Zinc as an adjunct for childhood pneumonia – interpreting early results

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Zinc supplementation has been consistently shown to reduce the incidence of childhood pneumonia, but its effect on the course of pneumonia when administered as an adjunct to antibiotic therapy is still unclear. Three trials published to date have shown mixed results, and a recent trial from India raises the possibility that zinc may be detrimental in some circumstances. Study sites and designs differ, particularly in the timing of zinc treatment and in determining recovery from pneumonia, which can explain the differences in study findings. Serum zinc concentrations are unreliable indicators of zinc status, particularly during acute infectious illnesses. Subgroup analyses, especially using serum zinc levels, must be cautioned against. Future studies are needed that are large enough to be sufficiently powered to accommodate larger treatment failure rates, an issue that ongoing trials will hopefully address.

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INTRODUCTION

Pneumonia or acute lower respiratory tract infections cause over 2 million deaths annually among children younger than 5 years of age.1 Responsible for about 20% of all child deaths, pneumonia is the leading cause of child mortality. The two-thirds reduction in child mortality needed to achieve the millennium development goal (MDG4) is not likely to be achieved without effective interventions to reduce mortality from pneumonia. About 150 million cases of pneumonia are estimated to occur every year in the developing world and 11–20 million of these cases are severe enough to require hospitalization, creating a huge burden on hospital services.2 Compared with the treatment of diarrhea, which requires adequate oral rehydration and intravenous fluids in severe cases, the management of pneumonia is more complicated, requiring prolonged intravenous antibiotics and oxygen or assisted ventilation in severe cases. The increase in antibiotic resistance and inadequate access to hospital facilities can be partly offset by interventions that reduce treatment failure and the duration of illness.

Despite being successful in reducing the incidence of pneumonia, vaccines against Haemophilus influenzae and Streptococcus pneumoniae are still too expensive to be implemented on a large scale in most parts of the developing world. Moreover, non-conjugate pneumococcal vaccines cannot be administered to children younger than 24 months.

Zinc deficiency is widely prevalent in the developing areas of the world, which also have a high incidence of pneumonia.3 Zinc supplementation holds promise as an intervention to reduce the incidence, case fatality rate, and duration of acute lower respiratory tract illnesses. However, evidence on the use of zinc to treat childhood pneumonia is limited, with only three randomized trials being performed to date comparing zinc to placebo when added to standard antibiotic treatment. Findings from the first two trials, conducted in Kolkata (eastern India) and Bangladesh, suggested that zinc reduces treatment failures and the duration of acute lower respiratory tract illnesses (ALRI).4,5 In contrast, the third trial, conducted in Vellore (southern India), reported prolongation of illness in subgroups of children who developed severe...
pneumonia in the hot months, or who had C-reactive protein (CRP) levels >40 mg/dL when treated with zinc – a finding that questions the use of zinc intervention in the treatment of pneumonia. Since the last finding contrasts with the beneficial effect of zinc found in the other two trials, an examination is warranted of the differences between this trial and the previous two studies.

ZINC SUPPLEMENTATION AND THE RISK OF CHILDHOOD INFECTIOUS DISEASES

Trials assessing the effect of zinc supplementation on the incidence of diarrhea and pneumonia, the two most common childhood infections, have consistently demonstrated a protective effect of zinc. Pooled analysis of four randomized trials estimated that children supplemented with zinc experience a 41% (95% CI 17–59%) reduction in the incidence of pneumonia episodes when compared with children given a placebo. Addition of results from another trial in Delhi, India, to the pooled analysis led to a revision of the estimated reduction to 34% (95% CI 17–47%). A recent trial in Bangladesh showed a 17% (95% CI 5%–27%) reduction in the incidence of pneumonia and a 49% (95% CI 12%–70%) reduction in severe pneumonia with a weekly administered, single large dose (70 mg) of zinc supplementation. The 85% (95% CI 33–97%) reduction in all-cause mortality noted in this trial was primarily influenced by the impressive reduction in mortality caused by pneumonia. This trial also demonstrated statistically significant reductions in the incidence of suppurative otitis media (42%), bronchiolitis (12%), upper respiratory infection (8%), and diarrhea (6%). The Zinc Investigators’ Collaborative Group also conducted a pooled analysis of nine randomized controlled trials which estimated an 18% (95% CI 7–28%) reduction in the incidence of acute diarrheal episodes. Subsequent zinc supplementation trials conducted in West Bengal (India) and Bangladesh have further documented significantly lower rates of diarrhea. The trial in West Bengal also demonstrated that weekly zinc supplementation was as effective as daily zinc supplementation. The point estimates for these protective effects of zinc have been relatively consistent across short-term supplementation (2–4 weeks) as well as long-term supplementation (>12 weeks) trials.

