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 1–3

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ABSTRACT

Background: Acute lower respiratory infection (ALRI) is a leading cause of childhood death. Zinc supplementation prevents ALRI. Vitamin A supplementation reduces childhood mortality, but its benefit concerning ALRI-specific mortality is unproven.

Objective: The objective was to evaluate the effect of zinc and vitamin A on the clinical recovery of children with severe ALRI.

Design: In a controlled trial with a factorial design, 153 children aged 2–24 mo who were hospitalized with severe ALRI were randomly assigned to receive 10 mg zinc as acetate (twice daily for 5 d) plus vitamin A placebo, 10 000 μg retinol equivalents vitamin A (twice daily for 4 d) plus zinc placebo, zinc plus vitamin A, or zinc and vitamin A placebos. The main outcome variable was the time for resolution of very ill status; other outcomes were resolution of fever, tachypnea, and feeding difficulty.

Results: Recovery rates from very ill status and from fever in zinc-treated boys were 2.6 times (P = 0.004) and 3 times (P = 0.003) those in non-zinc-treated children; feeding difficulty and tachypnea were not significantly different between groups after an adjusted analysis. Recovery rates were not significantly different between groups on the basis of vitamin A treatment. At discharge, serum zinc was 6.06 μmol/L higher (P = 0.001) in the zinc-treated children, and serum retinol was 0.387 μmol/L higher (P = 0.001) in the vitamin A–treated children.

Conclusion: Zinc treatment significantly reduces duration of fever and very ill status in boys, but not in girls, with severe ALRI. Vitamin A treatment of children with severe ALRI had no significant beneficial effect. Am J Clin Nutr 2004;79:430–6.

KEY WORDS Zinc, vitamin A, acute lower respiratory infection, ALRI, therapy, sex effect, clinical trial

INTRODUCTION

Acute respiratory infection is an important cause of morbidity globally and of mortality in children in developing countries (1). Several intervention studies that used a case management algorithm to treat children in developing countries with acute lower respiratory infection (ALRI) showed that mortality specific to acute respiratory infection decreased by an average of 42% and overall mortality by 23% (1). Therefore, any improvement in the case management of ALRI in children may contribute to a further reduction in mortality specific to acute respiratory infection.

Zinc supplementation has already been shown to benefit children with acute and persistent diarrhea by reducing the duration and severity of episodes (2, 3). Furthermore, zinc supplementation was shown to prevent pneumonia in children in developing countries (4). Zinc as a micronutrient plays a key role at the catalytic sites of a wide range of enzymes and is critical to human growth, metabolism, and immune function (5). The diets of children in many developing countries are often deficient in zinc and a high phytate:zinc ratio in their diet reduces zinc bioavailability (6).

Periodic supplementation of children with vitamin A was shown to substantially reduce overall childhood mortality (7–9). Furthermore, large-dose vitamin A supplementation during illness has been shown to reduce mortality (10–12), the severity of illness (11–13), and the duration of pneumonia (11, 12) in children with measles and to possibly reduce significantly the number of persistent diarrhea episodes in children with acute diarrhea (3). The results of trials in children with ALRI or pneumonia who were treated with vitamin A are conflicting (14–23). In general, no benefit or modestly adverse effect in well-nourished children and some benefit in malnourished children have been reported. In the current study, we examined whether infants and young children hospitalized with severe ALRI benefit from the administration of zinc or large doses of vitamin A. The main objective was to evaluate the effect on clinical recovery of the addition of zinc or large doses of vitamin A to the standard treatment for severe ALRI and pneumonia in infants and young children.

