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Zinc supplementation for the prevention of acute lower respiratory infection in children in developing countries: meta-analysis and meta-regression of randomized trials

Daniel E Roth, Stephanie A Richard and Robert E Black*

Department of International Health, The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

*Corresponding author. Department of International Health, The Johns Hopkins Bloomberg School of Public Health, 615 N. Wolfe Street, E8527, Baltimore, MD 21205, USA. Email: rblack@jhsph.edu

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Background Routine zinc supplementation is a potential intervention for the prevention of acute lower respiratory infection (ALRI) in developing countries. However, discrepant findings from recent randomized trials remain unexplained.

Methods Randomized trials of zinc supplementation in young children in developing countries were identified by a systematic literature review. Trials included in the meta-analysis met specific criteria, including participants <5 years of age, daily/weekly zinc and control supplementation for greater than 3 months, active household surveillance for respiratory morbidity and use of a case definition that included at least one sign of lower respiratory tract illness. ALRI case definitions were classified on the basis of specificity/severity. Incidence rate ratios (IRRs) were pooled by random-effects models. Meta-regression and sub-group analysis were performed to assess potential sources of between-study heterogeneity.

Results Ten trials were eligible for inclusion ($n = 49\,450$ children randomized). Zinc reduced the incidence of ALRI defined by specific clinical criteria [IRR 0.65, 95% confidence interval (CI) 0.52–0.82], but had no effect on lower-specificity ALRI case definitions based on caregiver report (IRR 1.01, 95% CI 0.91–1.12) or World Health Organization 'non-severe pneumonia' (0.96, 95% CI 0.86–1.08). By meta-regression, the effect of zinc was associated with ALRI case definition, but not with mean baseline age, geographic location, nutritional status or zinc dose.

Conclusions Routine zinc supplementation reduced the incidence of childhood ALRI defined by relatively specific clinical criteria, but the effect was null if lower specificity case definitions were applied. The choice of ALRI case definition may substantially influence inferences from community trials regarding the efficacy of preventive interventions.

Keywords Zinc, pneumonia, respiratory tract infections, developing countries, meta-analysis, systematic review

Introduction

Improvements in nutrition are a keystone of current global efforts to reduce the burden of mortality and morbidity due to acute lower respiratory infections (ALRIs) among children living in developing countries.[1] Zinc deficiency has been a particular focus of attention because of its high frequency in developing countries and its debilitating effects on immune function.[2] Observational studies and randomized controlled trials (RCTs) have revealed a range of functional outcomes associated with zinc status during childhood, including linear growth, motor development and susceptibility to infectious diseases.[3]

To summarize the effect of routine zinc supplementation on the incidence of ALRI in early childhood, Aggarwal *et al*.[4] previously reported a meta-analysis of RCTs of daily or weekly zinc administration for >3 months duration, in which pooling of four studies that reported an outcome classified as 'severe respiratory illness' (lower respiratory tract infection or pneumonia) yielded a rate ratio (RR) of 0.80 [95% confidence interval (CI) 0.70–0.92].[4] Using this estimate as a measure of the effect of zinc on ALRI incidence, combined with estimates of the effect of zinc supplementation on ALRI-related mortality,[5] it has been projected that 7% of the global ALRI-associated disability adjusted life years (DALYs) in <5-year olds are lost due to zinc deficiency.[6]

However, several relevant zinc trials not meta-analysed by Aggarwal, either due to exclusion or publication after November 2005, have reported null or negligible effects of supplemental zinc on the risk of incident ALRI,[7–12] leading to speculation about factors that may underlie the heterogeneous findings, including participants' nutritional status (anthropometry or zinc status), age and geographic location. Estimates of ALRI incidence are greatly affected by the specificity of the ALRI case definition,[13] which has also been observed to influence the magnitude of the effect of zinc supplementation on ALRI incidence within studies that considered more than one ALRI outcome measure.[14–16] However, it is unknown whether variations in case definition specificity can explain the different efficacy of zinc across studies.

In this study, we updated the meta-analysis of the effect of routine zinc supplementation on the incidence of childhood ALRI, and used subgroup analysis and meta-regression to understand sources of between-study heterogeneity. We aimed to clarify the extent to which population characteristics and methodological choices influenced the measured impact of zinc interventions on ALRI morbidity in children in developing countries.

Methods

Inclusion and exclusion criteria

Studies selected for inclusion fulfilled all of the following criteria: (i) individual- or cluster-randomized controlled trial of routine (i.e. daily or weekly) zinc supplementation administered to children <5 years of age, in a developing country; (ii) masked assignment to zinc or a similar-appearing control supplement. Other than placebos, acceptable control supplements were nutrient co-interventions (e.g. vitamin A, riboflavin) that were administered to both control and zinc arms. Trials in which iron was delivered as a simultaneous co-intervention were excluded because of potential interactions between iron and zinc;[17] however, we included trials in which iron was provided *ad hoc* to anaemic children; (iii) community- or facility-based participant recruitment, followed by active (i.e. at least weekly) household surveillance for respiratory morbidity; (iv) ALRI case definition that clearly aimed to distinguish lower from upper tract respiratory disease (see below); and (v) supplement administration and ALRI surveillance for >3 months.

Literature search

Using the Ovid platform, the following databases were simultaneously scanned using the search string 'zinc AND (respiratory OR morbidity OR mortality OR pneumonia OR infection OR ARI)': Cochrane Central Database of Controlled Trials, Medline (including in-process and non-indexed citations) since 1950, Excerpta Medica Database (EMBASE) since 1988 and Global Health since 1973, including articles cited up to January 2008 and without language restrictions. One author (D.R.) reviewed the titles and abstracts to identify studies in which supplemental zinc was administered to children in a controlled trial and in which morbidity outcomes were reported, yielding 33 articles for full-text review (Figure 1). A second author (S.R.) performed an independent search of Web of Science and Pubmed, using the search string 'zinc and (respiratory or pneumonia or infection or ARI)', with 'limit – clinical trial' and no date restrictions, yielding two articles not identified in the first author's search. Manual searches of reference lists from the above articles and a recent review article,[3] previous meta-analyses [4,18] and consultation with experts yielded seven additional references for review. Trials that clearly reported the administration of multiple micronutrient formulations rather than zinc alone was not further reviewed since they did not permit inferences regarding zinc-specific effects.