ADJUNCT TREATMENT OF CHILDHOOD INFECTIOUS DISEASES WITH ZINC

Zinc’s role in boosting the immune response and promoting mucosal integrity has prompted the study of its role in improving recovery from childhood infections. The addition of zinc to the therapy of acute diarrheal episodes has been estimated to result in a 15% (95% CI 5–24%) reduction in the probability of continuation of the diarrheal episode when compared to placebo. This pooled analysis by the Zinc Investigators’ Collaborative Group also reported a 24% (95% CI 9–37%) drop in the probability of the diarrheal episode continuing and a 42% drop in treatment failure or mortality when zinc was added to treatment in persistent diarrhea (≥14 days of diarrhea) in randomized placebo-controlled trials. In keeping with the consistent findings of these and subsequent diarrhea treatment trials with zinc, a World Health Organization Task Force, in 2001, recommended the use of zinc in the treatment of diarrhea at a dose of 2 RDAs per day (10–20 mg per day) for 14 days. Zinc treatment is now also part of standard case management for persistent diarrhea and severe malnutrition.

There is very little data from Africa on the effect of zinc supplementation during acute childhood illnesses. The Zinc Against Plasmodium Group reported no effect of zinc as an adjuvant in the treatment of uncomplicated Plasmodium falciparum malaria in children less than 5 years of age in Africa and Latin America. A small randomized trial in South Africa focused on the safety of zinc supplementation in HIV-1-positive children. Zinc-supplemented children did not experience a decrease in plasma HIV-1 viral loads, but the incidence of watery diarrhea was significantly reduced in the zinc-supplemented group. The effect of zinc on recovery from measles and tuberculosis has yet to be clearly established and its role in the resolution of upper respiratory tract infections is still ambiguous.

An interesting observation from the prevention trials is that the biggest reductions in incidence achieved with zinc supplementation when compared to placebo seem to be of illnesses that are more frequently bacterial, like childhood pneumonia and suppurative otitis media. The largest reductions have been observed in the incidence of severe and fatal pneumonias, which are more likely to have a bacterial etiology. In contrast, reductions in the incidence of predominantly viral illnesses like upper respiratory tract infections, bronchiolitis, and acute diarrhea are smaller. Similarly, the improvements in recovery afforded by zinc supplementation are larger for persistent diarrhea, which is more often bacterial, than for acute non-cholera diarrhea, which is predominantly viral.

TREATMENT OF CHILDHOOD PNEUMONIA WITH ZINC

The only three randomized controlled trials performed to date to study the effect of zinc as an adjuvant in the treatment on childhood pneumonia have been conducted in the Indian subcontinent with one in Kolkata, India, another in Matlab, Bangladesh, and the most recent trial in Vellore, South India. All three trials included...
children aged 2 years or under only and used a daily dose of 20 mg of elemental zinc. Despite considerable similarities in the studies, some differences exist in the methods and definitions of illness and recovery. The important design features and baseline parameters have been summarized in Table 1. The kind of hospital in which the trial was performed is a major determinant of these differences. The Vellore trial was conducted at a large tertiary referral hospital in South India. In comparison, the study in Bangladesh enrolled and treated children at a small rural hospital in Matlab district and the Kolkata trial was conducted at a large hospital that catered to an urban and periurban population.

