmol/L (zinc: 55.4%; placebo: 55.4%).

Clinical outcomes

The time until recovery from severe or very severe pneumonia was similar in both groups [median (IQR): zinc, 78.5 h (59, 122 h); placebo, 77.0 h (59, 117 h); HR: 0.98; 95% CI: 0.82, 1.17] (Table 2, Figure 2). Treatment failure could be assessed in 525 children (Table 2). Of the 27 children who were lost to follow-up, 2 children (given placebo) had the outcome of treatment failure before they withdrew consent for continuation in the study. Risk of treatment failure was similar in the 2 study groups (Table 2). We did a post hoc analysis and showed no significant difference between the proportion of children who recovered by day 2 or 5 (P = 0.63 and P = 0.97, respectively). The case fatality did not differ between the 2 intervention groups (Table 2). Risk of vomiting the first dose of the study intervention within 15 min of receiving it was similar in the 2 groups [zinc: 9 children (3.28%); placebo: 7 children (2.54%); RR: 1.3; 95% CI: 0.49, 3.43]).

The mean (±SD) change in serum zinc concentrations from enrollment to recovery was higher in the children given zinc (4.30 ± 5.6 μmol/L) than in children who received the placebo (1.06 ± 3.9 μmol/L), with a difference of 3.24 μmol/L (95% CI: 2.4, 4.1 μmol/L; P < 0.0001). The effect of zinc on laboratory markers of inflammation (CRP) did not differ between the 2 groups.

In the stratified analysis, zinc was shown to be efficacious in reducing the time to recovery in children with very severe pneumonia [median (IQR): zinc, 80 h (63, 114 h); placebo, 106 h [66, 177 h]] (Table 3) but not in children with severe pneumonia [median (IQR): zinc, 78 h (57, 122 h); placebo, 73 h (54, 106 h)].
In the very severe pneumonia group, the reduction in the time to recovery was also evident in the hazards model (HR: 1.52; 95% CI: 1.03, 2.23) (Figure 3). When adjusted for prespecified potential confounders such as the weight-for-age z score less than −2.3 (severely underweight) status, age, breastfeeding status, baseline serum CRP, and serum zinc, the effect of zinc on the time to recovery in subjects with very severe pneumonia (HR: 1.54; 95% CI: 1.02, 2.33) continued to be significant. Of note, the proportion of children with a weight-for-age z score less than −2.3 (severely underweight) in the very severe pneumonia group was lower in zinc recipients than in the placebo group (15.3% compared with 32.8%, respectively). Therefore, we also did an exploratory “time-to-event” analysis in which we adjusted for only severely underweight; in this

### TABLE 2

Effect of oral zinc on clinical outcomes in children with severe or very severe pneumonia

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Zinc</th>
<th>Placebo</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to recovery (h)</td>
<td>78.5 (59, 122)</td>
<td>77.0 (58, 117)</td>
<td>0.98 (0.82, 1.17)</td>
</tr>
<tr>
<td>Recovered by 2 d [n (%)]</td>
<td>33 (12.0)</td>
<td>37 (13.4)</td>
<td></td>
</tr>
<tr>
<td>Recovered by 5 d [n (%)]</td>
<td>194 (70.8)</td>
<td>195 (70.7)</td>
<td></td>
</tr>
<tr>
<td>Treatment failure [n (%)]</td>
<td>37 (14.1)</td>
<td>28 (10.6)</td>
<td>1.3 (0.8, 2.1)</td>
</tr>
<tr>
<td>Any failure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>4 (1.5)</td>
<td>4 (1.5)</td>
<td>1.0 (0.3, 4.0)</td>
</tr>
<tr>
<td>Need for intensive care</td>
<td>0 (0)</td>
<td>1 (0.4)</td>
<td></td>
</tr>
<tr>
<td>Not recovered by 14 d</td>
<td>2 (0.8)</td>
<td>1 (0.4)</td>
<td>2.0 (0.2, 22.0)</td>
</tr>
<tr>
<td>Change of antibiotics</td>
<td>31 (11.8)</td>
<td>22 (8.4)</td>
<td>1.4 (0.8, 2.4)</td>
</tr>
</tbody>
</table>