SUBJECTS AND METHODS

Children aged 2–24 mo of either sex who were sufficiently ill to be admitted to the BC Roy Memorial Hospital for Children, Kolkata (formerly Calcutta), India with a clinical diagnosis of...
severe ALRI were considered for inclusion in the study. This hospital provides free treatment to largely urban and periurban poor. The physician diagnosed ALRI on the basis of the presence of cough and fast breathing (respiratory rate >50/min for children aged 2–11 mo and >40/min for children aged 12–24 mo) or lower chest indrawing (1); severe ALRI was diagnosed when ALRI was associated with either 1) cough combined with crepitation or bronchial breathing on auscultation or with 2) one of the following severity indicators: inability to drink or feed, marked lethargy or irritability, nasal flare, or drowsiness. Children with severe ALRI, as defined above, were included in the study. Children with obvious marasmus or edema, with severe nonrespiratory infection (eg, meningitis, bloody diarrhea, congenital heart disease, or another gross congenital malformation) were excluded. After informed consent was obtained from the parents of eligible children, the children were entered into the study. The study protocol was approved by the Ethical Review Committee of the Society for Applied Studies. Patient recruitment took place from 25 March 1997 to 19 December 1998.

A factorial treatment trial design was used to evaluate the role of zinc or vitamin A supplementation as adjunct therapy of severe ALRI in infants and young children. This enabled us to make 2 treatment comparisons in one trial with a smaller number of patients in the trial. For 2 independent comparisons, patients were randomly assigned into 4 groups to receive supplements of 1) zinc acetate (10 mg elemental Zn twice daily for 5 d) plus a placebo for vitamin A, 2) vitamin A as retinyl palmitate [10 000 μg retinol equivalents (RE) twice daily for 4 d] plus a placebo for zinc, 3) zinc plus vitamin A according to the above schedule, or 4) placebo for zinc and for vitamin A. The effect of zinc was evaluated by comparing the children who received zinc (groups 1 and 3) with those who did not (groups 2 and 4). The effect of vitamin A was evaluated by comparing the children who received vitamin A (groups 2 and 3) with those who did not (groups 1 and 4). The design ensured that when one comparison was made, the distribution of the other intervention was balanced. However, we adjusted for the treatment effect of either supplement and their interaction in an appropriate multivariate analysis.

Randomization

A master randomization schedule was prepared by a person not associated with the study who used permuted blocks of random numbers. The medicine bottles and identical placebo were prepared by a pharmaceutical manufacturer under the supervision of a qualified pharmaceutical chemist acting as a consultant on our behalf. Random samples of the bottled mixtures were tested by atomic absorption spectrophotometry for zinc concentration and by HPLC for retinol. Randomization was incorporated in the serially numbered bottles containing drug or placebo by a pharmaceutical chemist not involved with the study. The serial number of the bottle corresponded with the serial number of the patient.

Intervention

A zinc acetate mixture containing 10 mg elemental Zn or placebo mixture was given twice daily for each day of stay for 5 d. Vitamin A (10 000 μg RE as retinyl palmitate) was given as a water miscible preparation twice daily for 4 d. Placebo for zinc consisted of the syrup base used for the zinc mixture, which was appropriately modified to give a taste similar to the zinc mixture. A trace amount of a widely used dry edible fruit (myrobalan), with an astringent taste, was added to the zinc placebo. Placebo for vitamin A was the syrup base used for vitamin A palmitate. Both the participants and those administering and evaluating the patients were unaware of the treatment allocation. All patients received a standard schedule of treatment for severe ALRI and associated problems that was based on the existing practice of the hospital, which included antibiotics, bronchodilators, and oxygen as required. All children were treated with a combination of cefixime and gentamycin parenterally as first-line antibiotic treatment. If no improvement was observed in 48 h or if the children’s conditions deteriorated during the course of treatment, the physicians made a clinical decision to change the antibiotic regimen to cefotaxime or ceftriaxone parenterally.

Sample size

On the basis of the consensus of the hospital pediatricians, 50% of the patients were expected to achieve “clinically cured” or “much improved” status after 4 d of treatment. With zinc as an adjunct therapy, we expected 75% of the children to achieve this status as judged by the clinician. The calculated number in each group (with 80% power and a 5% significance level) would be 76 children, assuming a withdrawal rate of 8% (24). On the basis of similar assumptions for the proportion of patients in whom tachypnea or fever would have resolved after 4 d of treatment, the calculated sample sizes would be similar. Similar assumptions were made for the effect of vitamin A. A total of 152 patients was the estimated sample size.

