Zinc Supplementation for Prevention or Treatment of Childhood Pneumonia: *A Systematic Review of Randomized Controlled Trials*

JOSEPH L MATHEW

From the Advanced Pediatrics Centre, PGIMER, Chandigarh 160012, India. jlmathew@rediffmail.com

RELEVANCE

Community acquired pneumonia (CAP) is reportedly the leading cause of childhood mortality, accounting for an estimated 1.9 million annual deaths among under-five children(1,2), of which India contributes nearly 20%. Co-existent HIV/AIDS, measles and other morbidities increase the burden of childhood pneumonia for individuals and the community. The WHO and UNICEF have recently prioritized interventions to reduce the burden of childhood pneumonia(1).

Over the past couple of decades, zinc is being recognized as an important element in maintaining immune function, reducing infections, and enhancing growth. Various research studies supported its role in the management of acute and persistent diarrhea(3), and it is currently included as the standard of care for this(4,5). This led investigators to evaluate the role of zinc in childhood pneumonia through a series of research trials.

The clinical question addressed in this systematic review of evidence is: "Does zinc supplementation (*intervention*), either improve the clinical outcome or prevent the occurrence of community acquired pneumonia (*outcome*) in children (*population*), compared to no supplementation (*comparison*)?" Two separate lines of inquiry are required to determine whether zinc has potential for therapy and/or prophylaxis. Relevant outcomes to assess therapeutic effect include reduction in duration and/or severity of pneumonia with zinc supplementation; the relevant outcome for prophylactic effect is reduction in occurrence (incidence/prevalence) of CAP and/or associated mortality and morbidity. Other surrogate outcomes have limited value in facilitating informed decisions on this issue.

CURRENT BEST EVIDENCE

An exhaustive literature search for randomized controlled trials (RCT) evaluating either a therapeutic or prophylactic role of zinc in childhood CAP was undertaken and updated on November 22, 2009. A Cochrane Library search using the term "*zinc*" and filter "*Record Title*" yielded 8 Cochrane Systematic Reviews and 2 Protocols, 12 Other (systematic) Reviews, 1240 (methodologically-appraised) Clinical Trials, 2 Methods studies and 6 Economic Evaluations. Simultaneous Pubmed search using "*zinc pneumonia*" and "*zinc (respiratory infection)*" with Limits "*Clinical trial, randomized controlled trial*" yielded 19 and 81 trials, respectively. Hand-searching of the bibliography of relevant citations yielded an additional 12 papers that were retrieved and examined.

Altogether 44 studies were short-listed, of which 29 were excluded for the following reasons: (*i*) pneumonia not included/reported as an outcome (*n*=9), (*ii*) respiratory infection evaluated but not consistent with pneumonia (*n*=6), (*iii*) not RCT (*n*=5), (*iv*) not community acquired pneumonia (*n*=5), (*v*) adult participants (*n*=2), and (*vi*) re-analysis of data from included RCT (*n*=2). The remaining 15 RCTs comprise current best evidence.

Eleven RCTs assessed the effect of zinc supplementation for prevention of CAP. ***Table* I** summarizes the trial characteristics and findings. All were community-based trials in developing countries. One was a cluster-randomized trial(7). Pneumonia and/or lower respiratory tract infection were defined in various ways, but all were consistent with the currently accepted IMNCI definition/ classifi-cation(17). However, three trials did not specify the respiratory rate for defining tachypnea(11,13,14). Nine of eleven trials were double-blind and placebo-controlled. Zinc dosage ranged from 5 to 20 mg/day. Two trials used smaller doses for younger infants(9,12). Duration of supplementation ranged from two weeks(7,16) to 12 months(20). Follow-up ranged from 4-12 months. The relevant outcomes – occurrence of pneumonia and/or severe pneumonia – were measured and expressed in various ways including incidence, prevalence, and episodes per person-time. Three trials reported mortality, but expressed the results differently(7,8,16). These differences made it difficult to derive a pooled estimate of effect, through meta-analysis. However, the balance of evidence (8 trials, 11701 participants) suggests that zinc supplementation does not prevent the occurrence of pneumonia. Only two trials (2230 participants) reported that zinc decreased pneumonia(6,13) and one trial (800 participants) showed that zinc supplementation increased the incidence and prevalence of pneumonia(10).