The Kolkata trial found that the benefit of zinc was restricted to boys and that zinc significantly improved recovery from very ill status and fever. At Matlab, in Bangladesh, the findings of Brooks et al. were more favorable, showing that it significantly reduced the duration of severe pneumonia, chest indrawing, tachypnea (>50 breaths/min), hypoxia, and hospitalization. In contrast, in the Vellore zinc study, Bose et al. found no effect of zinc on the duration of any of the clinical indicators of severe pneumonia and they found a significant association of zinc supplementation with a prolongation of pneumonia duration occurring in the hot season (March to August).

The varied results (Table 2) and the different subgroup analyses have generated many hypotheses to explain these findings. One possibility is that zinc supplementation benefits children with low serum zinc levels and is ineffective or detrimental when administered to children with adequate serum zinc concentrations. Other explanations are that the effects of zinc differ according to the cause of the pneumonia (bacterial vs. viral) or to gender. A third factor may be differences in study methodology, including definitions of pneumonia and recovery, the timing of zinc treatment during the course of pneumonia, and confounding introduced into the subgroup analyses. Each of these factors is discussed briefly.

Baseline zinc status of the study populations

All three trials collected blood samples for zinc estimation at enrollment and at discharge. The Kolkata trial had the lowest mean serum zinc levels at enrollment with 9.6 µmol/L followed by the Bangladesh trial with 10.1 µmol/L. Children enrolled in the Vellore trial were reported to have a statistically higher mean zinc level of 11.0 µmol/L. Plasma zinc levels are not the most reliable indicators of zinc status in the body. In children with pneumonia, zinc levels seem to drop as part of an acute-phase response to the infection and increase when they recover. Plasma zinc levels rise even in children who are not supplemented with zinc when they recover from pneumonia, a finding supported by the increase in plasma zinc at discharge among children who did not receive zinc in all three trials. Despite recording the lowest mean baseline zinc levels and receiving only 5 days of zinc supplementation, children in the Kolkata trial ended with the highest serum zinc levels at discharge; the Vellore trial found the smallest rise in serum zinc levels at discharge when compared to baseline levels (Table 1).

Zinc status, prior to pneumonia, is potentially a very important determinant of response to zinc treatment. The Vellore trial considered the possibility of effect modification by zinc status. The authors compared children with plasma zinc levels ≤9.18 µmol/L with those with levels ≥9.18 µmol/L and found no evidence of effect modification. Such an analysis assumes that a plasma zinc level of 10 µmol/L obtained from a child enrolled on day 5 of pneumonia symptoms is identical to a plasma zinc level of 10 µmol/L obtained from a child enrolled on day 2 of a pneumonia episode and is an accurate indicator of pre-infection zinc status. Given the acute-phase response to infection, the phase of illness would have an effect on plasma zinc concentrations limiting the utility of plasma zinc levels obtained during infection as comparable surrogates of true pre-illness zinc status.

Etiology of ALRI and seasonality

The etiology of ALRI varies significantly with age, region, and season. In the setting of these zinc treatment trials, microbiological investigations of the etiology of ALRIs have not been performed. The symptoms and signs of ALRI are nonspecific and can be notoriously poor when used to determine the cause of the ALRI. Even broad differentiation between bacterial and viral pneumonia on the basis of clinical signs is difficult. A large proportion of fatal and severe pneumonias are bacterial, with nearly three-fourths of lung aspirates yielding bacterial organisms, primarily Streptococcus pneumoniae and Haemophilus influenzae. To prevent mortality due to these bacterial pneumonias, the WHO currently recommends treating all young children with symptoms of cough and rapid breathing in developing countries with antibiotics. Seasonal changes do occur in pneumonia etiology, and studies from southern India have documented an increase in the proportion of viral pneumonias in the rainy seasons.

Methods of detecting viral pathogens responsible for ALRI have much greater yields than methods for bacterial pathogens. Respiratory syncytial virus, the commonest viral cause of ALRI can be considered pathological when detected in nasopharyngeal secretions, which it does not normally colonize. In contrast, the nasopharynx is colonized by multiple bacterial pathogens, making cultures from nasal secretions or swabs unreliable. Blood cultures have been used to detect bacteria and have very low
### Table 1  Trial characteristics and baseline parameters.

