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Zinc Supplementation Reduces the Incidence of Acute Lower Respiratory Infections in Infants and Preschool Children: A Double-blind, Controlled Trial

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ABSTRACT. *Background.* **Increased acute lower respiratory infection incidence, severity, and mortality are associated with malnutrition, and reduced immunological competence may be a mechanism for this association. Because zinc deficiency results in impaired immunocompetence and zinc supplementation improves immune status, we hypothesized that zinc deficiency is associated with increased incidence and severity of acute lower respiratory infection.**

Methods. **We evaluated the effect of daily supplementation with 10 mg of elemental zinc on the incidence and prevalence of acute lower respiratory infection in a double-blind, randomized, controlled trial in 609 children (zinc, n = 298; control, n = 311) 6 to 35 months of age. Supplementation and morbidity surveillance were done for 6 months.**

Results. **After 120 days of supplementation, the percentage of children with plasma zinc concentrations <60 μg/dL decreased from 35.6% to 11.6% in the zinc group, whereas in the control group it increased from 36.8% to 43.6%. Zinc-supplemented children had 0.19 acute lower respiratory infection episodes/child/year compared with 0.35 episodes/child/year in the control children. After correction for correlation of data using generalized estimating equation regression methods, there was a reduction of 45% (95% confidence interval, 10% to 67%) in the incidence of acute lower respiratory infections in zinc-supplemented children.**

Conclusions. **A dietary zinc supplement resulted in a significant reduction in respiratory morbidity in preschool children. These findings suggest that interventions to improve zinc intake will improve the health and survival of children in developing countries.** *Pediatrics* **1998;102:1–5;** ***experimental trial, nutrition, pneumonia, respiratory infections, zinc.***

ABBREVIATIONS. ALRI, acute lower respiratory infection; WHO, World Health Organization; RR, respiratory rate; LCI, lower chest indrawing; GEE, generalized estimating equations; OR, odds ratio; CI, confidence interval.

Acute lower respiratory infections (ALRIs), predominantly pneumonia, cause approximately 4 million deaths every year, accounting for one-third of all childhood deaths in developing countries.[1–3] Community-based trials have documented that a case-management approach, involving antibiotic treatment to all children with rapid breathing, can reduce ALRI mortality by 50%.[4] Currently, only a small proportion of all ALRI can be prevented, eg, by immunization against measles and pertussis.[5,6] Additional interventions to prevent ALRI are needed to complement the case-management approach and immunizations being implemented in developing countries.[7,8]

Malnutrition has been shown to increase both incidence and severity of ALRI, including pneumonia,[9–12] and is an important determinant of ALRI mortality.[13] The postulated mechanism for this effect is reduction in immunological capacity, especially in cellular immunity, which occurs in malnourished children.[11,14–16] In experimental models, isolated protein and energy malnutrition does not result in impaired cellular immunity.[17] The reduced immunological competence in malnourished children may be attributable to zinc deficiency, because this is associated with impaired cellular immune status,[18,19] an

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effect that is reversed by zinc supplementation.[20,21] We hypothesized that zinc deficiency in children is responsible for increased incidence and severity of ALRI. In this report, we describe the effects of zinc supplementation on ALRI morbidity in a large, community-based, controlled trial of infants and preschool children in India.

METHODS

Study Design, Eligibility, and Randomization

The details of the study population, design, methods, eligibility, recruitment, and randomization have been published.[22,23] Briefly, in a low socioeconomic population of urban India, 609 children, 6 to 35 months of age, presenting to a community-based clinic for acute diarrhea were enrolled and assigned to zinc or control groups. Home visitations daily for supplementation and every fifth day for morbidity assessment were started from the date of enrollment. At the first home visit after recovery from the enrollment diarrheal episode (passage of three or fewer liquid stools for 3 consecutive days), these children were enrolled in a 6-month trial. Before enrollment, a parent of the child was given an explanation of the study and written informed consent was obtained. The study was approved by the human research review committees at the All India Institute of Medical Sciences, the Johns Hopkins School of Hygiene and Public Health, and the World Health Organization (WHO).