Subsequent determination of study eligibility and data abstraction was based on independent review of full-text manuscripts by two authors (D.R. and S.R.); discrepancies were resolved by the third author (R.B.) and discussions aimed at reaching consensus among all three authors.

Data abstraction

Data extracted from each eligible study included the following primary outcome variables: the total number of ALRI episodes in each arm; the total

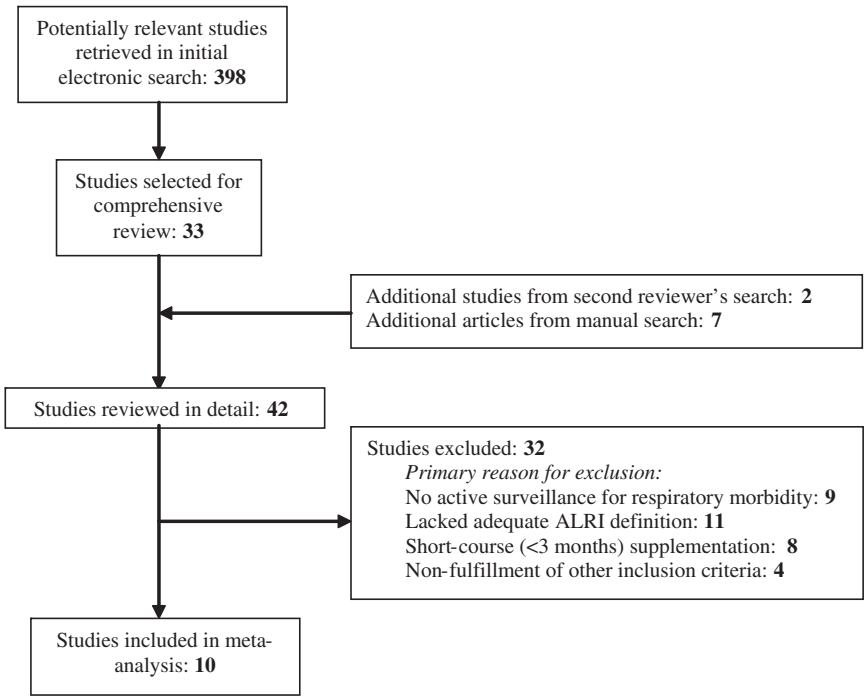

Figure 1 Flowchart of study selection process. Excluded studies were classified using the following hierarchy: (i) lack of community-based active surveillance for respiratory morbidity (e.g. hospital-based study, or respiratory outcomes not reported); (ii) there was active surveillance for respiratory symptoms, but an appropriate ALRI outcome definition was not reported (i.e. did not distinguish upper and lower respiratory tract infections); and (iii) there was active surveillance for respiratory symptoms and an appropriate ALRI outcome definition, but the duration of zinc supplementation was <3 months (e.g. 10–14-day regimens to treat acute or persistent diarrhoea).

amount of person-time accumulated in each arm (reported as person-days; e.g. if household visits were weekly, a child was considered under surveillance for all 7 days of each week during which a visit occurred and the child did not have an ongoing episode of ALRI); reported incidence rate ratio (IRR), standard error (SE) and 95% CIs. For studies that reported an IRR and SE adjusted for within-child clustering of repeated episodes by generalized estimating equations (GEEs), an empiric variance inflation factor (VIF) was calculated as the ratio of the variance of the adjusted IRR to the variance of the unadjusted IRR. The VIF was interpreted as a relative index of within-child clustering of ALRI episodes (i.e. a higher VIF indicated that a greater proportion of events were repeated in children who had already experienced at least one event).

For two studies in which effect estimates were not reported as IRRs in the published articles, the IRR was estimated by analysis of raw datasets provided by the investigators.[8,12] For a third trial,[9] we repeated the analysis including only those participants <5 years of age. In each analysis, a generalized linear model with log link and binomial dependent variable (the presence/absence of a new ALRI episode at each household visit) was modelled as a function of treatment group assignment (control or zinc). By using the number of child-days or child-weeks at risk as an offset, the regression coefficient for the treatment group represented an IRR instead of relative proportion. Children were not considered at risk during an ongoing ALRI episode (i.e. neither contributed person-days nor were eligible to experience a new ALRI event). To account for within-child clustering of repeated outcomes, robust SEs were calculated using GEE, assuming an exchangeable correlation structure.[19]

IRRs and 95% CIs were used exactly as reported if there was adjustment for within-child clustering of events by GEE. However, for studies that did not adjust the SE for within-child clustering and in which the case definition score was #1 (see below), 95% CIs were derived from a 'corrected SE' calculated by multiplying the unadjusted SE by a correction factor of 1.8 (the mean of the empiric VIFs in three studies that used case definition score #1). No correction was made to the SEs of the studies using case definitions #3 or #4, since the VIFs for these types of studies were ~1 (see 'Results' section). An association between VIF and case definition score was assessed by an extension of the non-parametric Wilcoxon rank-sum test executed in the Stata *nptrend* command.

Additional data abstracted from each study included details regarding: the ALRI case definition(s);

the study base (population- or clinic-based population at enrolment); sample size at randomization (zinc and control arms combined); mean age at enrolment (in control arm); proportion of participants with height/length-for-age *z*-score < –2 SD (in control arm); proportion of participants with weight-for-age *z*-score < –2 SD (in control arm); mean plasma zinc concentration at enrolment (in control arm); zinc dose, frequency, duration and preparation type; and nutrient controls and co-interventions.

Outcome definitions

There is no standard definition of childhood ALRI;[20] however, studies were included if they applied an outcome definition of respiratory illness that incorporated at least one lower respiratory tract sign reported by a caregiver and/or observed by study personnel (fast or difficulty breathing, chest wall indrawing) and/or abnormal findings on pulmonary auscultation (crackles/crepitations and/or bronchial breath sounds). Because definitions of ALRI were not directly comparable across studies and standard World Health Organization (WHO) definitions for 'pneumonia' were rarely used, we assigned each study outcome a score according to the specificity and severity qualitatively reflected in the case definition in the published report (Table 1). We assumed that, in general, specificity and/or severity (i.e. risk of death) were increased by the following elements: diagnosis based on examination by a trained observer rather than caregiver history; physical signs typically associated with lower rather than upper respiratory tract infection; and signs suggestive of very severe infection and/or hypoxaemia (e.g. lethargy, seizures).[21,22] The four-level scheme was developed through an iterative process that concluded when all three authors agreed on the assignment of every case definition from all included studies.