<table>
<thead>
<tr>
<th>Study characteristic</th>
<th>Mahalanabis et al. (2004)(^1)</th>
<th>Brooks et al. (2004)(^2)</th>
<th>Bose et al. (2006)(^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study location</strong></td>
<td>Kolkata, India</td>
<td>Matlab, Bangladesh</td>
<td>Vellore, India</td>
</tr>
<tr>
<td><strong>Sample size and design</strong></td>
<td>152, factorial design with vitamin A</td>
<td>270 (zinc, 135; placebo, 135)</td>
<td>300 (zinc: 150, placebo: 150)</td>
</tr>
<tr>
<td><strong>Hospital type</strong></td>
<td>Large urban hospital</td>
<td>Rural hospital</td>
<td>Tertiary referral hospital</td>
</tr>
<tr>
<td><strong>Zinc (formulation, dose)</strong></td>
<td>Zinc acetate (water miscible), 20 mg of elemental zinc for 5 days in 2 divided doses</td>
<td>Zinc acetate syrup, 20 mg of elemental zinc in 2 divided doses until discharge</td>
<td>Zinc sulfate tablets, 20 mg of elemental zinc in 2 divided doses until discharge or 15 days (whichever earlier)</td>
</tr>
<tr>
<td><strong>Severe pneumonia</strong></td>
<td>RR &gt; 50/min (age 2–11 months), RR &gt; 40/min (age 12–24 months), crepitations or bronchial breathing, lethargy, inability to feed, chest indrawing, or central cyanosis</td>
<td>RR &gt; 50/min, crepitations and chest indrawing, lethargy, inability to feed, chest indrawing, or central cyanosis</td>
<td>RR &gt; 50/min, crepitations and chest indrawing, lethargy, inability to feed, chest indrawing, or central cyanosis</td>
</tr>
<tr>
<td><strong>Children with diarrhea</strong></td>
<td>Not excluded</td>
<td>Excluded</td>
<td>Excluded</td>
</tr>
<tr>
<td><strong>Treatment failure</strong></td>
<td>No improvement or worsening in admission features used to diagnose severe pneumonia at the end of 48 h or the appearance of new features of severe pneumonia</td>
<td>No improvement or worsening in any one sign of severe pneumonia present at admission</td>
<td>Clinical judgment of attending pediatrician and each of the following three recovery points:</td>
</tr>
<tr>
<td><strong>Recovery from severe pneumonia</strong></td>
<td>Clinical judgment of attending pediatrician based on the following criteria:</td>
<td>RR &lt; 50/min, no chest indrawing, danger signs or hypoxia for 24 consecutive hours</td>
<td>RR &lt; 50/min and O(_2) saturation &gt;93%</td>
</tr>
<tr>
<td></td>
<td>i) RR &lt; 50/min (2–11 mo) and &lt;40/min (12–24 mo)</td>
<td>RR &lt; 50/min, no chest indrawing, danger signs or hypoxia for 24 consecutive hours</td>
<td>ii) RR &lt; 50/min, able to drink, O(_2) saturation &gt;93%</td>
</tr>
<tr>
<td></td>
<td>ii) Alertness and general well being</td>
