PEDIATRIC INFECTIOUS DISEASE SOCIETY OF THE PHILIPPINES

Vol.11 No.1
January-June 2010

PIDSP JOURNAL

Vol.10 No.1
January-June 2010

EFFICACY OF ZINC AS ADJUNCT IN THE TREATMENT OF PNEUMONIA IN CHILDREN LESS THAN FIVE YEARS: A META-ANALYSIS

AUTHORS: Kathlynne Anne Caling Abat, MD, Jacinto Blas V. Mantaring III, MD
University of the Philippines College of Medicine- Philippine General Hospital

KEYWORDS
pneumonia, zinc, meta-analysis

ABSTRACT

Background: Zinc supplementation has been shown to lower mortality and morbidity due to diarrhea and pneumonia. Because of the positive effect of zinc in the prevention of pneumonia, several studies have been conducted to investigate its effect as an adjunct therapy for pneumonia. For this reason, a systematic, quantitative review of available studies is needed to determine the overall effect of zinc as an adjunct in the treatment of pneumonia in children less than five years old.

Objectives: To assess from literature the effect of zinc, when given with antibiotics, in reducing mortality, treatment failure, length of hospital stay, and duration of symptoms of pneumonia in children less than five years old.

Design: Meta-analysis of randomized, placebo-controlled intervention trials.

Methods: Studies for inclusion were identified by PubMed search, journal handsearch, and other methods. The authors independently assessed study quality and extracted data.

Statistical Analysis: Revman Version 4.2 was used to analyze the data gathered. The summary relative risks (RRs) and 95% CI for each outcome variable were estimated using a fixed-effects model. Chi-square and I^2 were computed to assess for heterogeneity of results.

Results: A total of three acceptable studies were included in the meta-analysis. The summary RRs showed that zinc had no overall treatment effect on mortality from pneumonia (RR 0.69, CI 0.08, 5.70) and treatment failure (RR 1.05, CI 0.74, 1.49). These results were statistically insignificant with p-values of 0.73 and 0.77, respectively. Chi^2 and I^2 tests showed significant heterogeneity of results for treatment failure (Chi^2 = 5.06, I^2 = 60.5%). The same tests did not show significant heterogeneity of results for mortality (Chi^2 = 0.43, I^2 = 0%). In one study, the use of zinc reduced the duration of severe pneumonia with mean difference of four (4.2-4.9) versus five (4.5-5.5) days leading to shorter hospitalization [5 (4.8-5.5) versus six (5.1-6.1) days]. In another study, the zinc group's recovery rate from very ill status was 2.6 times (p = 0.004) more, and the resolution of fever was 3.1 times (p = 0.003) more than those in the placebo group. However, these results could not be combined due to lack of data on standard deviation.

Conclusion: There is not enough evidence to conclude that zinc is effective in reducing mortality, treatment failure and duration of symptoms of pneumonia. A large population, multi-center, randomized, placebo-controlled trial should be conducted to obtain statistically significant evidence.

INTRODUCTION

Pneumonia is the leading cause of morbidity and mortality in children less than five years old. Worldwide, about 20% of deaths in children ages zero-to-four years are attributable to pneumonia (1.9 million deaths per year).[1] Two-thirds of these deaths happen during infancy, and more than 90% are in developing countries.[2] Data gathered by the World Health Organization in 2002 on the leading causes of death showed pneumonia as the leading infectious cause for mortality—with 1.05 million deaths in children ages zero-to-four years. In the Philippines, pneumonia ranked first among the leading causes of mortality in the year 2000 and second among the leading causes of infant mortality in the year 2003.[3]

Recent data showed lower mortality and morbidity due to infectious disease in well-designed, randomized, and controlled trials of zinc supplementation in young children. The evidence highlighted zinc deficiency as a public health problem of global proportions;[4] this applies especially to diarrhea and pneumonia—the most prevalent causes of infectious disease mortality in young children worldwide. The most extensive and impressive data relate to the use of zinc as a preventive measure. Moreover, zinc administered as a therapeutic agent to young children with acute or persistent diarrhea also reduces the duration of the diarrhea, and is associated with a lower rate of treatment failure or death.[5] Because of the positive effect of zinc in the treatment of diarrhea, several studies have been conducted to investigate its effect as adjunct therapy for pneumonia. For this reason, a systematic, quantitative review of available studies is needed to determine the overall effect of zinc as an adjuvant therapy in the treatment of pneumonia in children less than five years old.