Study Treatments and Surveillance

Supplements were prepared and coded by Sandoz India Ltd (Mumbai, Maharashtra). Both formulations were liquid preparations, similar in color and taste. Each 5 mL contained vitamins A (800 units), B1 (0.6 mg), B2 (0.5 mg), B6 (0.5 mg), D3 (100 IU), and E (3 mg) and niacinamide (10 mg); the zinc preparation contained zinc gluconate (10 mg elemental zinc). A fixed dose of 5 mL per child was given daily for 6 months to all enrolled children; during diarrheal illness this was increased to 10 mL to provide for excess zinc losses. Field assistants different from the morbidity surveillance field workers visited the family every day and fed the preparation to the child. For Sundays, holidays, or in case of nonavailability of the child, a measured dose was left in a vial for a relative to feed. A detailed log of days when a field assistant and/or relative did or did not feed the supplement was maintained. Children were actually fed the supplement by a field worker on 78% of days in the zinc group and 79% in the control group. Additionally, a relative fed the preparation for 19% of days in the zinc group and 18% in the control group.

Anthropometric assessments were performed at the baseline and at monthly intervals.[23] Stunting was defined as a z score of <-2 for length or height for age (ie, more than 2 standard deviations below the median for the National Center for Health Statistics reference population) and wasting as a z score of <-2 for weight for length.[24] Plasma zinc was estimated at the baseline and after 120 days of supplementation.[22,23,25] The level to define deficiency (<60 μg/dL) was selected according to the literature and the standard of the laboratory where the assay was performed.[25,26]

At household visits every fifth day or on the next day if the child was absent, information was obtained on reported fever, cough, difficult breathing, and feeding for each of the previous 5 days. If fever was reported, axillary temperature was recorded. If cough was reported, respiratory rate (RR) was recorded twice for 1 minute and the child was examined for the presence of lower chest indrawing (LCI). All children with a RR of more than 50 in children below 1 year and more than 40 in children 1 year or more were given cotrimoxazole for 5 days per the current recommendations.[9] If the child did not improve in 5 days or developed LCI, drowsiness, convulsions, or refusal to feed at any time, the mother was advised to bring the child to the clinic where a physician examined and treated the child according to current recommendations of WHO and the Indian Ministry of Health.[7,8]

Data Quality Control and Processing

Before the study, extensive training of field workers for counting RR, recording temperature, and detecting LCI was undertaken. Both training videotapes from WHO and patient examinations at the Department of Pediatrics at All India Institute of Medical Sciences were used. The training was continued until there was more than 95% concordance within the workers and between workers and the trainer. Thermometers were calibrated at baseline and once every 2 months. An average of 10% of household visits were rechecked by supervisors and investigators. Daily data processing with double entry by two different operators and a system for consistency, range, and logical checks were used.

Outcome Definitions

Episodes of ALRI were defined as periods for which the child was reported to have had cough and at least one assessment documenting: a) an elevated RR more than the age-specific value on both 1-minute estimations;[7,8] and b) a recorded temperature of >101°F or LCI. Age on the day of RR measurement was used to evaluate the age-specific values for diagnosis. For days of ALRI, the presence of cough by recall was recorded for each day, whereas the RR and temperature at the fifth daily visit were used for that day and the previous 4 days. Resolution of illness was defined as two consecutive visits (5 days apart) with RR less than the age-specific value and no LCI. The last day meeting the criteria for ALRI was then considered the last day of the episode.

Analytical Approach

A total of 609 children (zinc group, n = 298; control group, n = 311) were enrolled for the 6-month study. Person time analysis was performed using days of actual follow-up as denominator and either episodes (for incidence) or days (for prevalence) as numerator. Additionally, to use generalized estimating equations (GEE) for longitudinal analysis,[26,27] surveillance data of each child was divided into 6 child-periods of 30 days each. This method of analysis does not assume independence of events and so prevents overestimation of significance because of correlation of morbidity within children. For a period to be included in the analysis, the child had to have at least 15 days of surveillance. A child who was absent continuously for more than a month was considered terminated from the study, but the information available for that child was included in the analysis. Out of 609 children enrolled, 603 children with 3296 child-periods (zinc, n = 1633; control, n = 1663) were included in the analysis; 6 children (zinc, n = 1; control, n = 5) did not contribute a child-period, as their total surveillance was less than 15 days. Age, feeding, nutritional status, and other time-dependent variables were estimated at the start of each child-period.