1 Number of patients in whom the primary outcome could be assessed was 274 in the zinc group and 276 in the placebo group.  
2 Median; IQR in parentheses  
3 HR; 95% CI in parentheses. Time-to-event analyses by using a Cox proportional hazards regression model.  
4 Number of patients in whom treatment failure could be assessed was 262 in the zinc group and 263 in the placebo group.  
5 Absolute risk reduction was 3.5% (95% CI: −2.2%, 9.1%).  
6 RR; 95% CI in parentheses.
pneumonia cause directly by using microbiological techniques. The prevalence of wheezing in the earlier studies has ranged from 37.4% to 62.5% (11, 14, 21, 22), whereas we observed wheezing in 54.7% if subjects. Some of these studies have reported a higher prevalence of hypoxemia at enrollment (11, 14, 22), which may have been due to differences in the oxygen-saturation cutoff used, altitude of the study site, and proportion of children with wheezing. In the current study, no difference in treatment outcomes were seen when patients were separated into categories based on sex, hot and cool or rainy and dry seasons, or the presence of wheezing (data not shown).

The significant benefits seen with zinc in treating very severe pneumonia could be important in the background of other recent studies that have shown beneficial effects of zinc therapy in children with more-severe infection. A trial conducted in our setting that looked at the treatment benefit of zinc in young infants admitted with probable serious bacterial infection showed a 40% reduction in the treatment failure rate in zinc recipients (23). In addition, a study from Nepal reported that the subgroup of children with endpoint consolidation seen in chest radiographs had a significantly faster recovery when they received zinc compared with a placebo (22). A recent study from Uganda showed a significant reduction in case fatality with zinc supplementation in the subgroup of HIV-infected children with severe pneumonia (24). The case fatality for very severe pneumonia can range from 10% to 50% even with hospitalization (25, 26). Therefore, effective adjunct-treatment options could be important (27). Although our findings could have been due to a higher rate of severe underweight in children with very severe pneumonia, these effects of zinc may be significant in extremely ill children and, therefore, need to be evaluated further.

It has been hypothesized that baseline zinc deficiency may alter the outcome of zinc treatment. In Bangladesh, where a clear benefit to treatment with zinc was seen, the baseline serum zinc concentration was 10.1 µmol/L, whereas in Vellore and Kolkata, which showed effects only in subgroup analyses, baseline concentrations were 11.0 and 9.6 µmol/L, respectively (11, 12, 14).

In the Chandigarh study, which saw no effect, children had

DISCUSSION

This study showed that there was no overall benefit of zinc supplementation in reducing the time to recovery in children with pneumonia. Risk of treatment failure was similar in zinc and placebo groups. We observed a significant effect of zinc supplementation in reducing the time to recovery in children with very severe pneumonia; however, this effect was attenuated when we controlled for severely underweight. Nevertheless, when we adjusted the analysis for effect of zinc supplementation on time to recovery controlling for severely underweight, the positive effect of zinc supplementation continued, which suggested that our sample size may not have been large enough to document this effect.

Overall results of our study were in line with the opinion expressed in a recent review of zinc for treatment of pneumonia in children (19). Studies that examined the treatment of pneumonia with zinc have shown mixed results. Two studies, one in Iran and one in Bangladesh, have shown treatment benefits of zinc (10, 11), which has not been reported from other studies done in different regions of the Indian subcontinent such as Kolkata, Vellore, Chandigarh, and Nepal (13, 14, 20–22). Some beneficial effects have been seen in certain subgroups; the trial based in Kolkata showed significant effect in male subjects (12), whereas the trial in Vellore showed a seasonal benefit of zinc treatment (14).

Several studies have inferred that the benefits of treating pneumonia with zinc are seen in bacterial but not viral infections. In Bangladesh, a greater effect of treatment with zinc was seen in children who presented without wheeze, which the authors suggested may have been due to a limited therapeutic benefit in children who presented with viral pneumonia (11). Similarly, Bose et al (14) hypothesized that the seasonal effect seen in Vellore may have been due to effects seen in pneumonia of bacterial origin, which are thought to be more common in the hot season. However, to our knowledge, no studies have assessed

![FIGURE 2. Kaplan-Meier survival estimates for the time to recovery in patients with severe or very severe pneumonia in the zinc (n = 274) compared with placebo (n = 276) groups. Median (IQR) time to recovery: zinc, 78.5 h (59, 122 h); placebo, 77.0 h (58, 117 h). HR (95% CI): 0.98 (0.82, 1.17); P = 0.838 (time-to-event analyses by using a Cox proportional hazards regression model).](image)