OBJECTIVE

The objective of this study is to assess from literature the effect of zinc, when given with antibiotics, in reducing mortality, treatment failure, length of hospital stay, and duration of symptoms of pneumonia in children less than five years old.

MATERIALS AND METHODS

Study Design: This study is a meta-analysis which included published, unpublished, and ongoing studies in order to meet the specified inclusion criteria.

Identification of Studies: The studies considered for possible inclusion in this meta-analysis were identified by searching PUBMED computerized bibliographic database. In the MeSH search engine, the following search terms were used ("Pneumonia"[Mesh] OR ("Pneumonia/drug therapy"[Mesh] OR "Pneumonia/mortality"[Mesh] OR "Pneumonia/prevention and control"[Mesh] OR "Pneumonia/therapeutic use"[Mesh] OR "Pneumonia/therapy"[Mesh])) AND ("Zinc/therapeutic use"[Mesh] OR "Zinc/therapy"[Mesh]). The search yielded 20 studies. The bibliographic citations of all the articles selected for inclusion in the analysis were also examined to identify other acceptable studies that were not captured by the electronic database search. From these, two studies were identified.

Literature search was also conducted using the PIMEDICUS database of the University of the Philippines, College of Medicine Library, which is a collection of locally published clinical researches. This search yielded one study. Two additional studies were identified by hand-searching articles published in the Philippine Journal of Pediatrics from January 1996 to June 2007. To identify unpublished trials, a hand-search of studies submitted by different training institutions to the Philippine Pediatric Society from 2000 to 2007 was conducted. Letters were sent to training institutions to inquire regarding unpublished and ongoing studies on zinc and its effect on pneumonia. One study conducted in 1999 was identified from the Philippine Children's Medical Center.

Inclusion Criteria: Studies were considered acceptable for inclusion in the meta-analysis if they met the following criteria:

1) the study was a hospital-based randomized, and placebo-controlled intervention trial in which the supplemented and control groups were enrolled concurrently;
2) the subjects were children aged less than five years old, diagnosed with severe pneumonia, and had no other co-morbidities;
3) the subjects were given antibiotics of any class along with daily supplemental zinc, with or without other adjuncts to treatment, during the acute phase of pneumonia;
4) the outcomes measured were reduction in mortality, treatment failure, length of hospital stay, and duration of symptoms of pneumonia.

The number of studies excluded is summarized by category of exclusion as shown in Figure 1.

Review of studies and extraction of summary data: Research assistants assessed the suitability of each study for inclusion in the meta-analysis using the defined criteria. Once the final set of studies for inclusion in the analyses was established, the authors independently assessed study quality in terms of randomization, concealment, intention to treat, equality of baseline characteristics, and complete follow-up. Data extraction was likewise done independently. Any conflicts were resolved by a third party.

Analysis of data: Revman Version 4.2 was used to analyze the data gathered. The summary relative risks and 95% CI for each outcome variable were estimated using a fixed-effects model. Chi-square and I^2 were computed to test for heterogeneity.

RESULTS

Description of studies

Three studies published between 2004 and 2006 were considered acceptable for inclusion in the analysis. The general characteristics of these studies and their participating subjects are shown in Table 1. These studies did not differ in study design and initial characteristics of subjects. Severe pneumonia was uniformly defined as respiratory rate > 50/minute (for children 2-11 months) or > 40/minute (for children > 12 months) with crepitations on auscultation and the presence of one or more of the following danger signs: lethargy, inability to feed, chest in-drawing or central cyanosis. Two studies[2,6] provided zinc as zinc acetate, while one[7] used zinc sulfate. The dose of zinc given was 20 mg/day, which was divided into two doses from the time of enrollment. The duration of zinc administration differed in the three trials. All studies adequately described the masking procedures used. All studies, but one, (Brooks et al, 2004) specified the use of allocation concealment.