<td>RR &lt; 50/min, no chest indrawing, danger signs or hypoxia for 24 consecutive hours</td>
<td>iii) RR &lt; 50/min, no chest indrawing, O(_2) saturation &gt;93%</td>
</tr>
<tr>
<td></td>
<td>iii) No respiratory distress</td>
<td>RR &lt; 50/min, no chest indrawing, danger signs or hypoxia for 24 consecutive hours</td>
<td></td>
</tr>
<tr>
<td></td>
<td>iv) Infant able to feed</td>
<td>RR &lt; 50/min, no chest indrawing, danger signs or hypoxia for 24 consecutive hours</td>
<td></td>
</tr>
<tr>
<td><strong>Criteria for discharge</strong></td>
<td>When recovered from severe pneumonia fulfilled by above criteria</td>
<td>When recovered from severe pneumonia fulfilled by above criteria</td>
<td>RR &lt; 50/min, entirely on oral feeds, no hypoxia, on oral antibiotics for 24 h or more and resolution decided by attending pediatrician</td>
</tr>
<tr>
<td><strong>Antibiotic treatment</strong></td>
<td>Intravenous cloxacillin + gentamicin</td>
<td>Intravenous ampicillin + gentamicin</td>
<td>Demand for beds required children to be discharged early (before RR &lt; 40/min)</td>
</tr>
<tr>
<td><strong>Proportion of infants</strong></td>
<td>78%</td>
<td>64%</td>
<td>70%</td>
</tr>
<tr>
<td><strong>Proportion of males</strong></td>
<td>63%</td>
<td>65%</td>
<td>70%</td>
</tr>
<tr>
<td><strong>Mean duration (SD) of illness before hospitalization</strong></td>
<td>Not provided</td>
<td>2.5 days (1.5)</td>
<td>Zinc: 5.8 days (11.0)</td>
</tr>
<tr>
<td><strong>Mean (SD) serum zinc levels at baseline</strong></td>
<td>Zinc: 9.91 μmol/L (2.5)</td>
<td>Zinc: 10.1 μmol/L (1.1)</td>
<td>Placebo: 4.7 days (6.2)</td>
</tr>
<tr>
<td></td>
<td>Zinc + Vit A: 9.46 μmol/L (2.3)</td>
<td>Placebo: 10.0 μmol/L (1.0)</td>
<td>Placebo: 10.9 μmol/L (2.4)</td>
</tr>
<tr>
<td></td>
<td>Placebo: 9.27 μmol/L (2.1)</td>
<td>Placebo: 10.0 μmol/L (1.0)</td>
<td>Placebo: 10.9 μmol/L (2.4)</td>
</tr>
<tr>
<td><strong>Mean (SD) serum zinc levels at discharge</strong></td>
<td>Zinc: 16.79 μmol/L (5.4)</td>
<td>Zinc: 14.5 μmol/L (2.8)</td>
<td>Zinc: 11.0 μmol/L (2.2)</td>
</tr>
<tr>
<td></td>
<td>Zinc + Vit A: 17.4 μmol/L (5.8)</td>
<td>Placebo: 11.2 μmol/L (2.1)</td>
<td>Placebo: 12.0 μmol/L (4.1)</td>
</tr>
<tr>
<td></td>
<td>Placebo: 11.28 μmol/L (2.1)</td>
<td>Placebo: 11.2 μmol/L (2.1)</td>
<td>Placebo: 12.0 μmol/L (4.1)</td>
</tr>
<tr>
<td></td>
<td>Vit A: 10.9 μmol/L (5.0)</td>
<td>Placebo: 11.2 μmol/L (2.1)</td>
<td>Placebo: 12.0 μmol/L (4.1)</td>
</tr>
<tr>
<td><strong>Proportion with wheezing at baseline</strong></td>
<td>Not provided</td>
<td>37.4%</td>
<td>62.5%</td>
</tr>
</tbody>
</table>