Table 1 ALRI case definition scoring scheme

Score	Case definition
1	Caregiver report of fast and/or difficult breathing (including, but not limited to, lower chest wall indrawing).
2	Fieldworker or physician diagnosis of ALRI[a] based on the finding of a rapid respiratory rate; other observed signs (e.g. lower chest wall indrawing) may be present but are not required for the diagnosis. This is equivalent to the WHO category of 'non-severe pneumonia'.
3	Fieldworker or physician diagnosis of ALRI[a] based on either a rapid respiratory rate and at least one other observed sign of ALRI[b]; or, abnormal sounds on pulmonary auscultation suggestive of pneumonia (bronchial breath sounds and/or crackles/crepitations).
4	Fieldworker or physician diagnosis of ALRI[a] based on a rapid respiratory rate and at least one additional sign of ALRI[b] and abnormal sounds on pulmonary auscultation suggestive of pneumonia (bronchial breath sounds and/or crackles/crepitations).

[a]Does not require the presence of caregiver-reported symptoms (e.g. cough).

[b]Observed clinical features that support the diagnosis of ALRI, other than elevated respiratory rate: lower chest wall indrawing, abnormal sounds on pulmonary auscultation suggestive of pneumonia (bronchial breath sounds and/or crackles/crepitations), nasal flaring, fever or 'danger signs' (i.e. cyanosis, lethargy/sleepiness, irritability, inability to drink or convulsions).

Meta-analysis

Effect estimates from individual trials were pooled in random-effects models with inverse-variance weighting, using the Stata *metan* command, to generate summary IRRs and 95% CIs. Because of the wide range of baseline event rates (~50-fold variation), relative rates were used as the primary effect measure since they were expected to be less dependent on baseline risk than absolute risk differences.[23] Multiple analyses from any single trial were assumed to have correlated errors; therefore, meta-analytic models included effect estimates for only the most-specific ALRI outcome measures reported for each trial (i.e. higher score), and were then repeated using the least-specific (i.e. lowest score) ALRI case definition from each trial. For six of the trials reporting only one outcome, the same effect estimate was used in both analyses.

Meta-regression and sub-group analyses

Between-study heterogeneity was explored visually using forest plots and quantified by the I^2 statistic, a measure of the proportion of variance of the effect estimates due to between-study variance.[24] Subgroup analyses and meta-regression were limited to five study characteristics suspected a priori of being modifiers of the magnitude of the effect of zinc of ALRI incidence: case definition score (categorical, as score 1–4), study location (categorical, as South Asia vs elsewhere), mean age at enrolment (continuous and categorical, as ⩾1 or <1 year of age), proportion of participants in the control group who were stunted at baseline (categorical, as ⩾ or <20% stunted at baseline), mean serum zinc concentration (continuous) and weekly cumulative zinc dose (continuous). The association between baseline incidence rate and IRR was not modelled because of the methodological problems in doing so.[25]

Meta-regression was performed using the Stata *metareg* command, in which the natural logarithm of the IRR (log IRR) was modelled as a linear function of a fixed study-level covariate and random study-specific intercepts: in these models, trials were weighted by their inverse within-study variances and residual between-study variances.[26] Because of the limited statistical power (small number of trials, exacerbated by missing data), each covariate was modelled separately. Meta-regression was performed twice

for each covariate, using effect estimates for either the most- or least-specific ALRI outcome measures reported for each trial. Results were reported as regression coefficients with 95% CIs and *P*-values.

Sensitivity analyses

In addition to pooling effect estimates based on both the most- and least-specific case definitions from each trial, the robustness of the inferences was assessed using the following sensitivity analyses: (i) exclusion of studies that did not report IRRs adjusted for within-child clustering of events by GEE; (ii) exclusion of studies that involved clinic-based recruitment; (iii) exclusion of the study that involved cluster-randomized design; and (iv) repetition of key analyses using fixed-effects models. Publication bias was assessed by visual inspection of funnel plots and the Begg and Egger tests performed using the Stata *metabias* command, based on separate analyses using effect estimates for either the most- or least-specific ALRI outcome measures reported for each trial.

All analyses were conducted using Stata IC, version 10 (Statacorp, TX, USA).

Results

Study selection

A total of 42 studies underwent comprehensive review, of which 10 were considered eligible (Figure 1).[7–12,14–16,27] Excluded studies either did not address the question of zinc efficacy for the prevention of ALRI or did not meet the methodological criteria required for meta-analysis and between-study comparisons (Table 2; Supplementary Appendix S1).

Table 2 Zinc supplementation trials not eligible for inclusion in the meta-analysis[a]

Primary reason for exclusion	Study	Country	Additional notes
Did not conduct prospective surveillance for respiratory morbidity	Bates, 1993	The Gambia	Supplement was delivered as a fortified drink; unsuitable control
	Bhandari, 2007	India	Iron and folic acid co-intervention to all children
	Bobat, 2005	South Africa	Clinic-based, HIV-infected population
	Castillo-Duran, 1987	Chile	Marasmic infants; short-course supplementation; unsuitable control
	Heinig, 2006	USA	Not conducted in a developing country
	Makonnen, 2003	Lesotho	Respiratory outcomes not reported
	Ruz, 1997	Chile	ALRI outcome not defined
	Sur, 2003	India	Respiratory data not collected
	Yang, 2002	China	ALRI outcomes not reported
Conducted prospective respiratory morbidity surveillance, but did not specify an adequate ALRI outcome	Berger, 2006	Vietnam	Respiratory infection defined as 'cough and/or difficulty breathing and/or elevated respiratory rate'
	Kikafunda, 1998	Uganda	School-based study
	Lind, 2004	Indonesia	Considered 'cough and fever' as ALRI outcome
	Lira, 1998	Brazil	Short-course; only cough reported
	Muller, 2001	Burkina Faso	Only cough reported
	Ninh, 1996	Vietnam	Respiratory outcome was cough and fever
	Rosado, 1997	Mexico	Respiratory outcome included 'any symptom such as runny nose, common cold, sore throat or cough'
	Ruel, 1997	Guatemala	Respiratory outcome was 'the presence of at least two of the following symptoms: runny nose, cough, wheezing, difficulty breathing or fever'
	Sazawal, 2001	India	Respiratory morbidity was not reported; small-for-gestational age infants
	Sazawal, 2007	Tanzania	ALRI incidence data not collected
	Umeta, 2000	Ethiopia	Cough was only reported respiratory outcome