Clinical evaluation

Before the study began, several briefing meetings were conducted with the pediatricians. It was decided that, in addition to documenting standard clinical features, the pediatricians would record their clinical judgement as to whether a child had attained a clinically cured or much improved status based on the following criteria: 1) alertness and general well being, 2) resolution of respiratory distress, 3) how well the infant feeds, and 4) resolution of fever and tachypnea (as defined later). The major outcome variable was the time taken for this composite illness indicator to resolve. No scoring system was used, and it was agreed that the introduction of a fresh scoring system would not be worthwhile. Clinical features were evaluated and recorded twice daily, in the morning and evening, by the 3 study pediatricians, who were unaware of the treatment allocation. Other outcome variables were also examined: the time for the resolution of tachypnea (ie, respiratory rate >50/min in ≤12 mo and >40/min in >12 mo), fever (ie, skin temperature >98 °F, or 36.7 °C), and feeding difficulty (as judged by the mother or caregiver staying with the patient).

Analysis

Data were recorded on standard forms, entered into a microcomputer, and edited with the use of EPI INFO version 6.03 software (Centers for Disease Control and Prevention, Atlanta, and the World Health Organization, Geneva). The major objective of the study was to evaluate the effect of zinc or vitamin A on the clinical course of illness due to pneumonia in infants and young children. We therefore used survival (time to an event) analysis techniques to compare the duration of the illness indicators, which also permitted us to adjust for censored data. The
clinical illness indicators used were the time to resolution of 1) very ill clinical status as judged by the pediatrician, 2) fever, 3) feeding difficulty or inability to feed, and 4) tachypnea. Indicator 1, the main outcome measure, is a composite indicator that is based on the clinician’s assessment of alertness, breathing difficulty, ability to feed well, fever, and tachypnea. Prognostic factors like age, sex, treatment with zinc for evaluating the effect of vitamin A, treatment with vitamin A for evaluating the effect of zinc, and any significant interaction between zinc and vitamin A supplementation were adjusted for, with the use of Cox proportional hazards regression analysis. The software program STATA release 7.0 (Stata Corporation, TX) was used for survival analysis. The median duration of illness indicators were obtained from the Kaplan-Meier product-limit estimate of the survivor function, and the SE of the median was calculated by the method of Klein and Maeschberger (25). The hazards ratio indicates the ratio of recovery rates from the illness indicators in supplemented to unsupplemented children at any time point during the study; values > 1 are associated with the probability of the duration of illness indicators being shorter in the zinc- or vitamin A-supplemented children.

We further examined the median duration of the illness indicators stratified by sex and noted that sex is an effect modifier for zinc effect but not for vitamin A. We, therefore, also analyzed the treatment effect for zinc in boys and girls separately. All analyses were done on an intention-to-treat basis. Results of the interaction tests involving sex are given in Results.

RESULTS
Two hundred twenty-two children were assessed for eligibility, and 153 children were enrolled (Figure 1). One child in the placebo group withdrew at 50 h, and one child in the vitamin A group withdrew at 63 h. One child in the zinc and vitamin A group died at 15 h. Thirty-nine children in the zinc group and 37 in each of the other 3 groups completed observation in the hospital. The variables at baseline were not significantly different between the supplemented and unsupplemented children (Table 1). Male preponderance reflected the pattern of admission in this hospital. Mean serum retinol concentrations at discharge were 1.647 μmol/L for the 2 vitamin A-supplemented groups and 1.288 μmol/L for the 2 non-vitamin A-supplemented groups ($P = 0.0007$) (Table 2). The mean difference in values at discharge between the groups when baseline serum retinol concen-

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**FIGURE 1.** Flow chart for patient recruitment.
trations were adjusted for was 0.387 μmol/L ($P = 0.001$). Mean serum zinc concentrations at discharge were 17.09 μmol/L in the zinc-supplemented group and 11.08 μmol/L in the 2 non-zinc-supplemented children ($P \leq 0.0001$) (Table 2). The mean difference in values at discharge between the groups when baseline serum zinc concentrations were adjusted for was 6.06 μmol/L ($P = 0.001$).