### TABLE 3

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Zinc</th>
<th>Placebo</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to recovery (h)</td>
<td>80 (63, 114)</td>
<td>106 (66, 177)</td>
<td>1.52 (1.03, 2.23)</td>
</tr>
<tr>
<td>Recovered by 2 d [n (%)]</td>
<td>4 (6.8)</td>
<td>5 (8.2)</td>
<td>—</td>
</tr>
<tr>
<td>Recovered by 5 d [n (%)]</td>
<td>43 (72.9)</td>
<td>31 (50.8)</td>
<td>—</td>
</tr>
<tr>
<td>Treatment failure [n (%)]</td>
<td>5 (8.8)</td>
<td>8 (14.0)</td>
<td>0.63 (0.2, 1.8)</td>
</tr>
<tr>
<td>Death</td>
<td>1 (1.8)</td>
<td>2 (3.5)</td>
<td>0.50 (0.05, 5.4)</td>
</tr>
<tr>
<td>Need for intensive care</td>
<td>0 (0)</td>
<td>1 (1.8)</td>
<td>—</td>
</tr>
<tr>
<td>Not recovered by 14 d</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>—</td>
</tr>
<tr>
<td>Change of antibiotics</td>
<td>4 (7.0)</td>
<td>5 (8.8)</td>
<td>0.80 (0.2, 2.8)</td>
</tr>
</tbody>
</table>

1 Number of patients in whom the primary outcome could be assessed was 59 in the zinc group and 61 in the placebo group.
2 Median; IQR in parentheses.
3 HR; 95% CI in parentheses.
4 Number of patients in whom treatment failure could be assessed was 57 in the zinc group and 57 in the placebo group.
5 RR; 95% CI in parentheses.
a high baseline serum zinc concentration of 22.9 μmol/L compared with in studies in which treatment benefits were seen (20). The baseline serum zinc concentration in this study was lower, at 9.3 μmol/L, than in any of the previous studies. The lack of correlations between baseline zinc concentrations and clinical outcomes may have been due to limitations of serum or plasma zinc as a marker of zinc status in the body, particularly during infections, or possibly because of effects of zinc that occur irrespective of zinc concentrations.

In our study, it is possible that the dose of zinc as adjunctive therapy for the treatment of pneumonia may have been low; however, this dose was similar to or more than the dose used in other studies (10–14, 22, 24). Doses >20 mg may be studied in future trials.

This study had some limitations. Although we completed our overall sample size of 492 children with severe or very severe pneumonia, in the subgroup of very severe pneumonia, we could enroll only 120 children compared with the proposed 200 children during the study period. And, despite a well-conducted stratified random assignment, the 2 groups in the strata of children with very severe pneumonia were substantially different in terms of the prevalence of severe underweight, which ultimately affected our results. This effect may not have happened if we had been able to enroll the proposed number of children with very severe pneumonia.

Our study provides important information on a possible benefit of zinc supplementation in a subgroup of children with very severe pneumonia. We did not show an overall benefit of zinc for pneumonia treatment. To date, a clear benefit of zinc in the treatment of pneumonia has been seen in 2 of 8 studies that examined the impact of zinc on pneumonia outcomes. In light of these varying results and differences seen in various subgroup analyses, a meta-analysis is warranted to determine whether there is any overall benefit of zinc for the treatment of pneumonia, but more importantly, additional research is needed in specific subgroups such as children with very severe pneumonia with stratification for severely underweight.

We thank the medical and nursing staff of the 3 hospitals for their contribution as well as the patients and their parents. We also thank Mohini Kumari, Ritu Chawla, Venod Kumar Sharma, Ashok Kumar Dutta, Arvind Bagga, and Madhulika Kabra for providing clinical support to patients enrolled in the study at the Deen Dayal Upadhyay Hospital, Kalawati Saran Children’s Hospital, and All India Institute of Medical Sciences, respectively. We are thankful to Arti Kapil for supervising blood cultures and Uma Chandra Mouli Natchu for helping us with data analysis and interpretation of data. We acknowledge the late Anil Kumar Sharma for assisting in quality assurance and supervision of the research staff. Mukesh Juyal for secretarial support, Shilpa Chopra for data-management support, and Dharmendra Sharma for data-management support and analysis of data. We are thankful to Olivier Fontaine, medical officer, Child and Adolescent Health at the WHO, for providing the intervention (zinc and placebo tablets from Nutriset) and helping with the design and periodic reviews of the conduct of the study.

The authors’ responsibilities were as follows—SB, AC, REB, and MS: designed the research; NW, SA, RL, SKE, MKC, JS, JC, BR, USK, SS, and SB: conducted the research; NW, RL, SPE, and SB: analyzed data; NW, AC, SA, RL, and SB: wrote the manuscript; NW and SB: had primary responsibility for the final content of the manuscript; and all authors: read and approved the final manuscript. None of the authors had a conflict of interest.

REFERENCES