(continued)

Table 2 Continued

Primary reason for exclusion	Study	Country	Additional notes
Conducted ALRI surveillance, but the duration of zinc supplementation was ⩽3 months	Baqui, 2002	Bangladesh	Cluster-randomized trial of 2-week supplementation for diarrhoea episodes
	Bhandari, 2008	India	Cluster-randomized trial of 2-week supplementation for diarrhoea episodes; follow-up by repeated cross-sectional surveys
	Meeks-Gardner, 1998	Jamaica	12 weeks supplementation and follow-up
	Rahman, 2001	Bangladesh	2 weeks of supplementation for diarrhoea episodes, with 6-month follow-up
	Roy, 1999	Bangladesh	2 weeks of supplementation for diarrhoea episodes, with 2-month follow-up
	Roy, 2007	Bangladesh	2 weeks of supplementation for diarrhoea episodes, and 3-month follow-up; multivitamin co-intervention
	Sempertegui, 1996	Ecuador	60 days supplementation, and 120 days of surveillance at a day-care facility
	Walker, 2007	Pakistan, India, Ethiopia	2 weeks supplementation and 2-month follow-up
Other	Brown, 2007	Peru	Iron included in both groups
	Garenne, 2007	Burkina Faso	Same study as Muller 2001
	Masoodpoor, 2008	Iran	Participants >5 years of age
	Meeks-Gardner, 2005	Jamaica	Iron included in both groups

[a]See Supplementary Appendix S1 for reference citations.

Characteristics of included studies

All 10 studies eligible for inclusion were randomized double-masked controlled trials of zinc vs a placebo or non-iron-containing nutrient co-intervention, and published within one decade. However, there were substantial differences in the participant characteristics and zinc dosing regimens across the studies (Table 3). Four of the studies reported analyses using two distinct ALRI case definitions, yielding data for 14 zinc–control comparisons (Table 4). A total of 49 450 children were randomized to either zinc or the control arm, contributing 5890 child-years of follow-up; 86.6% of participants were in a cluster-randomized trial in Nepal. Baseline incidence rates inferred from the control groups ranged from 0.05 to 2.56 episodes per child-year, point estimates of the IRR for the effect of zinc ranged from 0.51 to 1.45 and adjusted SEs ranged from 0.046 to 0.48 (Table 4). All but four of the studies applied GEE to account for within-child clustering of ALRI episodes. Comparing the variance of the GEE-adjusted results with unadjusted IRRs using the empiric VIF revealed that precision of the effect estimates diminished after adjustment in analyses using case definitions #1 and #2, but the effect of adjustment was negligible in analyses using case definitions that incorporated clinical observations more specific than the respiratory rate alone (Table 4). There was an inverse association between ALRI case definition score and VIF in a non-parametric test for trend ($P = 0.048$).

Meta-analysis

When analyses for the most specific ALRI outcomes from each of the 10 trials were pooled, there was a moderate effect of zinc on the incidence of ALRI with a 95% CI that included a null effect (IRR 0.86, 95% CI 0.74–1.01), and there was substantial heterogeneity across studies ($I^2 = 39.4\%$). Pooling effects based on the least specific outcomes from each of the trials attenuated the zinc effect (IRR 0.94, 95% CI 0.88–1.01) and greatly reduced the between-study heterogeneity ($I^2 = 0\%$). Stratification by case definition suggested a differential effect of zinc based on the relative specificity of the ALRI case definition, such that a robust effect was most evident when ALRI was diagnosed by clinical criteria more specific than an elevated respiratory rate (Figure 2). Pooling results from analyses involving only the most specific ALRI case definition from the three trials that reported case definitions #3 or #4 yielded an IRR of 0.65 (95% CI 0.52–0.82; $I^2 = 0.0\%$). All three of these trials were conducted in South Asia, using at least 70 mg zinc per week. Within each of these three trials, use of the more specific case definition

Table 3 Characteristics of the randomized controlled trials of zinc supplementation for the prevention of childhood ALRI that were eligible for inclusion in the meta-analysis

Study	Country	Study base[a]	N[b]	Mean age[c] (months)	Percentage UW[d]	Percentage ST[d]	Serum zinc[e] (μmol/l)	Zinc intervention				Nutrient control/ co-interventions
								Freq.[f]	Duration (months)	Weekly dose[g] (mg)	Zinc salt	
Baqui, 2003	Bangladesh	CB	318	6.3	13	19	10.0	W	6	20	Acetate	Riboflavin
Bhandari, 2002	India	CB	2482	15	–	–	9.5	D	4	70, 140[h]	Gluconate	Vitamin A
Brooks, 2005	Bangladesh	CB	1621	5.2	–	–	9.7	W	12	70	Acetate	None
Long, 2006[i]	Mexico	CB	786	10.3	9.3	9.6	–	D	12	140	Methionine	Vitamin A or none
Luabeya, 2007[j]	South Africa	CB	227	5.5	3.2	3.9	–	D	18	70	Gluconate	Vitamin A
Osendarp, 2002	Bangladesh	CB	301	0.9	5.8	13	11.7	D	5	35	Acetate	None
Penny, 2004	Peru	D	164	18.5	14	30	10.7	D	6	70	Gluconate	None[k]
Richard, 2006[l]	Peru	CB	125	39.3	0	59	10.7	D	7	140	Sulfate	None
Sazawal, 1998	India	D	609	18.6	–	51	9.8	D	6	70	Gluconate	Vitamins A, B1, B2, B6, D3, E
Tielsch, 2007	Nepal	CB	42 817	–[m]	–	–	–	D	12	70	Sulfate	Vitamin A

