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Zinc as an adjunct to antibiotics for the treatment of severe pneumonia in children <5 years: a meta-analysis of randomised-controlled trials

Hong-Tao Tie[1,†], Qi Tan[2,†], Ming-Zhu Luo[2], Qiang Li[1], Jia-Lin Yu[2]* and Qing-Chen Wu[1]*

[1]*Department of Cardiothoracic Surgery, The First Affiliated Hospital of Chongqing Medical University, Chongqing 400016, People's Republic of China*

[2]*Department of Neonatology, The Children's Hospital of Chongqing Medical University, Chongqing 400016, People's Republic of China*

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Abstract

The effect of Zn, as an adjunct to antibiotics, on the treatment of severe pneumonia in young children is still under debate; therefore, we performed a meta-analysis to evaluate the therapeutic role of Zn for severe pneumonia in children younger than 5 years. PubMed, Cochrane library and Embase databases were systematically searched from inception until October 2015 for randomised-controlled trials (RCT) that assessed the effect of Zn as an adjunct to antibiotics for severe pneumonia. Random-effects model was used for calculating the pooled estimates, and intention-to-treat principle was also applied. Nine RCT involving 2926 children were included. Overall, the pooled results showed that adjunct treatment with Zn failed to reduce the time to recovery from severe pneumonia (hazard ratios (HR) = 1·04; 95 % CI 0·90, 1·19; $I^2 = 39\,\%$; $P = 0{\cdot}58$), hospital length of stay (HR = 1·04; 95 % CI 0·83, 1·33; $I^2 = 57\,\%$; $P = 0{\cdot}74$), treatment failure (relative risk (RR) = 0·95; 95 % CI 0·79, 1·14; $I^2 = 20\,\%$; $P = 0{\cdot}58$) or change of antibiotics (RR = 1·07; 95 % CI 0·79, 1·45; $I^2 = 44\,\%$; $P = 0{\cdot}67$). In addition, continuous outcomes were consistent while meta-analysed with standard mean difference, and all outcomes remained stable in intention-to-treat analysis. No significant differences were observed in the two groups between death rate, adverse events or recovery times of severe pneumonia indicators. Our results suggested that adjunct treatment with Zn failed to benefit young children in the treatment of severe pneumonia. Considering the clinical heterogeneity, baseline characteristics of children, definition of severe pneumonia and Zn supplement way should be taken into consideration in future research. This study was registered at PRESPERO as CRD42015019798.

Key words: Children: Meta-analyses: Severe pneumonia: Zinc

Pneumonia is a leading disease and cause of death in children under 5 years in developing countries[1]. It is reported that 14·9 % of 6·3 million deaths of children <5 years old were caused by pneumonia worldwide[2]. With advances in medicine, economy and society, pneumonia with diarrhoea and measles was responsible for half of the reduction in mortality of children under 5 years from 2000 to 2013[2]. Although great progress was achieved, only a few countries could reach the goal of Millennium Development Goal 4 to reduce under 5 child mortality by two-thirds between 1990 and 2015, and pneumonia is still the leading cause of child mortality[3]. Therefore, intensive effort should be made in the research of pneumonia.

Under-nutrition has been reported to be strongly associated with impaired immune response,[4] and it has been proven to be responsible for greater severity of pneumonia, prolonged course of disease and increased mortality of pneumonia[5]. Zn, as an important micro-element, has an essential role in cellular growth and immune defence, and its deficiency is associated with significant increased susceptibility to various infection pathogens[6–8]. In a randomised-controlled trial (RCT), Brooks *et al.*[9] first found that adjunct treatment with Zn could reduce the duration of syndromes of severe pneumonia and hospital length of stay (HLOS) in 270 children. This promising finding was consistently confirmed by three other RCT[10,11]. However, the study conducted by Wadhwa *et al.*[11] demonstrated that only very severe pneumonia rather than all severe pneumonia could benefit from Zn. In addition, a relatively large-sample RCT with 610 children found that Zn supplement could reduce the duration of severe pneumonia and the incidence of treatment failure only marginally but not statistically significantly[12]. Moreover, some other RCT suggested that adjunct treatment with Zn failed to show any beneficial effect in children with severe pneumonia[13–17].

Abbreviations: HLOS, hospital length of stay; RCT, randomised-controlled trial; RR, relative risk; HR, hazard ratio; SMD, standard mean difference; LRTI, lower respiratory tract infection.

* **Corresponding authors:** J.-L. Yu, fax +86 023 63635567, email yujialin486@sohu.com; Q.-C. Wu, fax +86 023 68811360, email qcwucq@163.com

† These authors contributed equally to the study.

Given the controversial effect of Zn and accumulating evidence from RCT, a meta-analysis is warranted[12]. We, therefore, performed a meta-analysis to evaluate the effect of Zn as an adjunct to antibiotics in children with severe pneumonia.