Effect of zinc on mortality

The calculated relative risks and their 95% CIs showed contradicting results of the effect of zinc on mortality (Figure 2). The study by Mahalanabis, etal. showed a greater risk of mortality in the zinc group when compared to placebo (RR 1.50 [0.06, 35.98]). On the other hand, the study by Bose, et al. showed that zinc reduces the risk of mortality (RR 0.34 [0.01, 8.17]). Combining these results showed no overall treatment effect on mortality from pneumonia (RR 0.69 [0.08, 5.70]) (p-value 0.73). Chi^2 and I^2 tests did not show significant heterogeneity of results for mortality (Chi^2 = 0.43, I^2 = 0%).

Effect of zinc on treatment failure (Need to change antibiotics)

The calculated relative risks using fixed-effects model for treatment failure and their 95% CIs are displayed for the individual studies and for the combined set of studies in Figure 3.

FIGURE 1. Studies excluded and included in the meta-analysis and reasons for exclusions.

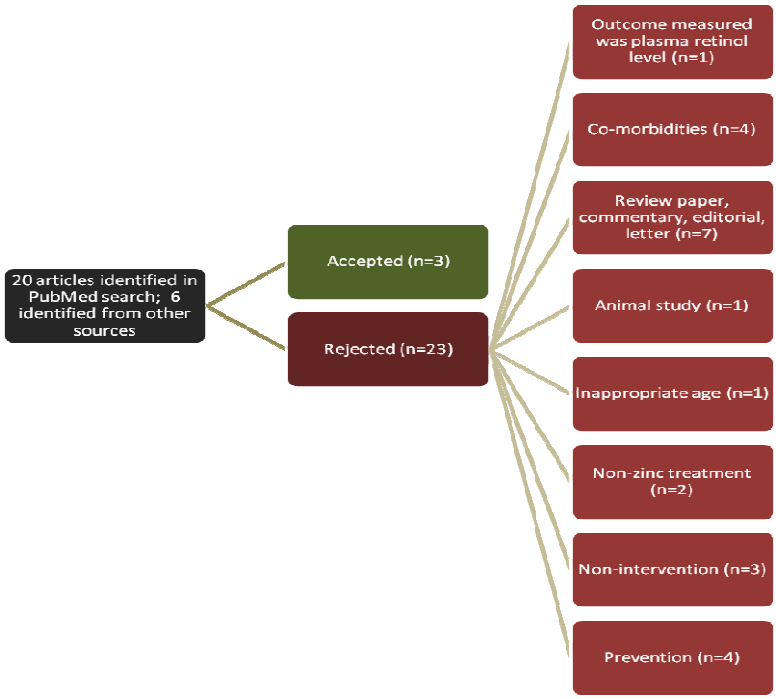


Table 1. Characteristics of included studies of Zinc and Pneumonia

Study	Methods	Participants	Zinc dose	Duration of intervention	Outcomes	Allocation concealment
Bose 2006	RCT Double-blind Intention to treat	2-23 mos old severe pneumonia Consent Admitted to CMC	10 mg zinc BID	14 days	treatment failure; death; time to resolution of symptoms; duration of hospitalization	Adequate
Brooks 2004	RCT Double-blind Non-Intention to treat	2-23 mos old with severe pneumonia consent	10 mg zinc BID	Until discharge	treatment failure; death; time to resolution of symptoms; duration of hospitalization	Unclear
Mahalana bis 2004	RCT Double-blind Intention to treat	2-24 mos old with severe pneumonia Admitted to BC Roy Memorial Hospital Consent	10 mg zinc BID	4 days	treatment failure; death; time to resolution of symptoms; duration of hospitalization	Adequate

Figure 2. Effect of zinc on mortality due to pneumonia.