[a]The source population from which children were recruited: CB, representative community-based sample; D, selected sample of children treated for diarrhoea.
[b]Number of children randomized to the zinc and control groups.
[c]Mean age of children in the control group, at the time of enrolment.
[d]The percentage 'underweight' (UW) and percentage 'stunted' (ST) reflected the proportions of participants in the control group with *z* scores <–2 SDs below the age- and sex-specific medians on the National Centre for Health Statistics (NCHS) weight-for-age and height-for-age growth references, respectively; for studies that did not report proportions of children underweight/stunted, figures were derived from reported mean and standard deviation z scores where such data were reported.
[e]Mean μmol/L concentration at baseline, in the control group.
[f]Frequency of supplement administration: D: daily; W: once weekly.
[g]'Weekly dose' refers to the cumulative dose administered per week, irrespective of frequency.
[h]A lower dose (70 mg) was administered to infants (i.e. <12 months of age).
[i]This trial was a 2 × 2 factorial design, in which zinc or vitamin A or both were administered. Because there was no interaction between zinc and vitamin A in the primary analysis, and vitamin A is not expected to affect ALRI incidence, any child who received zinc was considered to be in the zinc arm, and any child who did not receive zinc was in the control group, regardless of whether the co-intervention received was placebo or vitamin A.
[j]To facilitate more appropriate comparisons to the other included trials, only HIV-negative children (irrespective of HIV status of mothers) were included in this analysis.
[k]Iron supplements were provided to anemic children in both zinc and control groups.
[l]Only the subset of participants <5 years of age at enrolment was included in this analysis.
[m]Morbidity data relevant to this analysis were drawn from a 'morbidity sub-sample', for which mean age at baseline was not reported.

Table 4 Summary of data from randomized controlled trials of zinc supplementation included in the meta-analysis, stratified by type of case definition

Study	ALRI case def.[a]	Zinc group			Control group			Crude IRR[e]	Crude SE[f]	Reported/ adjusted IRR[g]	Reported/ adjusted SE[h]	Adjusted for within-child clustering[i]	Variance inflation factor[j]
		No. events[b]	Total child-years[c]	IR[d]	No. events[b]	Total child-years[c]	IR[d]						
Baqui, 2003	1	178	73.8	2.41	190	74.3	2.56	0.94	0.104	0.95	0.105	No	–
Bhandari, 2002a	2	581	361.6	1.61	594	368.2	1.61	1.00	0.058	0.98	0.070	Yes	1.42
Bhandari, 2002b	3	88	361.6	0.24	118	368.2	0.32	0.76	0.141	0.74	0.145	Yes	1.06
Brooks, 2005a	3	199	427	0.47	286	511	0.56	0.83	0.092	0.83	0.067	No	–
Brooks, 2005b	4	18	427	0.04	42	511	0.08	0.51	0.282	0.51	0.275	No	–
Long, 2006	1	13	312.9	0.04	15	309	0.05	0.86	0.379	0.85	0.480	Yes	1.61
Luabeya, 2007a	1	50	111.7	0.45	35	114.1	0.31	1.46	0.321	1.45	0.453	Yes	1.99
Luabeya, 2007b	2	24	112.4	0.21	18	114.5	0.16	1.36	0.423	1.35	0.470	Yes	1.23
Osendarp, 2002	1	75	56.3	1.33	74	55.4	1.33	1.00	0.164	0.99	0.168	No	–
Penny, 2004	2	71	34.9	2.04	84	35.4	2.37	0.86	0.138	0.81	0.223	Yes	2.60
Richard, 2006	1	58	24.8	2.34	28	23.7	1.18	0.98	0.230	0.98	0.310	Yes	1.81
Sazawal, 1998a	2	137	123.3	1.11	153	125.4	1.22	0.91	0.118	0.89	0.141	Yes	1.43
Sazawal, 1998b	3	24	123.3	0.19	44	125.4	0.35	0.55	0.254	0.55	0.256	Yes	1.02
Tielsch, 2007	1	1999	1395	1.43	1887	1351.1	1.40	1.03	0.032	1.01	0.046	No	–[k]

[a]See text and Table 1 for explanation of ALRI case definition classification system.
[b]Total number of incident ALRI episodes in the intervention group, irrespective of within-child clustering.
[c]Represents the total sum of person-time during which participants in the given intervention group were 'at risk' of an incident ALRI episode. Definitions of a 'new ALRI episode' and time at risk differed slightly among the trials.
[d]Unadjusted incidence rate (IR) within the intervention group, calculated as number of incident ALRI events/total child-years.
[e]Unadjusted IRR, calculated simply as the ratio of the IR in the zinc group to the IR in the control group.
[f]Unadjusted SE of the natural logarithm of the crude IRR (lnIRR), based on the following standard formula: $[(1/A)+(1/B)]^{1/2}$, where A is the number of events in the zinc group, and B the number of events in the control group.
[g]IRR reported in the published article or calculated in the re-analysis of the raw data performed to enable inclusion in the meta-analysis.
[h]SE reported in the published article, derived from confidence intervals reported in the published article, or calculated in the re-analysis of the raw data performed to enable inclusion in the meta-analysis.
[i]Indicates whether or not any kind of statistical adjustment was undertaken to account for 'within-child' clustering of ALRI events in the estimation of the IRR and 95% CIs in the original published analysis or re-analysis performed to enable inclusion in the meta-analysis.
[j]Ratio of the 'reported variance' (square of the SE derived as explained in footnote superscript h) to the unadjusted crude variance (square of the SE calculated as explained in footnote superscript f), for studies in which the SE was adjusted for 'within-child' clustering of events. The VIF can be interpreted as an index of the extent of within-child clustering of ALRI events.
[k]Reported SE calculated using GEEs to adjust for cluster-randomized design, but not for within-child clustering of ALRI events.