The median (SE) durations of the 4 illness indicators in the 4 groups, for boys and girls separately, are shown in Table 3. There was an interaction between zinc treatment and sex for 3 of the 4 illness indicators: ill status ($P = 0.08$), time to resolution of fever ($P = 0.033$), and feeding difficulty ($P = 0.045$). However, no significant interaction between vitamin A treatment and sex was found for any of the 4 illness indicators.

In boys in the zinc-supplemented groups, the rate of recovery for the composite illness indicator (ie, very ill status) at any given time point was 2.6 times ($P = 0.09$) and that for the resolution of fever was 3.1 times ($P = 0.003$) that in the children not supplemented with zinc (Table 4). We saw a similar trend for the resolution of feeding difficulty ($P = 0.09$) and tachypnea ($P = 0.11$). If sex is an “effect modifier,” the results of recovery rate ratios for the total would not be appropriate. However, the recovery rate ratios for the total sample tended to favor the zinc-supplemented children, which is probably a consequence of male preponderance in the sample. Globally, the recovery rate ratios (95% CI) for the vitamin A–supplemented children were not significantly different from those for the children not supplemented with vitamin A for any of the 4 illness indicators.

The pattern of recovery, analyzed by using survival analysis based on the Cox model, from a very ill status and fever in boys supplemented with zinc compared with those not supplemented with zinc is illustrated in Figure 2 (A and B, respectively). Recovery rates were consistently higher for the boys supplemented with zinc. This pattern was similar for the other 2 illness indicators, feeding difficulty and tachypnea (data not shown). In girls, the pattern was opposite that for boys for all 4 illness indicators (data not shown).

In view of the significant interaction in boys between zinc and vitamin A supplementation, we compared boys in the groups that received zinc alone with the group that received placebo only to

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Baseline variables by treatment groupa</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
</tr>
<tr>
<td>(n = 38)</td>
<td>(n = 38)</td>
</tr>
<tr>
<td>Age (mo)b</td>
<td>6 (2–20)</td>
</tr>
<tr>
<td>Age group (mo)</td>
<td></td>
</tr>
<tr>
<td>&gt; 4–7</td>
<td>13</td>
</tr>
<tr>
<td>&gt; 7–11</td>
<td>10</td>
</tr>
<tr>
<td>&gt; 11</td>
<td>5</td>
</tr>
<tr>
<td>Breastfed (n [%])</td>
<td>37 [97]</td>
</tr>
<tr>
<td>Received antibiotics before admission (n [%])</td>
<td>24 [63]</td>
</tr>
<tr>
<td>Mothers with ≥6 y of schooling (n [%])</td>
<td>18 [47]</td>
</tr>
<tr>
<td>Weight-for-age z score (n [%])</td>
<td>-1.64 [1.06]</td>
</tr>
<tr>
<td>At admission (n [%])</td>
<td></td>
</tr>
<tr>
<td>Feeding difficulty</td>
<td>36 [95]</td>
</tr>
<tr>
<td>Chest indrawing</td>
<td>37 [97]</td>
</tr>
<tr>
<td>Feverc</td>
<td>24 [63]</td>
</tr>
<tr>
<td>Very ill statusd</td>
<td>37 [97]</td>
</tr>
</tbody>
</table>

a Differences between groups were not significant (chi-square test and ANOVA).
b Median; range in parentheses.
c Skin temperature > 98°F (36.7°C).
d As judged by the clinician.