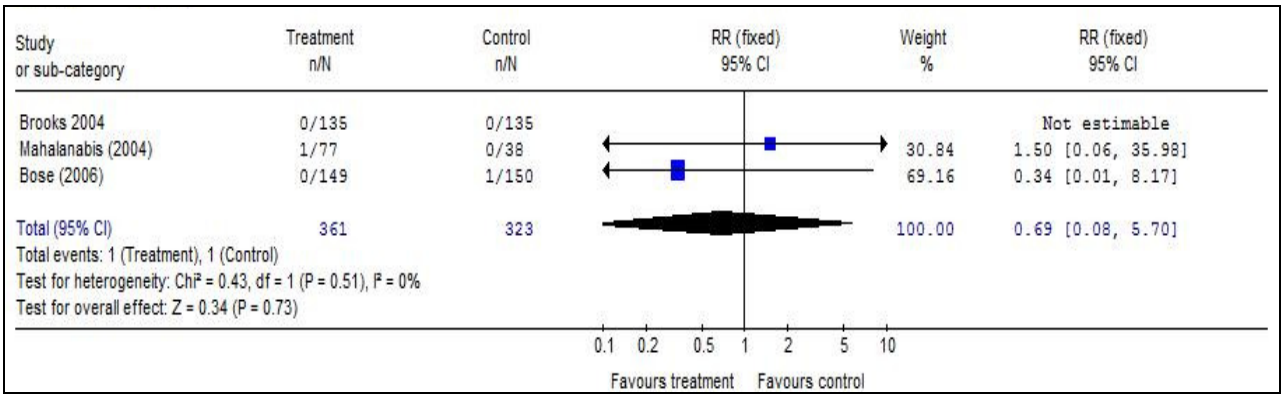
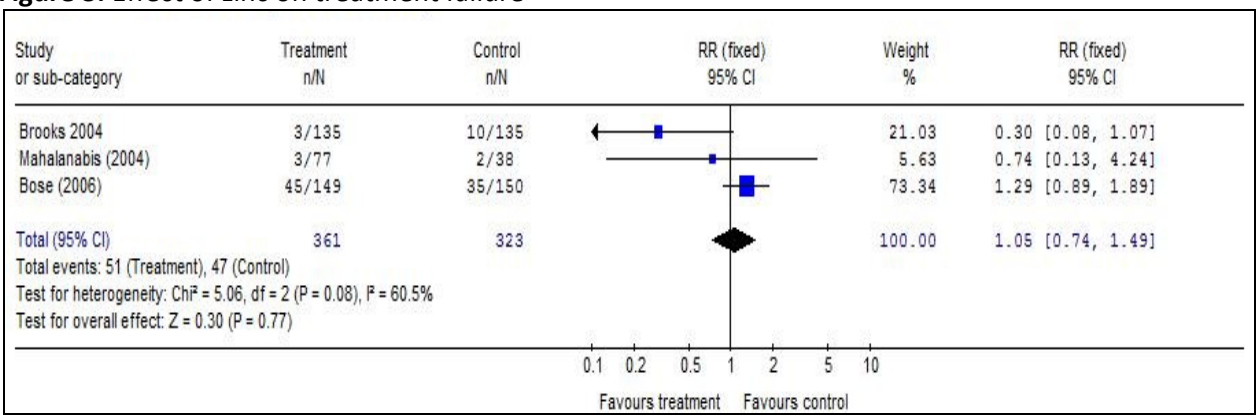


Figure 3. Effect of zinc on treatment failure



Two studies, Brooks (2004) and Mahalanabis (2004), showed that zinc administration decreased the risk for treatment failure with RR 0.30 [0.08, 1.07] and 0.74 [0.13, 4.24], respectively. However, these results were not statistically significant. The summary relative risk RR 1.05 [0.74, 1.49] showed no overall effect on treatment failure (p-value 0.77). Chi^2 and I^2 tests showed significant heterogeneity of results for treatment failure (Chi^2 = 5.06, I^2 = 60.5%).

Effect of zinc on duration of symptoms and hospitalization

The study by Brooks, et al. showed shorter durations of chest indrawing, respiratory rate >50/min and hypoxia, leading to shorter overall duration of pneumonia and length of hospital stay. This resulted in a mean difference of four (4.2-4.9) versus five (4.5-5.5) days of severe pneumonia, and five (4.8-5.5) versus six (5.1-6.1) days of hospitalization for the zinc and placebo groups, respectively. On the other hand, Bose, et al. found that there was no significant difference in the time of recovery from severe pneumonia between the zinc and placebo groups. Likewise, the median length of hospital stay did not differ significantly between the two groups.