Four RCTs looked for a possible therapeutic effect of zinc supplementation in addition to antibiotic therapy(18-21). All were hospital-based, double-blind, placebo-controlled RCTs, although the process of allocation concealment and blinding were not clearly described in one(18). The trials used various definitions for pneumonia, but these were consistent with the WHO definitions of pneumonia and severe pneumonia. All but one(19) reported sample size calculations, and examined multiple outcomes including time for recovery and/or duration of hospitalization. Three (18,20,21) compared the time for resolution of severe pneumonia, and three (18,19,21) evaluated duration of hospitalization. Since all four RCTs presented results as median duration, meta-analysis was not possible. The trial characteristics and results are summarized in ***Table* II**. The balance of evidence suggests that there is no therapeutic benefit of adding zinc to antibiotic therapy. One trial in Australian indigenous children(19) followed participants for an additional 120 days and found that zinc supplementation resulted in a 2.4 times higher risk of readmission for pneumonia.

CRITICAL APPRAISAL

The fifteen RCTs included in this systematic review had generally high methodological quality. Some of them included additional refinements such as direct observation of zinc/placebo intake, frequent field-worker visits to measure outcomes, multiple/serial outcome measurements, pre-post estimation of zinc levels in the participants, and measurement of compliance.

Based on adequacy of randomization and allocation concealment procedures, blinding of outcome assessors and low attrition rate, 8 of the 15 RCTs (5 prophylaxis and 3 therapy) had low risk of bias; 6 had moderate risk of bias (1 or 2 of 4 elements unclear) and only 1 trial had high risk of bias. Nine trials reported sample size calculations for the specific outcomes measured; 5 trials used intention-to-treat analysis. Therefore, it is reasonable to conclude that the RCT methodology were robust to support the conclusions stated. However, it was not possible to pool data through meta-analysis owing to variations in the measurement and reporting formats.

The findings of this review are contrary to two previous meta-analyses of a limited number of RCTs(22,23). This is easily explained by noting that seven additional trials with robust methodology have been included in this review, and all included studies had definitions consistent with pneumonia.

Some additional interesting findings were picked up during the systematic review. There was limited data suggesting benefit of zinc in zinc-deficient children(8). If this is borne out by further studies, it may be possible to identify a sub-group of children who could benefit from zinc supplementation. However, the issue is complicated by the fact that serum zinc levels do not reflect tissue levels(21), and

TABLE I SUMMARY OF RCTs EXAMINING ZINC SUPPLEMENTATION FOR PROPHYLAXIS OF CHILDHOOD PNEUMONIA

No.	Participants	Definition of P, SP, ALRI	N (Zinc/ placebo)	Dose and duration	Follow-up	Outcomes	Pneumonia episodes/ person-time	Severe pneumonia episodes/ person-time	Ref
1	1-12mo	P = tachypnea + crepts. SP = additional ID and/ or danger sign	809/ 812	70mg/wk ×12 mo	324 d	P, SP, M	Zn 0.47 Pl 0.56 Rel Risk = 0.83 (0.73-0.95)	Zn 0.04 Pl 0.08 RR = 0.51 (0.30-0.88)	6
2	3-59mo	ALRI = cough, breathing difficulty and rapid breathing or ID	2483/ 2502	20mg/d × 14 d	NS	H, M	Zn 1543/ 20669 Pl 1700/ 21089 RR = 0.93 (0.78-1.10)		7
3	3-5wk old	ALRI = cough + difficult breathing ± fever >1d + rapid breathing or ID	152/ 149	5mg/d x 6mo	6 mo	ALRI In, Pr	Zn 0.7 Pl 0.7 RR = 0.99 (0.71-1.37)		8
4	6-30mo	ALRI = cough, tachypnea or ID. P = cough + crepts/ bronchial breathing or ALRI with at least 1 severe disease symptom	1241/ 1241	10mg/d in <1y 20mg/d in >1y For 4 mo	4mo	ALRI/severe ALRI In	Zn 0.53 Pl 0.54 OR = 0.98 (0.86-1.13)*	Zn 0.08 Pl 0.11 RR = 0.72 (0.56-0.99)*	9
5	12-35 mo	ALRI = cough + rapid or difficult breathing + fever Severe ALRI = ALRI + ID	400/400	20mg/d x 14d	6mo	ALRI / severe ALRI In, Pr	Incidence Zn 1.14, Pl 0.79 RR = 1.62 (1.16-2.25) Prevalence Zn 5.10, Pl 2.94 RR = 2.07 (1.76-2.44)	Incidence Zn 0.59, Pl 0.32 RR = 2.03 (1.24-3.33) PrevalenceZn 2.13, Pl 1.28 RR 2.06 (1.60-2.64)	10
6	0.5-15 y	ALRI = cough + tachypnea (rate NS)	214/ 215	20mg/d x 7d	7 mo	ALRI	GEE Risk Ratio = 1.00 (0.27)		11
7	2-4 wk old term LBW	ALRI = cough or breathing difficulty + tachypneaSevere ALRI = ALRI + 1 or more severe symptoms	1026/ 1026	5mg/d <6mo 10mg/d >6mo Till 12 mo old	11.5 mo	ALRI Pr **	ALRI / severe **	**	12
8	6-35 mo	ALRI = cough + tachypnea or temperature >101 deg F	298/ 311	10mg/d x 4mo	120 days	ALRI In. Pr	***		13
9	<6mo	LRI= fever + cough + difficult/rapid breathing (as per mothers' report)	170/ 164	10mg/d x 6mo	6mo	ALRI + others	Zn 3.6 Pl 3.7 RR = 0.97 (CI ns)		14