TABLE 2
Serum retinol and zinc concentrations at admission and dischargec

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Vitamin A</th>
<th>Zinc</th>
<th>Zinc and vitamin A</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>µmol/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum retinol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission</td>
<td>0.712 ± 0.616 [30]</td>
<td>0.705 ± 0.532 [28]</td>
<td>0.70 ± 0.73 [26]</td>
<td>0.812 ± 0.503 [34]</td>
</tr>
<tr>
<td>Dischargec</td>
<td>1.260 ± 0.549 [33]</td>
<td>1.564 ± 0.658 [28]</td>
<td>1.317 ± 0.407 [32]</td>
<td>1.723 ± 0.651 [31]</td>
</tr>
<tr>
<td>Serum zinc</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

c ± SD; n in brackets. Values are for children in whom an adequate blood sample was collected.
c Significantly higher in the respective supplemented groups than in the unsupplemented groups after adjustment for baseline value for both zinc ($P < 0.0001$) and retinol ($P < 0.0007$) by multiple regression analysis.
see the direction of the effect when the interaction was not confounding. The pattern of resolution of the 2 illness indicators, i.e., very ill status and fever (Kaplan-Meier survival curve), for this comparison is shown in Figure 2 (C and D, respectively). For boys, the results consistently favored the zinc-supplemented children for all 4 illness indicators (data for feeding difficulty and tachypnea not shown) and the recovery rate ratios were 1.39 (P = 0.006) for very ill status, 1.59 (P = 0.002) for fever, 1.23 (P = 0.076) for feeding difficulty, and 1.27 (P = 0.044) for tachypnea. The incidence of adverse events and a need to change antibiotics by treatment group are shown in Table 5. Diarrhea was associated with vitamin A supplementation (P = 0.028) but not with zinc supplementation (rate ratio: 0.25; 95% CI: 0.23, 2.16). Antibiotic change tended to be more common in the vitamin A-supplemented children (rate ratio = 3.55; P = 0.098). Any adverse effect or a need for antibiotic change was higher in the children supplemented with vitamin A and zinc and in 1 child supplemented with zinc but not with vitamin A.

### DISCUSSION

We studied a group of sick infants and young children with severe ALRI who required hospitalized care. Recovery time from an ill status, a composite illness indicator, was the main outcome of interest. We also used 3 additional illness indicators (ie, recovery time from tachypnea, fever, and feeding difficulty) as outcome measures largely to check for consistency. Because of a significant interaction between zinc and vitamin A supplementation, analysis results adjusted for this interaction was used where relevant.

#### Zinc treatment of pneumonia

Zinc deficiency is thought to be common in children in developing countries whose diets are low in animal products and high in phytate (6). Repeated episodes of diarrhea exacerbate zinc deficiency because of the loss of zinc in stool (26). Unlike some other micronutrients of public health importance, zinc deficiency is not associated with specific clinical features, and no reliable biomarkers of deficiency are available to identify populations

### TABLE 3

<table>
<thead>
<tr>
<th>Group</th>
<th>Boys (n = 56)</th>
<th>Girls (n = 56)</th>
<th>Boys (n = 56)</th>
<th>Girls (n = 56)</th>
<th>Boys (n = 56)</th>
<th>Girls (n = 56)</th>
<th>Boys (n = 56)</th>
<th>Girls (n = 56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n = 38)</td>
<td>97 (7.03)</td>
<td>71.5 (2.195)</td>
<td>73 (4.63)</td>
<td>66.5 (4.74)</td>
<td>56.5 (4.30)</td>
<td>26 (0.86)</td>
<td>79 (3.93)</td>
<td>50 (2.16)</td>
</tr>
<tr>
<td>Vitamin A (n = 38)</td>
<td>75 (1.44)</td>
<td>75 (2.79)</td>
<td>65 (1.54)</td>
<td>43.5 (0.41)</td>
<td>35.5 (5.77)</td>
<td>31.5 (0.92)</td>
<td>63 (5.11)</td>
<td>57.5 (0.84)</td>
</tr>
<tr>
<td>Zinc (n = 39)</td>
<td>60 (1.42)</td>
<td>92 (4.15)</td>
<td>54.5 (1.71)</td>
<td>67 (3.45)</td>
<td>23 (0.53)</td>
<td>61 (0.76)</td>
<td>70.5 (9.23)</td>
<td>78.5 (0.70)</td>
</tr>
<tr>
<td>Zinc and vitamin A (n = 38)</td>
<td>83.5 (4.59)</td>
<td>77 (5.47)</td>
<td>59.5 (3.09)</td>
<td>67 (5.76)</td>
<td>35.5 (1.75)</td>
<td>29 (2.46)</td>
<td>77 (4.19)</td>
<td>93.5 (2.08)</td>
</tr>
</tbody>
</table>