Mahalanabis, et al. described a significant interaction between zinc treatment and sex for ill status (p = 0.08), time to resolution of fever (p = 0.033) and feeding difficulty (p = 0.045). Among boys in the zinc group, the rate of recovery from very ill status was 2.6 times (p = 0.004) and for the resolution of fever was 3.1 times (p = 0.003) more than that in the placebo group. A similar trend was observed for the resolution of feeding difficulty (p = 0.09) and tachypnea (p = 0.11).

DISCUSSION

The recommended daily allowance for zinc is only 10mg elemental zinc, but many people in both developing and industrialized countries do not have this in their diet.[8] Adequate zinc intake is critical in maintaining cellular growth, cellular differentiation, and metabolism of higher plants and animals. The importance of zinc for human nutrition and health was not recognized until the second half of the 20th century.[9] It was only 30 years ago, when clinicians first noted that human zinc deficiency, secondary to acrodermatitis enteropathica—an inborn error of metabolism that causes reduced intestinal absorption of zinc—is associated with impaired growth, increased susceptibility to infections, and other functional abnormalities.[10] Since then, a number of trials have been undertaken in different countries to assess the effect of zinc supplementation on child health.

Zinc deficiency is biochemically defined as a serum concentration of less than 9 µmol/l. It is common in children in developing countries whose diets are low in animal products and are high in phytate.[11] Repeated episodes of diarrhea exacerbate zinc deficiency because of the loss of zinc in stool.[12] Unfortunately, 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.

Studies have shown that zinc deficiency affects cells of the immune system: it reduces the number of B lymphocytes and T lymphocytes (CD4 lymphocytes in particular) through increased apoptosis; and it reduces their functional capacity. The functions of the macrophage are compromised and the production and potency of several cytokines are also perturbed. Many of these changes occur even in the early stages of deficiency.[13]

Zinc plays a part in the maintenance of epithelial and tissue integrity by promoting cell growth and suppressing apoptosis. Moreover, its antioxidant properties protect one against free radical damage during inflammatory responses. Thus, in cases of diarrhea, the varied functions of zinc help maintain the integrity of the gut mucosa to reduce or prevent fluid loss. Notably, these responses can occur within 48 hours, which are much more rapidly than the direct effects of zinc on cellular development[13].

Randomized, controlled trials of zinc supplementation provide the best evidence for the roles of zinc in infectious diseases, which are mediated through alterations in host defenses, including epithelial barriers and immune responses. Results of these trials have been reviewed and summarized with regard to the effects on diarrhea and pneumonia incidence, as well as, on total child mortality. A pooled analysis of the results of trials in nine countries and in four continents showed odds ratios (ORs) in zinc-supplemented groups of 0.82 (95% CI: 0.72, 0.93) and 0.75 (0.63, 0.88) for diarrheal incidence and prevalence, respectively.[14] The data for pneumonia prevention were even more impressive: the OR was 0.59 (0.41, 0.83). Moreover, the use of zinc supplements as a preventive modality has been associated with lower mortality, notably in cases due to pneumonia.[15] Since then, additional studies that were larger in size and scope than those included in the pooled analysis have been published; these studies were reviewed in a meta-analysis published in June 2007.[16] This meta-analysis conducted included studies that examined the efficacy of zinc supplementation, lasting more than or equal to three months, in preventing diarrhea and respiratory illnesses among children. Results showed that children who received a zinc supplement had fewer episodes of diarrhea (rate ratio: 0.86) and respiratory tract infections (rate ratio: 0.92), and had significantly fewer attacks of severe diarrhea or dysentery (rate ratio: 0.85), persistent diarrhea (rate ratio: 0.75), and lower respiratory tract infection or pneumonia (rate ratio: 0.80), than those who received placebo. They also had significantly fewer total number of days with diarrhea (rate ratio: 0.86), but not in the

number of days with respiratory illness (rate ratio: 0.95).

These studies led to the use of zinc supplementation among children in the attempt to treat common childhood infections like pneumonia and diarrhea. This is based on the premise that zinc acts in the acute phase in response to infection, thus helping to boost the body's immune response through a defense cascade: beginning with mobilization and sequestration of zinc to metallothionein-rich tissue, then the rapid upregulation of immune defense-specific protein synthesis, to the activation of immune defense activity such as macrophages, lymphocytes, and natural killer cells, and antibody-dependent cytotoxicity.