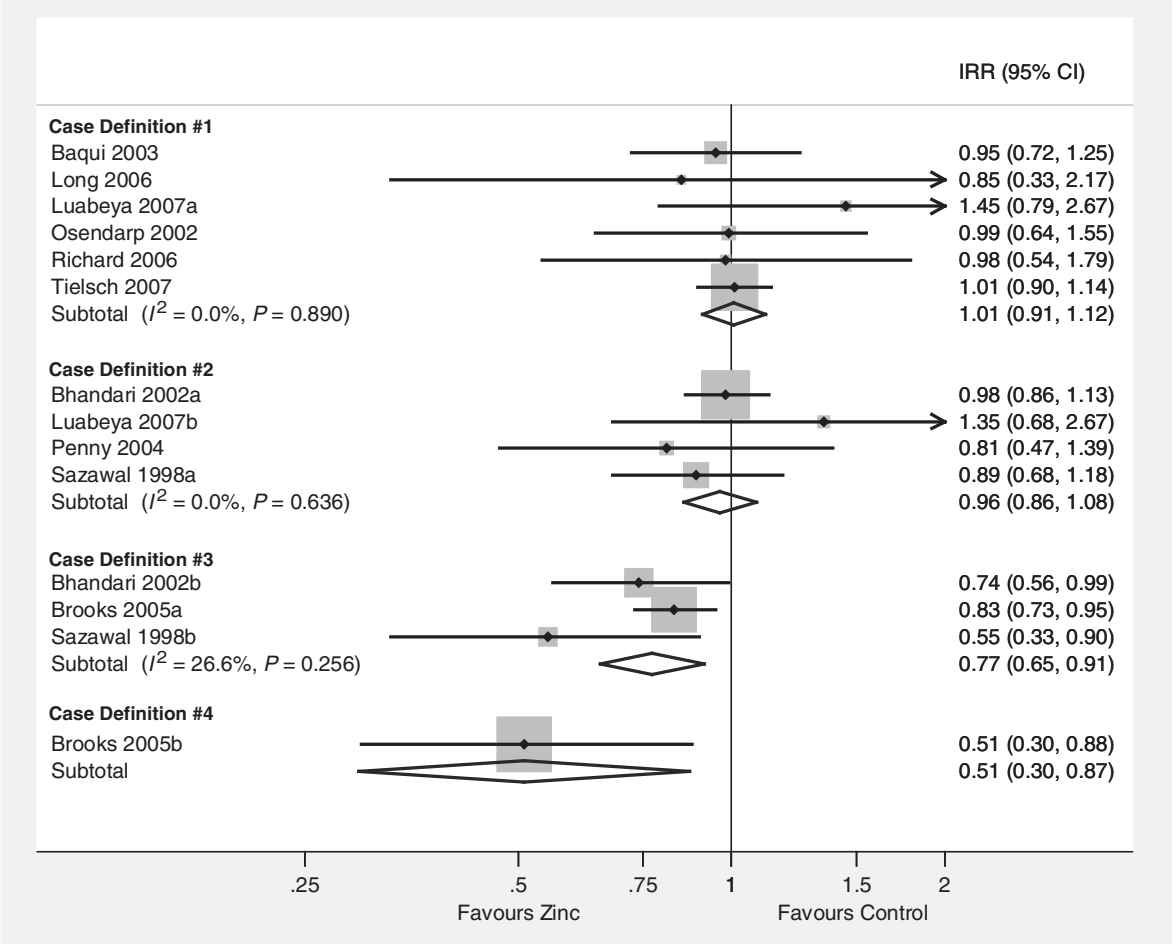

Figure 2 Pooled IRRs and 95% CIs for the effect of routine zinc supplementation on the incidence of ALRI, stratified by ALRI case definition (1–4). Horizontal lines represent confidence bounds, and the size of the box surrounding each point estimate reflects the relative weight compared with other studies in the stratum. I^2 reflects the degree of between-study heterogeneity.

(i.e. higher score) also consistently conferred an IRR further from the null (Table 4; Figure 2).

Meta-regression

The effect of zinc on ALRI incidence (log IRR) was associated with ALRI case definition, but there were no discernible associations with mean age of participants, geographic location, participants' baseline nutritional status (prevalence of stunting or mean serum zinc) or zinc dose (Table 5). The meta-regression coefficients were attenuated towards zero when effect estimates using less-specific ALRI case definitions were pooled, compared with the co-efficients generated by pooling effect estimates based on the most specific ALRI case definition from each trial (Table 5). For example, the apparently large (albeit imprecisely estimated) magnitude of the association between mean height-for-age *z*-score at baseline and log IRR using the most specific ALRI case definitions was greatly attenuated when the lower-specificity case definitions were used (Table 5).

Sensitivity analyses and publication bias

None of the ancillary sensitivity analyses altered the inferences. The Begg and Egger tests did not suggest the presence of publication bias (data not shown); however, the funnel plots were asymmetric, with relatively low representation by small studies with negative effects.

Discussion

Previous meta-analyses concluded that routine zinc supplementation reduced the risk of incident ALRI in young children in developing countries.[4,18] Beyond confirming the protective effect of zinc (at least 70 mg cumulative dose per week for >3 months), this review has updated and refined this observation in several respects. First, a prior meta-analysis did not address the pervasive non-uniformity of ALRI case-finding methods and case definitions in zinc supplementation studies, to the extent that a non-respiratory outcome was

Table 5 Estimated average differences in the effect of zinc supplementation on the risk of ALRI associated with selected study characteristics, based on univariate random-effects meta-regression involving effect estimates from analyses involving the most- or least-specific ALRI case definition reported for each trial

Study characteristic	n[a]	Highest-specificity ALRI case definition from each trial: Difference in log IRR (95% CI)	*P*	Lowest-specificity ALRI case definition from each trial: Difference in log IRR (95% CI)	*P*
Case definition	10				
#2 (vs #1)		−0.114 (−0.522 to 0.295)	0.585	−0.054 (−0.211 to 0.103)	0.502
#3 (vs #1)		−0.370 (−0.639 to −0.102)	0.007	−0.188 (−0.356 to −0.021)	0.028
#4 (vs #1)		−0.670 (−1.218 to −0.122)	0.017		
Mean age at enrolment in control group	9				
⩾1 year (vs <1 year)		−0.179 (−0.467 to 0.108)	0.222	0.092 (−0.070 to 0.254)	0.264
Per month increase in age (continuous)		−0.004 (−0.021 to 0.014)	0.686	0.005 (−0.007 to 0.017)	0.405
Africa or Latin America (vs South Asia)	10	0.105 (−0.302 to 0.512)	0.614	−0.017 (−0.345 to 0.312	0.920
Nutritional status at baseline in control group	7				
Prevalence of stunting ⩾20% (vs <20%)		−0.269 (−0.633 to 0.094)	0.146	−0.106 (−0.415 to 0.203)	0.500
Per 1-U increase in height-for-age *z*-score		−0.812 (−1.937 to 0.314)	0.157	−0.232 (−1.129 to 0.666)	0.613
Per 1 μmol/l increase in serum zinc concentration		0.168 (−0.071 to 0.407)	0.167	0.004 (−0.186 to 0.194)	0.969
Cumulative weekly zinc dose (per 1 mg increase)	10	−0.001 (−0.006 to 0.003)	0.535	0.000 (−0.003 to 0.004)	0.806