1 Median; SE in parentheses. Medians were derived from the Kaplan-Meier product limit estimates; the SEs of the medians were estimated by using survival analysis techniques for censored data (25). A comparison of the 4 groups of boys with the use of survivor functions (log-rank test) showed significant differences for very ill status (P = 0.06) and fever (P = 0.02). Difference among treatment groups for girls were not significant for any of the 4 outcome variables.

2 Interaction between zinc treatment and sex: very ill status (P = 0.08), fever (P = 0.033), feeding difficulty (P = 0.045), and tachypnea (P = 0.29). No interaction between vitamin A treatment and sex was significant. None of the 3-factor interactions (vitamin A × zinc × sex) were significant.

### TABLE 4

<table>
<thead>
<tr>
<th>Recovery rate ratio (95% CI)</th>
<th>Very ill status</th>
<th>Feeding difficulty</th>
<th>Fever</th>
<th>Tachypnea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (n = 153)^2</td>
<td>1.01 (0.72, 1.42)</td>
<td>0.99 (0.70, 1.39)</td>
<td>0.97 (0.66, 1.44)</td>
<td>1.02 (0.73, 1.43)</td>
</tr>
<tr>
<td>Vitamin A</td>
<td>0.59 (0.29, 1.19)</td>
<td>0.80 (0.39, 1.63)</td>
<td>0.66 (0.29, 1.45)</td>
<td>0.71 (0.35, 1.42)</td>
</tr>
<tr>
<td>Zinc × vitamin A^4</td>
<td>0.80 (0.44, 1.43)</td>
<td>0.67 (0.38, 1.20)</td>
<td>0.68 (0.35, 1.35)</td>
<td>0.65 (0.36, 0.68)</td>
</tr>
</tbody>
</table>

1 A Cox proportional hazards model was used with duration of illness indicators (very ill status, feeding difficulty, fever, and tachypnea) as dependent variables, analyzed by sex. Interactions between zinc and sex were significant for 3 of the 4 illness indicators (see Table 3). No significant interaction between vitamin A and sex was noted for any of the 4 variables, and none of the 3-factor (vitamin A, zinc, and sex) interactions were significant.

2 Hazard rates for recovery in groups supplemented with zinc or vitamin A compared with no zinc or no vitamin A. Values > 1 favor the zinc or vitamin A group.

3 Proportional hazards model for each illness indicator, adjusted for zinc intervention and age-group quartiles as dummy variables.

4 Interaction between zinc and vitamin A; none of the interactions were significant.

5 Separate proportional hazards models were fitted for each illness indicator and were adjusted for vitamin A intervention, interaction between zinc and vitamin A (except for feeding difficulty), and age-group quartiles as dummy variables.
with mild-to-moderate zinc deficiency. In the current study, zinc treatment significantly increased serum zinc concentrations in infants and children with severe ALRI compared with controls.