Statistical Methods

Statistical analysis was performed using SPSSPC+ (version 6.0), Epi-Info (version 6.0), and SAS (version 6.11) software. Regression models using GEE[27,28] with logit link, binomial variance, and exchangeable correlation were used. For incidence, occurrence of a new ALRI episode in the child-period was modeled as a bivariate dependent variable with group allocation (zinc or control) as the independent variable. For prevalence, days with ALRI were modeled as the dependent variable using the events/trials option (days of ALRI as events and days of surveillance as trials), with group allocation as the independent variable. To evaluate interactions of treatment effect with age, nutritional status, zinc status, and gender, similar models with these variables and appropriate interaction terms were used. GEE estimations were done within SAS with GEE macro version 2.02.[29] To be conservative, the robust estimates from GEE were used. Interaction terms in models were assessed by the Wald test.

RESULTS

The baseline characteristics for the child-periods included in the analysis were similar between the two groups (Table 1). A more detailed evaluation of comparability for baseline morbidity, feeding, and socioeconomic status variables between the two randomized groups has been presented previously, documenting that the two groups were similar.[23] The mean plasma zinc concentration was similar at baseline in the two groups (Table 1), but was significantly

TABLE 1. Baseline and Surveillance Characteristics of Child-periods of Observation According to the Intervention Group*

Characteristic	Zinc Group	Control Group
Age at beginning of period (mo)	18.6 ± 8.5	18.6 ± 8.7
6–11 mo (% of child-periods)	24.6	25.7
12–23 mo	46.3	47.3
>23 mo	29.1	26.9
Nutritional status†		
Normal (%)	32.8	31.5
Stunted	52.6	51.4
Wasted	3.1	3.9
Wasted and stunted	11.5	12.9
Baseline plasma zinc (μg/dL)‡	64.3 ± 14.4	64.1 ± 19.1
Males (% of child-periods)	51.4	51.7
Surveillance information		
Children	297	306
Child-periods	1633	1663
Days of surveillance	45 019	45 768
Days with cough	9121	8090
RR measurements	1985	1801
Number of episodes/child		
0	274	263
1	22	42
2	1	1

Abbreviation: RR, respiratory rate.
* Plus-minus values are means ± SD.
† Stunting and wasting were defined as < -2.0 z scores for height for age and weight for height, respectively, using the National Center for Health Statistics reference population.[24]
‡ To convert zinc concentration to micromoles per liter, multiply by 0.153.

higher at 120 days postenrollment in the zinc group (87.4 ± 35.6 μg/dL vs 63.6 ± 19.2 μg/dL; $P < .01$). The percentage of children with plasma zinc concentration <60 μg/dL decreased from 35.6% to 11.6% in the zinc group, whereas in the control group it increased from 36.8% to 43.6% ($P < .01$). Cough was reported in the zinc group on 20.3% of days of observation and in the control group on 17.7% of days [odds ratio (OR) 1.18; 95% confidence interval (CI) using conservative GEE analysis, 1.06 to 1.32; $P <$ .001]. As the RR measurements were done only if cough was reported, the zinc group had more RR measurements (OR 1.13; 95% CI, 1.03 to 1.23; using conservative GEE analysis, $P < .001$) (Table 1).

Effect on ALRI Incidence

There were 24 episodes of ALRI in the zinc group (0.19 episodes/child/year) compared with 44 episodes in the control group (0.35 episodes/child/year). In an uncorrected traditional analysis, zinc supplementation resulted in a 45% reduction in the incidence of ALRI (Table 2). Because the outcome variable, ALRI, may be correlated between periods for a child, we performed a more conservative analysis using GEE corrected for correlation. When this was done, the zinc group had a 45% reduction in incidence (Table 2).

Using WHO criteria for respiratory disease episodes based on fast breathing alone, the zinc group had 137 episodes (1.11 episodes/child/year), whereas the control group had 153 episodes (1.22 episodes/child/year). Zinc supplementation was associated with an 11% reduction (95% CI, −18% to 68%) in these illnesses in the corrected analysis.