Methods

This study was conducted and reported in adherence to the Preferred Reporting Items for Systematic Reviews and Meta-analysis statement[18] (online Supplementary Material). PROSPERO database registration: CRD42015019798, http://www.crd.york.ac.uk/PROSPERO/

Literature search and search strategy

PubMed, Cochrane library and Embase databases were systematically searched (last search date: October 2015), with the search strategy conducted by combining MeSH terms and free terms related to severe pneumonia, children and Zn. No limitation was imposed. To avoid missing potentially relevant RCT, the reference lists of the retrieved studies and relevant reviews were manually searched. Conference abstracts that met the inclusion criteria were also eligible. Two investigators performed the study selection independently, and any disputes were solved by discussion and judged by the third investigator.

Inclusion criteria

Inclusion criteria were as follows: (1) population: children <5 years of age with severe pneumonia; (2) intervention: standard antibiotics treatment with Zn supplementation; (3) comparative intervention: standard antibiotics treatment; (4) study design: RCT.

Data extraction and outcome measure

Data extraction was performed by two investigators using a pre-designed Excel sheet. The extracted information was as follows: first author, publication year, location, recruitment period, sample size, children age, serum Zn concentration at admission, percentage of male, percentage of wheezing, standard antibiotics therapy, intervention of Zn, intervention of control and reported outcomes. Corresponding authors were contacted repeatedly while essential data were not available. The extracted information was collated by two investigators and rechecked by the third investigator.

The primary outcomes were the time to recovery from severe pneumonia, HLOS, change of antibiotics and treatment failure. Secondary outcomes included time to recovery from severe pneumonia indicators (tachypnoea, hypoxaemia, chest indrawing and fever), the death rate and adverse events (vomiting and deterioration).

Assessment for risk of bias

Risk of bias was evaluated by two authors in adherence to the guideline of *Cochrane handbook for systematic review of interventions*[19], and assessment items included selection bias, detection bias, reporting bias, blinded bias, outcome assessment bias and some other potential bias. Each item was assigned a value of 'high', 'unclear" or 'low', and the pooled risk of bias for one study was regarded as high (high risk of bias in one or more items), unclear (low or unclear risk of bias in all items) or low (low risk of bias in all items)[20].

Statistical analyses

Relative risks (RR) with 95 % CI were used for calculating the pooled estimate of dichotomous outcomes. Standard mean differences (SMD) with 95 % CI were used for calculating the pooled estimate of continuous outcomes. Continuous outcomes of time to recovery and HLOS were treated as time-to-event data and expressed as hazard ratios (HR) with 95 % CI in some studies, and thus HR with 95 % CI were also used to pool the results. For continuous data reported as medians with ranges, we used an elementary inequality and approximation to estimate the means and related variances[21]. Random-effects model was used in all meta-analyses. The Q test and I^2 statistic were applied to assess the heterogeneity among studies. It was perceived to have high heterogeneity ($I^2 \geq 75\,\%$), moderate heterogeneity ($50\,\% \leq I^2 < 75\,\%$) and low heterogeneity ($25 \leq I^2 < 50\,\%$)[22]. Sensitivity analysis was performed by excluding one study in each turn and pooling the remaining ones, to detect the influence of a single study on the overall estimate. In addition, intention-to-treat analysis was also conducted to avoid bias from missing participants. In intention-to-treat analysis, we assumed that all the missing participants did not experience the event for dichotomous data and imputed data of missing participants as the average difference according to control and Zn group separately for continuous data. We did not assess publication bias because fewer than ten studies were included. Review Manager version 5.1 (The Cochrane Collaboration, Software Update) was used for all statistical analyses and risk of bias. A value of $P < 0{\cdot}05$ was considered statistically significant, and $P < 0{\cdot}1$ for the significance level of the Q test.

Results

Literature search

Study selection and identification process are shown in Fig. 1. Through initial database search, 333 articles were identified after eliminating eighty-two duplications. A total of thirteen studies remained after screening titles/abstracts. Among the thirteen studies, four were excluded, of which one[23] was an advanced abstract of an included study, two[24,25] focused on children with severe acute lower respiratory tract infection (LRTI) but not severe pneumonia and one[26] used the same data from the included trial. Finally, nine RCT[9–17] were included.

Baseline characteristics and risk of bias

Baseline characteristics of included RCT are summarised in Table 1. The nine studies were published between 2004 and 2014, and all were conducted in developing countries. The sample sizes varied from 117 to 610, with a total of 2926. Severe pneumonia was defined mainly based on clinical syndromes