Meta-analysis techniques are utilized to consolidate results from multiple studies on the same topic and to develop evidence-based policies for clinical practice and public health programming. The reliability of the conclusions derived depends on the methodological quality of the original studies, the appropriateness of the study inclusion criteria, and the thoroughness of the review and synthesis of information. In this analysis, only three trials on the effect of zinc as an adjunct in the treatment of pneumonia met the inclusion criteria that were set by the authors.

The results of this analysis indicate no statistically significant overall effect of zinc in reducing the risk of treatment failure and mortality from pneumonia in children less than five years old. Moreover, the results for the effect of zinc use on treatment failure showed significant heterogeneity, which may be attributed to: 1) the small cumulative sample size; 2) the pre-existing zinc status of the study subjects; 3) the content and bioavailability of zinc in the local diets; and 4) the methodological aspects of these studies, which include the variations in the chemical form, method of administration and duration of supplementation of zinc. Two of the three studies (Brooks and Mahalanabis) showed beneficial effects of zinc in the reduction of recovery time and duration of hospitalization. These results, however, could not be combined due to lack of data on standard deviations.

CONCLUSIONS

Due to the lack of statistically significant data on the effect of zinc in the acute management of pneumonia, there is not enough evidence to conclude that zinc is effective in reducing mortality, treatment failure and duration of symptoms of pneumonia.

RECOMMENDATIONS

A large-population, multi-center, randomized, placebo-controlled trial should be conducted to obtain statistically significant evidence.

REFERENCES

1. Williams BG, Gouws E, Boschi-Pinto C, Bryce J, Dye C. Estimates of world-wide distribution of child deaths from acute respiratory infections. Lancet Infect Dis. 2002;2:25–32.
2. Brooks WA , Yunus M, Santosham M, Wahed MA , Nahar K, Yeasmin S, Black RE. Zinc for severe pneumonia in very young children: double-blind placebo-controlled trial. THE LANCET. 2004 May 22;363:1683-1688.
3. Department of Health. Health Indicators - Infant and Child Mortality. Department of Health. 2006. Available from: http:\\www.doh.gov.ph\Health Indicators Department of Health child mortality.mht.
4. Jones G, Steketee RW, Black RE, Bhutta ZA, Morris SS. How many child deaths can we prevent this year? Lancet. 2003;362:65–71.
5. Bhutta ZA, Bird SM, Black RE, et al. Therapeutic effects of oral zinc in acute and persistent diarrhea in children in developing countries: pooled analysis of randomized controlled trials . AmJ Clin Nutr. 2000;72:1516–22.
6. Mahalanabis D, Bhan MK. Micronutrients as adjunct therapy of acute illness in children: impact on the episode outcome and policy implications of current findings. Br J Nutr. 2001 May; 85 Suppl2:S151-8.
7. Bose, A, Coles CL, Gunavathi HJ, Prabhakar M, Kirubakaran C, Black RE, Brooks WA, Santosham M. Efficacy of zinc in the treatment of severe pneumonia in hospitalized children <2 years old. Amer J of Clin Nutr. 2006; 83(5):089-1096.
8. Gibson RS, Vanderkooy PD, MacDonald AC, Goldman A, Ryan BA, Berry M. A growth-limiting, mild zinc deficiency syndrome in some southern Ontario boys