Effect on ALRI Prevalence

There was a 40% reduction in the prevalence of ALRI (95% CI, 27% to 51%; $P < .001$) in the zinc group compared with the control group in the uncorrected analysis and a reduction of 41% (95% CI, 0% to 65%; $P = .54$) in the corrected analysis (Table 2). Zinc group children had 1.92% of days of observation with RR higher than the age-specific value, compared with 2.10% of days in control group children, a reduction of 9% (95% CI, 0% to 17%) in the uncorrected analysis and a reduction of 9% (95% CI, −17% to 29%) in the corrected analysis.

Effect in Subgroups

There were no significant interactions for the effect of zinc in preventing ALRI with age (6 to 11 months vs >11 months), zinc deficiency (<60 μg/dL vs ≥60 μg/dL), stunting (<-2.0 z score for height for age vs ≥ -2.0 z score), gender, or period (months 1 to 6). There were trends of greater reductions in the incidence of ALRI among children more than 11 months of age (OR, 0.46; 95% CI, 0.25 to 0.86) and males (OR, 0.49; 95% CI, 0.25 to 0.95), but the differences were not statistically significant (Fig 1). For prevalence, there were similar trends of greater effect in children who were older (OR, 0.56; 95% CI, 0.29 to 1.06), zinc-deficient (OR, 0.35; 95% CI, 0.09 to 1.31), stunted (OR, 0.54; 95% CI, 0.26 to 1.11), and male (OR, 0.49; 95% CI, 0.23 to 1.05).

DISCUSSION

This study in low socioeconomic preschool children experiencing high rates of morbidity documents a substantial efficacy of zinc supplementation in reducing ALRI morbidity. Zinc supplementation

TABLE 2. Effect of Zinc Supplementation on Incidence and Prevalence of ALRI

Outcome	Zinc Group	Control Group	Effect of Zinc on ALRI		
			Odds Ratio	95% CI	P Value
ALRI Incidence	24 (1.47)†	44 (2.65)			
Uncorrected for correlation of data			0.55	0.33–0.91	.018
Corrected for correlation by GEE*			0.55	0.33–0.90	.02
ALRI Prevalence	155 (0.34)‡	264 (0.58)			
Uncorrected for correlation of data			0.60	0.49–0.73	<.0001
Corrected for correlation by GEE*			0.59	0.35–1.00	.054

Abbreviations: ALRI, acute lower respiratory infection, GEE, generalized estimating equations.
* Results presented are from the logistic regression analysis using robust estimates with GEEs.
† Number (percentage of child-periods) with ALRI.
‡ Number (percentage of days of observation) with ALRI.

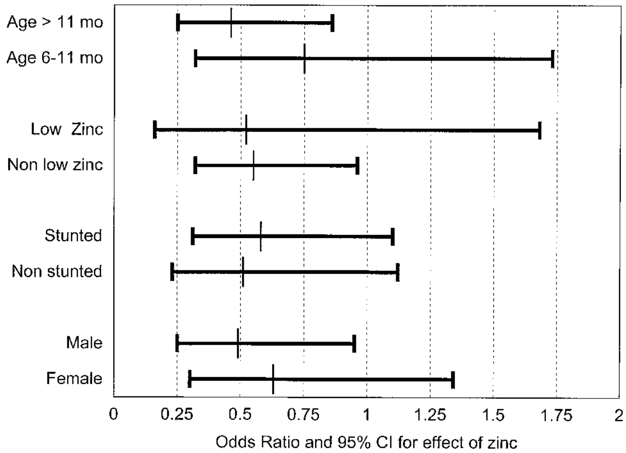

Fig 1. Effect of zinc supplementation on incidence of acute lower respiratory infection by subgroups of age, baseline zinc concentration, nutritional status, and gender.

was associated with statistically significant and clinically important reductions of 45% in the incidence of pneumonia and of 41% in the days spent with ALRI. The effect was observed in a setting with excellent access to antibiotic case management for ALRI, as recommended by WHO.