[a]*n* refers to the number of studies included in the meta-regression.

included in the pooled analysis of 'respiratory illness'.[4] In the present review, decisions regarding study inclusion/exclusion and stratified analyses of eligible studies were based on explicit and reproducible ALRI criteria, and between-trial heterogeneity was explored by meta-regression and *a priori* subgroup analysis rather than simply controlled in meta-analytic models. Secondly, the present analysis provided evidence of an association between the relative specificity of the ALRI case definition and the observed strength of the zinc effect, such that efficacy was most evident in analyses that incorporated a diagnosis of ALRI based on clinical criteria other than elevated respiratory rate. Thirdly, we preliminarily related the relative specificity of the ALRI case definitions to the magnitude of 'variance inflation' caused by adjustment for within-child clustering of repeated ALRI episodes. Lastly, there was a lack of evidence that geographic location, prevalence of stunting, average zinc status, average age at enrolment or zinc dosage accounted for between-study differences.

The finding that ALRI case definition was associated with effect size was important but unsurprising, since it is known that poor specificity due to a non-differential error in outcome ascertainment (i.e. high number of false positive diagnoses in all exposure categories) classically biases relative risks, RRs and odds ratios towards the null.[28] This phenomenon has been well documented in the vaccine literature;[29,30] for example, in a pneumococcal conjugate vaccine trial in The Gambia, efficacy was markedly higher for a radiological pneumonia endpoint than the much less specific diagnosis of 'clinical pneumonia' (i.e. WHO definition of ALRI).[31] Bhandari *et al*. hypothesized that an observed within-study difference in zinc effects on two ALRI outcomes was due to lower specificity of one of the case definitions.[14] The present review suggests that this phenomenon also likely explains between-study differences in measured effects of zinc on ALRI incidence, and challenges the notion that negative findings in recent trials undermine earlier findings of efficacy.

Clinical criteria with high sensitivity and specificity for radiologically- and/or bacteriologically-confirmed paediatric pneumonia have eluded researchers for decades.[32] The diagnosis of ALRI is notoriously unreliable when based on a caregiver history of respiratory symptoms[33,34] (case definition #1) or health worker-documented WHO criteria for non-severe pneumonia (case definition #2).[35] We found that the benefit of zinc was only apparent if ALRI was ascertained through clinical observation of at least one sign of lower respiratory tract disease other than tachypnoea, and/or a sign suggestive of invasive infection (case definitions #3 and #4). The criteria for definitions #3/4 were not exclusively diagnostic of bacterial pneumonia, as they likely captured

moderate–severe viral ALRI (e.g. bronchiolitis), sepsis or other systemic infections associated with respiratory manifestations (e.g. tachypnoea due to metabolic acidosis); however, they did reflect the presence of an acute process for which susceptibility was responsive to zinc supplementation. Moreover, they corresponded to the category of respiratory diseases most liable to cause mortality and thus of greatest public health interest (i.e. bacterial pneumonia or severe bronchiolitis).[21,22] By logical extension, we proposed that the best overall estimate of the effect of zinc (at a dose of at least 70 mg per week for >3 months) was a reduction in ALRI incidence of ~35% (95% CI 18–48), based uniquely on analyses of trials that employed case definitions #3 and #4.[14–16]

The mechanisms by which zinc alters human susceptibility to ALRI likely include the regulation of pro-inflammatory cytokine secretion,[36] lymphocyte proliferation,[37] T lymphocyte function[38] and protection of the integrity of respiratory epithelial cells in the setting of acute inflammatory lung injury.[39] Effects on neutralizing antibody production are less likely to be involved.[40,41] A potential biological explanation for the attenuating effect of low outcome specificity is that improvements in zinc status do not greatly influence the susceptibility to non-respiratory illnesses or viral upper respiratory tract infections,[15] which may be misclassified as ALRI. However, because zinc may have prophylactic effects against viral respiratory tract infections,[42] we suspect that case definitions #1/#2 were primarily contaminated by non-infectious respiratory conditions (e.g. asthma, respiratory complications of sickle cell disease, chronic/recurrent cough due to air pollutants)[43] or sub-acute/chronic or opportunistic infections (e.g. tuberculosis, HIV-related diseases). Howie *et al*. aptly noted that current ALRI case definitions do not adequately distinguish between bacterial pneumonia and viral bronchiolitis, even though immune functions that protect against these diseases would be expected to respond differently to nutrient interventions.[44] Coles *et al*. have similarly postulated that the pleiotropic effects of zinc on immune and inflammatory responses may result in pathogen-dependent effects.[45] Neutral or aggravating effects of zinc supplementation on the susceptibility to infections misclassified as ALRI would predictably attenuate the overall effect measure.

In addition to effect attenuation, low case definition specificity was also associated with an increase in the within-child clustering of ALRI episodes; clustering reduced the precision of effect estimation by variance inflation upon adjustment for outcome non-independence (i.e. using GEE). A non-specific symptom complex or mild diagnostic entity may be likely to recur within a child, particularly if based on subjective perceptions of caregivers; for example, some mothers may be more inclined than others to routinely report that their child has cough or fast breathing. Recurrence of respiratory events in a child diagnosed with 'pneumonia' in a resource-poor setting points to an underlying chronic respiratory condition (asthma, in particular) rather than ALRI,[46] highlighting the existence of a subset of children who would benefit from alternative preventive measures (e.g. environmental controls, allergen avoidance, inhaled corticosteroids). We believe that this subgroup would be less likely to overwhelm diagnostic categories based on more specific or severe physical signs (e.g. definitions #3 and #4).