Contd...

No.	Participants	Definition of P, SP, ALRI	N (Zinc/ placebo)	Dose and duration	Follow-up	Outcomes	Pneumonia episodes/ person-time	Severe pneumonia episodes/ person-time	Ref
10	6-36mo, with >14d diarrhea	ALRI = cough + tachypnea P = cough + crepts	81/ 83	10mg/d x 6 mo	6mo	P	Zn 1.11±0.96 Pl 1.26±1.19 RR = 0.88 (CI ns)****		15
11	3-24 mo*****	LRTI = Tachypnea + breathing difficulty + cough + fever >38 deg or ID	76/ 78	20mg/d x 14d	6 mo	RTI In, duration, M	*****		16

*ALRI = acute lower respiratory infection, GEE = general estimating equation H = hospitalization, ID = indrawing, In = incidence, LBW = low birth weight, M = mortality, NS = not specified, OR = odds ratio, P = pneumonia, PL = placebo, Pr = prevalence, RTI = respiratory tract infection (upper and lower), RR = rate ratio, Rel Risk = relative risk, SP = severe pneumonia, Zn = zinc *Study definition of ALRI was consistent with WHO pneumonia and study definition of 'Pneumonia' was consistent with WHO 'severe pneumonia'. ** Pneumonia and severe pneumonia estimated during a 24 hour as well as a seven-day recall period at four time-points (12 observations), of which 11 did not show any difference between the groups. *** This study reported incidence and prevalence per person-time; the respective odds ratios were 0.55 (0.33-0.90) and 0.59 (0.35-1.00). **** This study presented data in a figure showing the comparative difference in incidence of ALRI and pneumonia relative to placebo; the former was about 3% lower, while the latter was not different. The study also reported the effect of zinc plus vitamins, which resulted in a 20% higher incidence of pneumonia. ***** Participants were recruited for a trial of zinc in persistent diarrhea; this study followed-up a sub-group of the original participants for respiratory infection and presented results in an even smaller sub-group of malnourished infants. Data were combined for URTI and LRTI.*