**Abbreviations:** RR, respiratory rate; SD, standard deviation.
microbial detection rates, being of use only when bacte-
remia has occurred. 20 Lung aspirates have significant side
effects and require considerable expertise, so they are
rarely performed. In children who have received anti-
biotics, the rates of detection for bacterial pathogens are
dramatically reduced, while this is not the case for detec-
tion of viruses. Therefore, most studies that set out to
determine the etiology of pneumonias are likely to find a
larger percentage of viral pneumonias than bacterial or
mixed infections.

A previous etiological study from Vellore reported a
seasonal increase in bronchiolitis during the rainy season,
presumably due to outbreaks of respiratory syncytial
virus.19 Only one-third of all hospitalized children with
ALRI were diagnosed with bronchiolitis, and the etiology
of ALRI in the remaining two-thirds was not reported.
Therefore, it is uncertain whether most of the pneumo-
nias in Vellore during the rainy season are viral or if the
incidence of bacterial respiratory infections in the rainy
season is reduced. Wheezing is considered to be associ-
ated with viral respiratory infections, and the proportion
of children with a wheeze at enrollment was much higher
in the Vellore trial than in the Bangladesh trial (62.5% vs.
37%). Subgroup analysis based on the presence of wheez-
ing was performed in both trials. While the Bangladesh
trial found that exclusion of children with wheezing from
the analysis strengthened the beneficial effect of zinc on
recovery, the Vellore trial found no effect modification by
wheeze, suggesting that the effect of zinc is not dimin-
ished in infants without wheezing. An earlier trial of zinc
supplementation to treat measles-associated pneumonia
at the same center in Kolkata found no benefit of zinc
when compared to placebo.21 Brooks et al., 5 in the Bang-
ladesh zinc study, hypothesized that the addition of zinc

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Boys: 2.63 (1.35, 5.10)</th>
<th>Overall: 0.70 (0.61–1.05)</th>
<th>Overall: 0.93 (0.72, 1.21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to resolution of very ill status or severe pneumonia</td>
<td>Girls: 0.80 (0.44, 1.43)</td>
<td></td>
<td>Hot season: 0.60 (0.41, 0.91)</td>
</tr>
<tr>
<td>Time to resolution of feeding difficulty</td>
<td>Boys: 1.36 (0.87, 2.13)</td>
<td>NP</td>
<td>Rainy season: 1.11 (0.78, 1.57)</td>
</tr>
<tr>
<td></td>
<td>Girls: 0.67 (0.38, 1.20)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to resolution of fever</td>
<td>Boys: 3.12 (1.47, 6.60)</td>
<td>NP</td>
<td>Overall: 0.94 (0.74, 1.18)</td>
</tr>
<tr>
<td></td>
<td>Girls: 0.68 (0.35, 1.35)</td>
<td></td>
<td>Hot season: 0.58 (0.39, 0.88)</td>
</tr>
<tr>
<td>Time to resolution of tachypnea</td>
<td>Boys: 1.70 (0.89, 3.23)</td>
<td>For 50/min: 0.74 (0.57–0.98)</td>
<td>Overall: 0.97 (0.57, 0.87)</td>
</tr>
<tr>
<td></td>
<td>Girls: 0.65 (0.36, 0.68)</td>
<td>For 40/min: 0.75 (0.57–0.98)</td>
<td>Rainy season: 1.19 (0.89, 1.60)</td>
</tr>
<tr>
<td>Time to resolution of chest indrawing</td>
<td>NP</td>
<td>Overall: 0.80 (0.61–1.05)</td>
<td>Overall: 0.92 (0.70, 1.22)</td>
</tr>
<tr>
<td>Time to resolution of hypoxia</td>
<td>NP</td>
<td>Overall: 0.79 (0.61–1.04)</td>
<td>Hot season: 0.43 (0.26, 0.72)</td>
</tr>
<tr>
<td>Duration of hospitalization</td>
<td>NP</td>
<td>Overall: 0.75 (0.57–0.99)</td>
<td>Rainy season: 1.34 (0.96, 1.87)</td>
</tr>
<tr>
<td>Treatment failure</td>
<td>NP</td>
<td>Overall: 3.4 (0.86–19.9)</td>
<td>Overall: 1.21 (0.90, 1.61)</td>
</tr>
<tr>
<td>Time to resolution of wheeze</td>
<td>NP</td>
<td></td>
<td>Rainy season: 0.93 (0.74, 1.17)</td>
</tr>
<tr>
<td>Time to resolution of lethargy</td>
<td>NP</td>
<td></td>
<td>Hot season: 0.57 (0.38, 0.86)</td>
</tr>
</tbody>
</table>

* Ratios >1 favor zinc.
+ Removal of children with wheezing from the analysis increased the differences between the zinc and placebo groups.

Abbreviation: NP, not provided.

Table 2 Summary of outcomes and effect estimates.
to pneumonia treatment may benefit bacterial pneumonias more than viral pneumonias, which contrasts with the hypothesis of Bose et al. in the Vellore study.