This study was conducted in a well-defined community, rather than in a hospital, so the results are not likely to be affected by selection bias. The household visits every fifth day to assess morbidity should have identified all serious respiratory illness. Although this frequency of visits may have limited the precision of information on daily outcomes, it would not have biased the results, because the study was double-blind and all children had identical illness surveillance. For ethical considerations, all ALRI episodes were treated with appropriate antibiotics free of charge, including drugs for children who did not recover on initial cotrimoxazole therapy. This may have reduced the prevalence and recurrence of pneumonia, which makes the estimate of the effect on prevalence more conservative than would be expected under conditions with less optimal treatment. Because the intervention provided vitamins to both groups, the results of this study are indicative of the effect on zinc in the absence of deficiency of these vitamins.

The reported literature on relationships of zinc and respiratory morbidity in children is limited. Three studies reported a higher respiratory morbidity in zinc-deficient children,[30–32] identified in two studies by low hair zinc[30,31] and in a third by low plasma zinc.[32] In malnourished children, zinc supplementation trials have shown mixed results in regard to respiratory infections,[20,33,34] but two recent trials reported a reduction in respiratory morbidity.[35,36] No published study could evaluate the effect of zinc supplementation on ALRI or pneumonia, because of their small sample size and/or their inadequate methods of detection and diagnosis.

The RR criteria for treatment of respiratory illness recommended by WHO, although appropriate as a screening method for further assessment and intervention, have a low predictive value for pneumonia,[37] especially when used with household surveillance rather than in a health facility with more ill children. In a study with household surveillance for respiratory infections in low socioeconomic children of Lima, Peru, a definition of reported cough and fast breathing plus twice-documented elevated RR had a positive predictive value of only 8% for pneumonia diagnosed by clinical and radiographic criteria (C. Lanata, personal communication). A poor predictive value would lead to misclassification errors and hence a bias toward no effect of supplementation on pneumonia or ALRI. Therefore, we included fever or LCI in addition to elevated RR to have a more specific definition of ALRI that was likely closer to pneumonia. However, respiratory infection defined simply by cough and elevated RR was also decreased in the zinc group.

The increase in cough seen in the zinc group, despite reduction in ALRI, was probably an indication of improved host defense mechanisms and is consistent with our finding of improvements in immune status of these children.[38] This indicates that the use of study outcomes combining cough and symptoms of upper respiratory infections with ALRI, as was done in most previous trials, may obscure an effect on ALRI. As the RR was measured only when cough was reported, the number of RR measurements made in the zinc group were 11% higher. This resulted in a higher probability of detection of ALRI in the zinc group. Correction for this bias would increase the magnitude of the effect on ALRI, but is not presented in this article, which provides a more conservative estimate of effect.

The comparison of the effects of supplementation among subgroups indicates that there was a trend toward greater impact in children who were more than 11 months old, male, zinc-deficient, or stunted, but these differences were not statistically significant. Much larger studies would be required to investigate differences between such subgroups.

A possible mechanism for the effects for zinc supplementation on ALRI morbidity is enhanced immune status, preventing establishment of infection or improving the clearance of infectious agents.[38–41] Another possible mechanism of zinc is a direct antiviral effect;[42–45] however, the magnitude of effect in this trial suggests that bacterial infections must have been reduced, because bacteria cause most ALRI (pneumonia) in children in developing countries.[2,7,8]

CONCLUSION

A dietary supplement of zinc resulted in a significant reduction of ALRI morbidity in preschool children. These findings, along with previously documented effects of zinc on diarrhea, immunity, and growth, indicate that interventions to improve zinc intake deserve more attention as means to improve child health. Such interventions might include supplements with zinc and possibly other micronutrients, as well as dietary modification or fortification of staple foods.