with low height percentiles. Am J Clin Nutr. 1989;49:1266–1275.
9. Prasad, AS. Discovery of human zinc deficiency and studies in an experimental human model. Am J Clin Nutr. 1991;53:403–12.
10. Moynahan, EJ. Acrodermatitis enteropathica: a lethal inherited human zinc-deficiency disorder . Lancet. 1974;2:399–400.
11. Gibson RS, Ferguson EL, Lehrfeld J. Complementary foods for infant feeding in developing countries: their nutrient adequacy and improvement. Eur J Clin Nutr. 1998;52:764–70.
12. Castillo-Duran C, Vial P, Uauy R. Trace mineral balance during acute diarrhea in infants. J Pediatr. 1988; 113:452–7.
13. Berger A. Science commentary: What does zinc do? BMJ. 2002;325(7372):1062.
14. Bhutta ZA, Black RE, Brown KH, et al. Prevention of diarrhea and pneumonia by zinc supplementation in children in developing countries: pooled analysis of randomized controlled trials. J Pediatr. 1999;135:689–97.
15. Brooks WA, Santosham M, Naheed A, et al. Effect of weekly zinc supplements on incidence of pneumonia and diarrhoea in children younger than 2 years in an urban, low-income population in Bangladesh: randomised controlled trial. Lancet. 2005;366:999–1004.
16. Aggarwal R, Sentz J, Miller M. Role of Zinc Administration in Prevention of Childhood Diarrhea and Respiratory Illnesses: A Meta-analysis. Pediatrics. 2007; 119:1120-1130.
17. Berger MM, Baines M, Raffoul W, Benathan M, Chiolero RL, Reeves C, Revelly JP, Cayeux MC, Senechaud I, Shenkin A. Trace element supplementation after major burns modulates antioxidant status and clinical course by way of increased tissue trace element concentrations. Am J Clin Nutr. 2007 May; 85(5):1293-300.
18. Berger MM, Eggimann P, Heyland DK, Chiolero RL, Revelly JP, Day A, Raffoul W, Shenkin A. Reduction of nosocomial pneumonia after major burns by trace element supplementation: aggregation of two randomized trials. Crit Care. 2006; 10(6):R153.
19. Black RE, Sazawal S. Zinc and childhood infectious disease morbidity and mortality. Br J Nutr. 2001;85(suppl 2):S125–S129.
20. Edejer TT, Aikins M, Black R, Wolfson L, Hutubessy R, Evans DB. Cost effectiveness analysis of strategies for child health in developing countries. BMJ. Nov 2005; 19:331(7526):1177.
21. Hambidge KM. Zinc and pneumonia. Am J Clin Nutr. May 2006; 83(5):991-2.
22. Hambidge M, Krebs N. Zinc, diarrhea, and pneumonia. J Pediatr. 1999 Dec; 135(6):661-4.
23. Howie S, Zaman SM, Omoruyi O, Adegbola R, Prentice A. Severe pneumonia research and the problem of case definition: the example of zinc trials. Am J Clin Nutr. 2007 Jan; 85(1):242-3.
24. Jaffe BF. Postoperative hoarseness. Am J Surg. 1972 Apr; 123(4):432-7.
25. Manlangit EB, Alba AA. The effect of zinc supplementation on the incidence and duration of respiratory infections in adolescents: a double-blind randomized controlled trial. The Philippine Journal of Pediatrics. 2002; 51(3):102-106.
26. Nielsen GD, Fogh A, Pedersen LM. Aspiration of talcum or powder containing zinc stearate by children. Ugeskr Laeger. 1979 May; 141(21):1407-9. Danish.
27. Sazawal S, Dhingra U, Deb S, Bhan MK, Menon VP, Black RE. Effect of zinc added to multi-vitamin supplementation containing low-dose vitamin A on plasma retinol level in children--a double-blind randomized, controlled trial. J Health Popul Nutr. 2007 Mar; 25(1):62-6.
28. Shpak BIu, Zapadniuk VI, Neiko EM. Use of orcomin in combined treatment of acute pneumonia. Vrach Delo. 1976 Mar ;(3):93-6.
29. Strand TA, Briles DE, Gjessing HK, Maage A, Bhan MK, Sommerfelt H. Pneumococcal pulmonary infection, septicaemia and survival in young zinc-depleted mice. Br J Nutr. 2001 Aug; 86(2):301-6.
30. Tan MP, Juan M, Yap CL, de la Cruz L, Atienza MM. Serum zinc levels among a group of malnourished Filipino children. The Philippine Journal of Pediatrics. 1997;46(1):14-19
31. Villanueva AC. Zinc supplementation reduces the incidence of respiratory infection and diarrhea in malnourished children: a double-blind randomized controlled trial. The Philippine Journal of Pediatrics. 2001;50(2):122-127