Another analysis from the data of the Vellore trial has been published, which suggested that zinc supplementation may be harmful for children with bacterial infections. Among 72 of the 295 (24.4%) children in the Vellore trial with serum CRP levels >40 mg/dL, the median duration of hospitalization was 20 hours longer in the zinc-supplemented group (p = 0.025). Only 25.9% (7/27) of culture-confirmed cases of bacterial pneumonia had serum CRP levels >40 mg/dL and a majority of children with culture-confirmed bacterial pneumonia had serum CRP levels ≤40 mg/dL. In the analysis, 20 of the 27 culture-confirmed cases of pneumonia with serum CRP levels ≤40 mg/dL would have been categorized as non-bacterial pneumonia. If CRP levels were a good marker of bacterial disease we would have expected the CRP positivity rate (>40 mg/dL) to be much greater among culture-confirmed pneumonias than among all pneumonias, unlike the 25.9% and 24.4%, respectively, observed here. Serum CRP concentration is not widely accepted as a valid marker of bacterial pneumonia and appropriate cutoffs remain to be determined for specific populations.

**Antibiotic use, trial endpoints, and timing of zinc treatment**

The efficacy of zinc in the treatment of pneumonia may differ depending on what kind of antibiotic therapy zinc is added to and when. Errors in determining recovery from pneumonia and premature discharges from hospitals may introduce biases that may obfuscate a trial’s ability to detect an effect of zinc. These three trials differed in the protocols that were followed in the treatment of ALRI. Though gentamicin was consistently included in the treatment of children in all trials, the accompanying beta-lactam antibiotic varied. In the Kolkata trial, cloxacillin was used; while this agent covers staphylococci well, it treats *Haemophilus influenzae* less comprehensively. In the Bangladesh trial, injectable ampicillin was provided. In Vellore, children received benzyl penicillin, with cloxacillin available for those whose X-rays were suggestive of staphylococcal pneumonia. Up to 40% of *H. influenzae* cases in India have been found to be resistant to ampicillin.23 While benzyl penicillin is effective against *Streptococcus pneumoniae*, it is not effective against gram-negative bacteria, including *H. influenzae*, and over 25% of the children in the Vellore study were switched to second-line antibiotics after failing to respond to first-line agents. In comparison, only 5% and 6% of subjects failed to respond to first-line antibiotics in Bangladesh and Kolkata, respectively. In all three zinc trials, children were shifted to a third-generation cephalosporin (cefotaxime or ceftriaxone) if they failed to respond to the first-line treatment.

The mean duration of illness at enrollment in the Vellore trial was 5.8 days (standard deviation [SD] 11.0) in the zinc-treated group and 4.7 days (SD 6.2) in the placebo group. This is nearly 3 days longer than the average duration of illness in the Bangladesh trial. It has been suggested that the longer duration of illness at enrollment may indicate that the children in the Vellore trial suffered from milder illnesses or were in recovery at admission. However, with the five times greater rate of treatment failure in Vellore, it seems unlikely that the illnesses were milder in that study than in the Bangladesh trial. The large proportion of study subjects needing second-line antibiotics would lead to a reduction in power, and it may be difficult to detect any differences caused by zinc in the two groups. The high efficacy of third-generation cephalosporins will lead to recovery rates and durations that are unlikely to capture the relatively smaller benefits of adding zinc to the treatment. Field trials or trials at smaller treatment centers on less severe cases of pneumonia may be more useful in demonstrating the effect of zinc. Survival analyses from these trials have indicated that survival curves tend to remain similar until the first 48–72 hours after enrollment, indicating that, even when effective, zinc treatment needs a period of 2–3 days before it can improve recovery. Therefore, early outcomes such as treatment failure at 48 –72 hours are unlikely to be meaningful for assessing the effect of zinc.

Depending on the setting of the study, different proportions of enrolled children would have received antibiotics prior to enrollment into the trial. It is likely that most children reaching a referral hospital (as in the Vellore trial) would have been exposed to antibiotics prior to enrollment and hospitalization, unlike in the Bangladesh trial, which was carried out at a rural hospital. Prior antibiotic exposure can modify recovery, and information on prior antibiotic use must be included in the baseline data in order to allow for comparisons between trials.