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REFERENCES

1. Leowski J. Mortality from acute respiratory infections in children under 5 years of age: global estimates. *World Health Stat Q*. 1986;39:138–144
2. Denny FW, Loda FA. Acute respiratory infections are the leading cause of death in children in developing countries. *Am J Trop Med Hyg*. 1986;35:1–2
3. Garenne M, Ronsmans C, Campbell H. The magnitude of mortality from acute respiratory infections in children under 5 years in developing countries. *World Health Stat Q*. 1992;45:180–191
4. Sazawal S, Black RE. Meta-analysis of intervention trials on case-management of pneumonia in community settings. *Lancet*. 1992;340: 528–533
5. Fauveau V, Stewart MK, Chakraborty J, Khan SA. Impact on mortality of a community-based programme to control acute lower respiratory infections. *Bull World Health Organ*. 1992;70:109–116
6. Koenig MA, Khan MA, Wojtyniak B, et al. Impact of measles vaccination on childhood mortality in rural Bangladesh. *Bull World Health Organ*. 1990;68:441–447
7. World Health Organization. A programme for controlling acute respiratory infections in children: memorandum from a WHO meeting. *Bull World Health Organ*. 1984;62:47–58
8. World Health Organization. *Acute Respiratory Infections in Children: Case Management in Small Hospitals in Developing Countries. A Manual for Doctors and Other Senior Health Workers*. Geneva, Switzerland: World Health Organization; 1990:WHO/ARI/90.5
9. Tupasi TE, Mangubat NV, Sunico Ma ES, et al. Malnutrition and acute respiratory tract infections in Filipino children. *Rev Infect Dis*. 1990;12: S1047–S1054
10. James JW. Longitudinal study of the morbidity of diarrheal and respiratory infections in malnourished children. *Am J Clin Nutr*. 1972;25: 690–694
11. Zaman K, Baqui AH, Yunus MD, et al. Association between nutritional status, cell-mediated immune status and acute lower respiratory infections in Bangladeshi children. *Eur J Clin Nutr*. 1996;50:309–314
12. de Francisco A, Morris J, Hall AJ. Risk factors for mortality from acute lower respiratory tract infections in young children. *Int J Epidemiol*. 1993;22:1174–1182
13. Spooner V, Baker J, Tulloch S, et al. Clinical signs and risk factors associated with pneumonia in children admitted to Goroka Hospital, Papua New Guinea. *J Trop Pediatr*. 1989;35:295–300
14. McMurray DN, Loomis SA, Casazza LJ, et al. Development of impaired cell-mediated immunity in mild and moderate malnutrition. *Am J Clin Nutr*. 1981;34:68–77
15. Chandra RK. Nutrition and immunity: lessons from the past and the new insights into the future. *Am J Clin Nutr*. 1991;53:1087–1101
16. Neumann CG, Lawlor GJ, Stiehm ER, et al. Immunologic responses in malnourished children. *Am J Clin Nutr*. 1975;28:89–104
17. Good RA, Fenandez G, West A. Nutrition immunity and cancer – a review: Part I: Influence of protein or protein calorie malnutrition and zinc deficiency on immunity. *Clin Bull*. 1979;9:3–12
18. Fraker PJ, Jardieu R, Cook J. Zinc deficiency and immune function. *Arch Dermatol*. 1987;123:1699–1701
19. Schoen LA, Fernandez G, Garafalo JA, Good RA. Nutrition immunity and cancer—a review: Part II: Zinc, immune function and cancer. *Clin Bull*. 1979;9:63–75
20. Castillo-Duran C, Heresi G, Fisberg M, Uauy R. Controlled trial of zinc supplementation during recovery from malnutrition: effects on growth and immune function. *Am J Clin Nutr*. 1987;45:602–608
21. Sazawal S, Black RE, Jalla S, Mazumdar S, Sinha A, Bhan MK. Effect of zinc supplementation on cell-mediated immunity and lymphocyte subsets in preschool children. *Indian Pediatr*. 1997;34:589–597
22. Sazawal S, Black RE, Bhan MK, et al. Zinc supplementation in young children with acute diarrhea in India. *N Engl J Med*. 1995;333:839–844
23. Sazawal S, Black RE, Bhan MK, et al. Zinc supplementation reduces the incidence of persistent diarrhea and dysentery among low socioeconomic children in India. *J Nutr*. 1996;126:443–450