Geographic location, mean participant age, zinc dose and baseline population zinc status (indicated by the height-for-age *z*-score or serum zinc concentration)[47] would be expected to influence the nutritional impact of zinc supplementation, but we did not find evidence that these study-level factors were associated with the magnitude of the effect of zinc on ALRI incidence. We did not interpret this as evidence of a lack of effect modification of zinc efficacy at the individual level, but rather that they did not readily explain between-study heterogeneity. Compared with the magnitudes of association of each of these factors with the zinc effect when the analysis incorporated the most specific ALRI case definition from each of the trials, the associations were attenuated when the analysis incorporated the least specific case definitions. We speculate that because the latter analyses involved greater homogeneity in ALRI case definition scores, they partially adjusted for case definition and thus reduced confounding of the associations between zinc effect size and study-level covariates. However, the small number of trials limited the robustness of our inferences, in part because it precluded the use of multivariate models or pure stratification by ALRI case definition score. Although zinc dose and study location were not associated with the effect size, it is important to note that beneficial effects of zinc were only clearly demonstrated in studies conducted in South Asia, in which children were administered at least 70 mg zinc per week (either 10 mg daily or 70 mg weekly). Therefore, the present analysis does not resolve the question of whether zinc supplementation would be less effective at lower doses, or would have less of an impact on ALRI incidence in developing regions outside South Asia.[8]

There were several limitations in this review. First, all meta-analyses are subject to potential biases due to non-publication of negative trials (which was apparent in this study, as was previously observed)[4], as well as biases in the selection of included trials. However, we aimed to reduce these biases by using detailed inclusion criteria, relying on independent reviews by two authors and performing analyses of raw data from two trials that would not otherwise have been included because the original publications did not report incidence rates. Although we chose not to use a standard score for trial quality assessment based on generic criteria, we used strict study

inclusion criteria (i.e. randomized and concealed intervention allocation) and focused our quality appraisal on methodological elements specific to ALRI primary prevention trials (e.g. case definition). Secondly, we relied on *post hoc* classification of the ALRI case definitions, because the disparate approaches of the studies and rarity of the use of standard WHO categories precluded the use of any pre-existing ALRI classification scheme; nonetheless, the definitions we used corresponded closely to conventional entities (caregiver-reported respiratory illness, WHO non-severe pneumonia and ALRI with features predictive of mortality), and adequately discriminated the studies with respect to effect size in meta-regression. Thirdly, we chose not to use methods to incorporate multiple outcomes from trials within the same meta-analytic or meta-regression model, but rather used only the most- or least-specific outcome from each trial. This approach had the advantage of acting as a sensitivity analysis and served to partially adjust for the potential confounding effect of ALRI case definition on associations between study characteristics and effect size; however, it had the disadvantage of further diminishing the statistical power of the meta-regression by reducing the number of units of analysis within each stratum. Lastly, the meta-regression and subgroup meta-analyses had low power to precisely estimate associations, and inferences were subject to the same potential for confounding bias as in any observational epidemiological study. Although confounding could explain the positive findings by meta-regression, ALRI case definition was a strong modifier of the effect of zinc on ALRI incidence within three of the studies,[14–16] observations that could not be due to confounding because all other characteristics of the study populations and methods were identical. The consistency of the observation both within and between studies, as well as the biological plausibility of the assertion, support the inference that ALRI case definition specificity was an important cause of between-trial variation in estimates of the IRR.

The above inferences have implications for the design of future ALRI prevention trials, not limited to those assessing nutritional interventions. Most importantly, investigators should recognize that the choice of case definition may alter the ability to detect important intervention effects and will affect power/sample size calculations. Moderate–severe ALRI established by a relatively specific case definition (#3/#4) occurs at a rate of only approximately 0.3 events per child-year[13] (in contrast to event rates as high as 2.6 events/child-year in studies using non-specific case definitions), requiring >800 child-years in each group to detect a risk reduction of >30%; this implies the need for statistical power that few previous trials have achieved. However, because variance inflation after adjustment for within-child clustering is attenuated by use of more specific case definitions, some precision may actually be gained by increasing specificity, even though overall power is reduced by a lowered baseline event rate. Future large-scale trials should aim to standardize and validate case-finding methods and case definitions in pilot or sub-studies, as demonstrated in the recent indoor air pollutant reduction trial in Guatemala.[48] A gold-standard definition of 'pneumonia' based on radiological, bacteriologic or molecular tools remains unavailable for use in most field trials, thus consideration should be given to the validation of feasible clinical ALRI definitions based on operational performance (i.e. specificity that is adequate to demonstrate interventional effects as demonstrated here) and association with mortality. Further work is also required to explore the effect of within-child event recurrence on the estimation of nutrient effects on ALRI incidence, to assess the potential role of the empiric VIF as an index of ALRI case definition specificity and to delineate the bias-variance trade-offs related to variations in ALRI case definition specificity.

In summary, a protective effect of routine zinc supplementation of >3 months duration on the incidence of ALRI in children in developing countries was confirmed. Negative findings in some recent trials may be due to non-specific case definitions, coupled with low power to detect effects based on specific ALRI outcomes. Future trials should explicitly consider the specificity of the ALRI case definition and its implications for precision of the effect measure and power to detect effects on clinically meaningful outcomes.

Supplementary Data

Supplementary data are available at *IJE* online.

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KEY MESSAGES

- Provision of routine oral zinc supplements to young children in developing countries has been shown to reduce the incidence of ALRI in prior meta-analyses of randomized controlled trials; however, some recent studies have not observed beneficial effects, engendering doubt about earlier findings.
- In an updated and expanded meta-analysis, variations in clinical ALRI case definitions explained between-study differences in the magnitude of the effect of zinc on ALRI incidence. Recent studies have used case definitions that may not have been specific enough to enable detection of a preventive zinc effect.
- Meta-analysis of studies in which relatively specific ALRI case definitions were applied demonstrated that routine zinc supplementation (at least 70 mg cumulative dose per week, for >3 months) reduced the risk of childhood ALRI by about one-third.
- Investigators' decisions about ALRI case definitions may substantially influence inferences from community trials regarding the efficacy of preventive interventions.

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