An analysis of the data resulted in an unexpected finding. Sex appeared to be a strong effect modifier in that zinc treatment showed a clear benefit in boys but not in girls, in whom the effect may have even been adverse. Taking advantage of the factorial study design, we found additional support for the beneficial effect of zinc treatment in boys with severe ALRI through a direct comparison of boys who received zinc only with boys who received placebo only. The rate of adverse events or a need for a change in antibiotic was not higher in children supplemented with zinc than in children not supplemented with zinc.

In a pooled analysis (4) of the results of 4 zinc supplementation trials that evaluated the effect of zinc supplementation on the prevention of diarrhea and pneumonia in children in developing countries, in whom morbidity was assessed concurrently, zinc-supplemented children had a 41% reduced rate of pneumonia (95% CI: 17%, 59%). In a trial in Bangladesh (27), in which the children were supplemented with zinc for 14 d only and morbidity was assessed over the subsequent 6 mo, zinc supplementation showed no favorable effect on the incidence and prevalence of pneumonia. We note, however, that zinc is not stored in the body in the same way that iron or vitamin A is. We were unable to locate any trial of zinc supplementation in children with pneumonia or ALRI to compare our results.

The beneficial results of zinc supplementation in boys with pneumonia were based on a subgroup analysis and, therefore, require confirmation. We also acknowledge our inability to adequately explain why only boys with pneumonia benefited from treatment with zinc. The results should encourage investigators of earlier zinc supplementation trials in children for the prevention of diarrhea and pneumonia to examine their data for any sex effect. Mean serum zinc concentrations at admission were similar in boys and girls. Mean serum zinc concentrations at discharge in both the zinc-supplemented and unsupplemented children showed a similar increase in boys and girls (data not shown).

Vitamin A treatment of severe ALRI

As stated earlier, trials of vitamin A treatment in both developing and developed countries showed conflicting results (14–23). In general, no benefit and even adverse effects were reported. Some studies reported a benefit of vitamin A supplementation in malnourished children. The current study was conducted in infants and young children hospitalized with severe disease due to ALRI. Serum retinol concentrations at admission were low, which may indicate both a deficiency and a consequence of severe infection. Apart from an acute phase response after infection, retinol may also be lost in urine, particu-
larly in febrile illness (28). Serum retinol concentrations improved in both supplemented and unsupplemented children. However, serum retinol values at discharge in the vitamin A–supplemented children were significantly higher than those in the unsupplemented children, which suggests an underlying vitamin A deficiency in the study population.

In the current study, as in the earlier trials mentioned (14–23), vitamin A treatment of infants and young children hospitalized with pneumonia did not render any worthwhile benefit. Furthermore, the rate of adverse events particularly diarrhea or a need to change antibiotics due to lack of clinical response or deterioration was higher in vitamin A treated children compared with no-vitamin A children. The total dose of vitamin A was relatively large, which may partly explain some of the adverse events. We note, however, that there is a slightly increased incidence of pneumonia in boys in developing countries (29). The results of the current study, however, do not help explain why vitamin A supplementation of children in developing countries substantially reduces all-cause mortality (7).

We conclude that zinc treatment significantly reduces the duration of fever and of a composite illness indicator (ie, very ill status) in boys with ALRI, but has no significant effect in girls with severe ALRI. Vitamin A treatment of children with severe ALRI has no significant beneficial effect and was associated with adverse events, particularly diarrhea. Zinc treatment increased mean serum zinc concentrations, and vitamin A treatment increased mean serum retinol concentrations in this population, who had low concentrations at baseline.

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DM was responsible for designing the study, analyzing the data, and writing and interpreting the manuscript. ML, DP, and AG took part in designing the study, evaluating the illness indicators, and writing and interpreting the manuscript. SG took part in designing the study and collecting and interpreting the manuscript. ML, DP, and AG took part in designing the study and collecting and interpreting the data. MAK took part in designing the study, in the quality control of laboratory tests, and in writing and interpreting the manuscript. MAW was responsible for analyzing the serum zinc and vitamin A concentrations and interpreting the results. None of the authors had any financial or personal interest in the foundation supporting this research.

REFERENCES