TABLE II SUMMARY OF RCTS EXAMINING THERAPEUTIC ROLE OF ZINC SUPPLEMENTATION IN CHILDHOOD PNEUMONIA

No.	Setting	Participants	Definitions used	N (Zinc/ placebo)	Dose and duration	Outcomes	Time for resolution of SP	Duration of hospitalization	Ref
1	Bangladesh	2-23 mo with SP	P = cough + tachypnea + crepts; SP = P + ID or danger sign	135/ 135	20mg/d till discharge	TR of SP, H TR of tachypnea, ID, hypoxia	Median (95%CI) Zn: 72 (72-96) Pl: 96 (72-96)	Median (95% CI) Zn: 112 (104-112) Pl: 112 (111-129) RH 0.75 (0.57-0.99)	18
2	Australia (indigenous population)	<11y	ALRI = tachypnea + fever/ID or pneumonia on x-ray	111/ 104	< 12mo 20mg/d > 12 mo 40mg/d ×5 d	Readmission within 120d, H, TR of hypoxia, fever, tachypnea.		Median (range) Zn: 5 (1-46)Pl: 5 (1-25) p = 0.75	19
3	India	2-23mo with SP	SP = tachypnea + crepts + 1 severe symptom	150/ 150	20mg/d till discharge	TR of tachypnea, ID, hypoxia, poor feeding, fever, cough	Median (95%CI) Zn: 111.3 (88.5-138) Pl: 96.7 (78.2-112.9) RR 0.86 (0.62-1.18)	Median (95% CI) Zn: 71.1 (68.1-88.0) Pl: 72.3 (67.7-79.6) RR 0.93 (0.74-1.17)	20
4	India	9mo-15y with measles + P	ALRI = tachypnea, ID, auscultation signs or both	42/ 43	20mg/d x 6 days*	TR of fever, tachypnea and "significant illness" as judged by clinician	Median (quartile) Zn: 132 (117-139) Pl: 122 (107-141) RH 1.07 (0.64-1.78)		21

*RH = relative hazard, TR = time for resolution; * Both groups received 1 dose vitamin A.*

EURECA CONCLUSION IN THE INDIAN CONTEXT

- There is no benefit of adding zinc to the standard treatment of childhood community acquired pneumonia.
- The current best evidence does not support zinc supplementation to prevent childhood pneumonia.

may be higher(16) or lower in severe infection. This apparent contradiction is explained by divergent views on zinc homoeostasis in response to infection. Besides this, although children in developing countries are assumed to be zinc deficient, data suggests that this is true only in a minority(12,13). These data argue strongly against considering population-based supplementation for pneumonia prophylaxis. Trials reporting harmful effects of zinc supplementation(10,13,19) advocate further caution.

A small number of trials used additional vitamin A, other vitamins, or iron supplementation in addition to zinc in both the intervention and control groups(12-14,19). From a methodological standpoint, it is appropriate to combine data from these studies with the others. However, the exact nature of interaction between zinc and other nutritional supplements is unclear, as there is evidence for benefit as well as harm. This may be an avenue for further research.

Should more RCTs be conducted to evaluate a therapeutic or prophylactic role of zinc? This systematic review shows that rather than undertaking more trials, it would be prudent to await updates in statistical methodology, and combine data from the existing RCTs to derive the pooled estimate. These developments are anticipated from the Cochrane Collaboration in the near future.

EXTENDIBILITY

The RCTs in this review shared the common characteristics of developing-country setting, lower/ middle socio-economic population, clinical definitions of pneumonia, clinical measurement of outcomes, and standard treatment protocols. Further, two therapeutic trials and four prophylaxis trials were conducted in our country itself. Therefore it is easy to extend the results and interpretations to the Indian context.

Funding: None.

Conflict of interest: None stated.

REFERENCES

1. No authors listed. Pneumonia: the forgotten killer of children. Geneva: The United Nations Children’s Fund (UNICEF)/World Health Organization (WHO); 2006.
2. Rudan I, Boschi-Pinto C, Biloglav Z, Mulholand K, Campbell H. Epidemiology and etiology of childhood pneumonia. Bull WHO 2008; 86: 408-416.
3. Zinc Investigators Collaborative Group. Therapeutic effects of oral zinc in acute and persistent diarrhea in children in developing countries: pooled analysis of randomized controlled trials. Am J Clin Nutr 2000; 72: 1516-1522.
4. Bhatnagar S, Lodha R, Choudhury P, Sachdev HPS, Shah N, Narayan S, *et al*. IAP Guidelines 2006 on management of acute diarrhea. Indian Pediatr 2007; 44: 384-389.
5. World Health Organization Department of Child and Adolescent Health and Development. Clinical management of acute diarrhoea: WHO/UNICEF joint statement [WHO/FCH/CAH/04.7]. Geneva: World Health Organization; 2004.
6. Brooks WA, Santosham M, Naheed A, Goswami D, Wahed MA, Diener-West M, *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.
7. Baqui AH, Black RE, El Arifeen S, Yunus M, Chakraborty J, Ahmed S, *et al*. Effect of zinc supplementation started during diarrhoea on morbidity and mortality in Bangladeshi children: community randomised trial. BMJ 2002; 325: 1059-1065.
8. Osendarp SJ, Santosham M, Black RE, Wahed MA, van Raaij JM, Fuchs GJ. Effect of zinc

supplementation between 1 and 6 mo of life on growth and morbidity of Bangladeshi infants in urban slums. Am J Clin Nutr 2002; 76: 1401-1408.