24. National Center for Health Statistics. *Growth Curves for Children Birth-18 Years. United States. Vital and Health Statistics. Series 11*. Washington, DC: Government Printing Office; 1977: No. 165. Department of Health Education and Welfare publication (PHS) 78–1650
25. Hambidge KM, King JC, Kern DL, et al. Pre-breakfast plasma zinc concentrations: the effect of previous meals. *J Trace Elem Electrolytes Health Dis*. 1990;4:229–231
26. Pilch SM, Senti FR. *Assessment of the Zinc Nutritional Status of the US Population Based on Data Collected in the Second National Health and Nutrition Examination Survey, 1976–1980*. Bethesda, MD: Life Sciences Research Office; FASEB; 1984
27. Liang K-Y, Zeger SL. Longitudinal data analysis using generalized linear models. *Biometrika*. 1986;73:13–22
28. Zeger SL, Liang K-Y. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics*. 1986;42:121–130
29. Groemping U. *GEE: A SAS Macro for Longitudinal Data Analysis*, version 2.02. Dortmund, Germany: Fachbereich Statistik, Univrsitaet Dortmund; 1994
30. Lombeck I, Wilhelm M, Hafner D, Roloff K, Ohnesorge FK. Hair zinc of young children from rural and urban areas in North Rhine-Westphalia, Federal Republic of Germany. *Eur J Pediatr*. 1988;147:179–183
31. Van Wouwe JP, de Wolff FA, van Gelderen HH. Zinc in hair and urine of paediatric patients. *Clin Chim Acta*. 1986;155:77–82
32. Bondestam M, Foucard T, Gebre-Medhin M. Subclinical trace element deficiency in children with undue susceptibility to infection. *Acta Paediatr*. 1985;74:515–520
33. Schlesinger L, Arevalo M, Arredondo S, Diaz M, Lonnerdal B, Stekel A. Effect of a zinc-fortified formula on immunocompetence and growth of malnourished infants. *Am J Clin Nutr*. 1992;56:491–498
34. Bates CJ, Evans PH, Dardenne M, et al. A trial of zinc supplementation in young rural Gambian children. *J Nutr*. 1993;69:243–255
35. Sempértegui F, Estrella B, Correa E, et al. Effects of short-term zinc supplementation on cellular immunity, respiratory symptoms, and growth of malnourished Ecuadorian children. *Eur J Clin Nutr*. 1996;50: 42–46
36. Ninh NX, Thissen JP, Collette L, et al. Zinc supplementation increases growth and circulating insulin-like growth factor I (IGF-I) in growth-retarded Vietnamese children. *Am J Clin Nutr*. 1996;63:514–519
37. Falade AG, Tschappeler H, Greenwood BM, Mulholland EK. Use of simple clinical signs to predict pneumonia in young Gambian children: the influence of malnutrition. *Bull World Health Organ*. 1995;73:299–304
38. Zeng B, Qian Y, Zheng D. Changes of T lymphocyte subsets in peripheral blood of children with malnutrition and zinc deficiencies. *Hua Hsi I Ko Ta Hsueh Hsueh Pao*. 1991;22:337–339
39. Singh KP, Zaidi SI, Raisuddin S, et al. Effect of zinc on immune functions and host resistance against infection and tumor challenge. *Immunopharmacol Immunotoxicol*. 1992;14:813–840
40. Lincastro F, Chiricolo M, Mocchegiani E, et al. Oral zinc supplementation in Down's syndrome subjects decreased infections and normalized some humoral and cellular immune parameters. *J Intellect Disabil Res*. 1994;38:149–162
41. Driessen C, Hirv K, Rink L, et al. Induction of cytokines by zinc ions in human peripheral blood mononuclear cells and separated monocytes. *Lymphokine Cytokine Res*. 1994;259:161–175
42. Eby GA, Davis DR, Halcomb WW. Reduction in duration of common colds by zinc gluconate lozenges in a double-blind study. *Antimicrob Agents Chemother*. 1984;25:20–24
43. Farr BM, Conner EM, Betts RF, et al. Two randomized controlled trials of zinc gluconate lozenge therapy of experimentally induced rhinovirus cold. *Antimicrob Agents Chemother*. 1987;1183–1187
44. Al-Nakib W, Higgins PG, Barrow I, et al. Prophylaxis and treatment of rhinovirus colds with zinc gluconate lozenges. *J Antimicrob Chemother*. 1987;20:893–901
45. Potter YJ, Hart LL. Zinc lozenges for treatment of common colds. *Ann Pharmacother*. 1993;27:589–592