Determining trial endpoints in large tertiary-care hospitals can be tricky. The pressure on vital life-saving hospital resources, including beds, often makes it necessary to make clinical decisions early and aggressively. In the Vellore trial, early discharges and antibiotic changes may have led to a non-differential misclassification of recovery status in the analysis, making relatively smaller differences due to zinc supplementation impossible to detect.

Irrespective of the etiology of pneumonia, the timing of instituting zinc treatment in the illness may have a bearing on the outcome of pneumonia. The Bangladesh
study found a beneficial effect of zinc treatment and had a mean duration of 2.5 days of symptoms at enrollment, while the Kolkata study found a beneficial effect limited to boys. All three studies had a preponderance of male children among the enrolled participants. It is unlikely that pneumonia is more frequent among boys or that zinc interacts with the immune system and influences recovery from pneumonia differently in boys and girls. It is possible that the subgroup analyses based on gender were confounded by some other characteristic that was associated with both gender and recovery from pneumonia.

The preponderance of male participants in these trials can be explained by the preferentially better care afforded to male children in households in these areas. By virtue of this better care, it is also to be expected that male children will reach the hospital earlier in the course of their illness than girls. Boys have been found to be five times more likely than girls to be brought to a healthcare institution for earlier treatment of common childhood illnesses like diarrhea and pneumonia. The mean time taken to consult a health professional for girls (21.2 h) is more than twice the time taken for boys (8.3 h). Similarly, during the hot months, there may be a perception that respiratory illnesses tend to be less severe or fatal, and parents and care providers may be willing to wait longer before taking the child to a referral center. Conversely, in the rainy season, respiratory symptoms may be considered more ominous and may prompt parents to seek medical care early in the course of the illness. The rainy season also happens to be when diarrheal diseases peak and these concurrent diarrheal episodes may lead to significant zinc losses. It is, therefore, possible that children, being more zinc deficient, benefit differently from zinc treatment in the rainy season than in the hot season. These trials were not designed to examine the effect of zinc treatment based on the duration of symptoms at enrollment. Therefore, the lack of a statistically significant difference in time to recovery in a subgroup analysis based on duration of symptoms (≤3 days vs. >3 days) does not imply that early initiation of zinc is not more beneficial. Since the exact nature of the biological basis of zinc’s effect on recovery from pneumonia is unclear, the possibility must be entertained that the addition of zinc late in the course of illness may have a different effect on the duration of pneumonia symptom.

CONCLUSION

The different results from the three trials reviewed here suggest that the benefit from zinc supplementation during ALRI is not universal. The zinc status of children enrolled in these trials, the differences in etiologies, definitions of pneumonia, and recovery, and the timing of zinc supplementation in the course of the illness are some of the possibilities that may explain the variation in results. Serum zinc levels during infections will be determined by prior zinc status as well as disease phase and severity of illness, and these effects cannot be adjusted for while analyzing results in subgroups according to serum zinc levels.

In such a scenario, it is important to determine if zinc supplementation during ALRI leads to adverse outcomes in any group of children, and caution must be exercised while interpreting subgroup analyses. Trial definitions must remain objective and be based on criteria for the diagnosis and grading of pneumonia, recovery, and discharge from the World Health Organization’s case management approach in order to avoid misclassification of outcomes. Incorporating diagnostic methods to determine the microbiological etiology of pneumonia, rather than depending on unreliable clinical markers and seasonality to suggest the microbiological etiology of infection, in at least a subpopulation of these trials may help determine if the effects of zinc differ by etiology. The variation in findings from three separate zinc supplementation trials within a single region, such as the Indian subcontinent, indicates additional zinc supplementation trials need to be performed in other developing regions of the world where pneumonia mortality and zinc deficiency are common, and the results will need to be replicated before recommendations for adjunctive zinc supplementation can be added to the WHO case management of pneumonia in children. Ongoing randomized controlled trials are examining the effect of zinc supplementation on the clinical course of pneumonia among children in The Gambia, Uganda, Bangladesh, and Nepal. Findings from these trials will account for geographical differences in zinc status and the etiology of severe pneumonia and help determine if zinc supplementation has a place in the treatment of childhood pneumonia.

REFERENCES