9. Bhandari N, Bahl R, Taneja S, Strand T, Mølbak K, Ulvik RJ, *et al*. Effect of routine zinc supplementation on pneumonia in children aged 6 months to 3 years: randomised controlled trial in an urban slum. BMJ 2002; 324: 1358-1362.

10. Rahman MM, Vermund SH, Wahed MA, Fuchs GJ, Baqui AH, Alvarez JO. Simultaneous zinc and vitamin A supplementation in Bangladeshi children: randomised double blind controlled trial. BMJ 2001; 323: 314-318.

11. Richard SA, Zavaleta N, Caulfield LE, Black RE, Witzig RS, Shankar AH. Zinc and iron supplementation and malaria, diarrhea, and respiratory infections in children in the Peruvian Amazon. Am J Trop Med Hyg 2006; 75: 126-132.

12. Taneja S, Bhandari N, Rongsen-Chandola T, Mahalanabis D, Fontaine O, Bhan MK. Effect of zinc supplementation on morbidity and growth in hospital-born, low-birth-weight infants. Am J Clin Nutr 2009; 90: 385-391.

13. Sazawal S, Black RE, Jalla S, Mazumdar S, Sinha A, Bhan MK. Zinc supplementation reduces the incidence of acute lower respiratory infections in infants and preschool children: a double-blind, controlled trial. Pediatrics 1998; 102: 1-5.

14. Lind T, Lönnerdal B, Stenlund H, Gamayanti IL, Ismail D, Seswandhana R, *et al*. A community-based randomized controlled trial of iron and zinc supplementation in Indonesian infants: effects on growth and development. Am J Clin Nutr 2004; 80: 729-736.

15. Penny ME, Marin RM, Duran A, Peerson JM, Lanata CF, Lönnerdal B, *et al*. Randomized controlled trial of the effect of daily supplementation with zinc or multiple micronutrients on the morbidity, growth, and micronutrient status of young Peruvian children. Am J Clin Nutr 2004; 79: 457-465.

16. Roy SK, Tomkins AM, Akramuzzaman SM, Chakraborty B, Ara G, Biswas R, *et al.* Impact of zinc supplementation on subsequent morbidity and growth in Bangladeshi children with persistent diarrhoea. J Health Popul Nutr 2007; 25: 67-74.

17. World Health Organization. Division of Child Health and Development. Integrated management of childhood illness. Geneva, Switzerland: World Health Organization; 1997. (Document ref. WHO/CHD/97.3E.)

18. Brooks WA, Yunus M, Santosham M, Wahed MA, Nahar K, Yeasmin S, *et al*. Zinc for severe pneumonia in very young children: double-blind placebo-controlled trial. Lancet 2004; 363: 1683-1688.

19. Chang AB, Torzillo PJ, Boyce NC, White AV, Stewart PM, Wheaton GR, *et al*. Zinc and vitamin A supplementation in indigenous Australian children hospitalised with lower respiratory tract infection: a randomised controlled trial. Med J Aust 2006; 184: 107-112.

20. Bose A, Coles CL, Gunavathi, John H, Moses P, Raghupathy P, *et al*. Efficacy of zinc in the treatment of severe pneumonia in hospitalized children <2 y old. Am J Clin Nutr 2006; 83: 1089-1096.

21. Mahalanabis D, Chowdhury A, Jana S, Bhattacharya MK, Chakrabarti MK, Wahed MA, *et al*. Zinc supplementation as adjunct therapy in children with measles accompanied by pneumonia: a double-blind, randomized controlled trial. Am J Clin Nutr 2002; 76: 604-607.

22. Bhutta ZA, Black RE, Brown KH, Gardner JM, Gore S, Hidayat A, *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: 689-697.

23. Aggarwal R, Sentz J, Miller MA. Role of zinc administration in prevention of childhood diarrhea and respiratory illnesses: a meta-analysis. Pediatrics 2007; 119: 1120-1130.