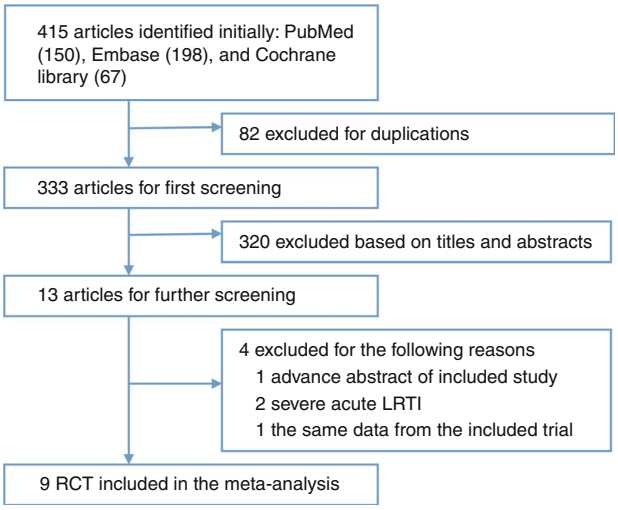

Fig. 1. Flowchart of study screening in this meta-analysis. LRTI, lower respiratory tract infection; RCT, randomised-controlled trial.

and signs according to the WHO criteria. The detailed definitions of severe pneumonia and outcomes are listed in online Supplementary Table S1. The intervention of Zn or placebo was given accompanied with standard antibiotics therapy. Children received 20 mg of Zn or placebo/d in five studies[9,12,14,16,17], whereas in other three studies[11,13,15] 10 mg of Zn or placebo was given for children <12 months and 20 mg for children ≥12 months. In the remaining one, Zn was given at a dose of 2 mg/kg per d, with a maximum of 20 mg/d[10]. The supplementation duration was 5–14 d or until discharge from a hospital. For primary outcomes, eight studies[9,10,12–17] reported time to recovery from severe pneumonia, with five[9,12–15] reporting HR and 95 % CI; five[9,10,14–16] reported HLOS, with three[9,14,15] reporting HR and 95 % CI; six[9,12,14–17] reported treatment failure; and five[9,12,14,16,17] reported change of antibiotics.

The risk of bias of nine RCT is shown in Fig. 2. Risk of bias of allocation concealment was unclear in one study[9], as there was no detailed description of the allocation methods. In addition, risk of bias was rated as unclear in detection bias because whether investigators, study nurses and caretakers were masked or not was not stated[16].

Primary outcomes

Compared with children in the control group, those who received Zn supplementation needed a similar period of time to recovery from severe pneumonia (HR = 1·04; 95 % CI 0·90, 1·19; $I^2 = 39\,\%$; $P_H = 0{\cdot}16$; $P = 0{\cdot}58$; Fig. 3) and HLOS (HR = 1·04; 95 % CI 0·82, 1·33; $I^2 = 57\,\%$; $P_H = 0{\cdot}10$; $P = 0{\cdot}74$; Fig. 3). No significant difference between Zn and placebo groups was found while analysing by pooling with SMD and 95 % CI (Table 2). In addition, no significant difference between the two groups was observed in risks of treatment failure (RR = 0·95; 95 % CI 0·79, 1·14; $I^2 = 20\,\%$; $P_H = 0{\cdot}28$; $P = 0{\cdot}58$; Fig. 3) or change of antibiotics (RR = 1·07; 95 % CI 0·79, 1·45; $I^2 = 44\,\%$; $P_H = 0{\cdot}13$; $P = 0{\cdot}67$; Fig. 3).

The primary outcomes were consistently non-significant when intention-to-treat analysis was used (online Supplementary Table S2). Moreover, sensitivity analysis also confirmed consistency and robustness of the pooled results (Table 3).

Secondary outcomes

Time to recovery from severe pneumonia indicators. The results by pooling HR with 95 % CI manifested that adjunct treatment with Zn could not decrease time to recovery from tachypnoea (HR = 1·04; 95 % CI 0·82, 1·33; $I^2 = 65\,\%$; $P_H = 0{\cdot}06$; $P = 0{\cdot}74$; Fig. 4), hypoxaemia (HR = 1·07; 95 % CI 0·89, 1·29; $I^2 = 28\,\%$; $P_H = 0{\cdot}25$; $P = 0{\cdot}49$; Fig. 4), chest indrawing (HR = 1·07; 95 % CI 0·80, 1·45; $I^2 = 58\,\%$; $P_H = 0{\cdot}12$; $P = 0{\cdot}64$; Fig. 4) or fever (HR = 0·97; 95 % CI 0·82, 1·16; $I^2 = 0\,\%$; $P_H = 0{\cdot}66$; $P = 0{\cdot}77$; Fig. 4). In addition, these results were consistently non-significant while analysed by SMD and 95 % CI (Table 2).

Death rate and adverse events. Excluding children with HIV in one study[11], ten of 905 children in the Zn group and fifteen of 904 in the control group died, and the pooled RR was 0·69 (95 % CI 0·31, 1·52; $I^2 = 0\,\%$; $P_H = 0{\cdot}83$; $P = 0{\cdot}36$; Fig. 5) for the death rate. The adverse effects were also evaluated, and the results revealed that adjunct treatment with Zn was not associated with risk of clinical deterioration (RR = 0·89; 95 % CI 0·59, 1·34; $I^2 = 0\,\%$; $P_H = 0{\cdot}55$; $P = 0{\cdot}57$; Fig. 5) or vomiting (RR = 1·58; 95 % CI 0·99, 2·51; $P = 0{\cdot}05$; Fig. 5). Consistently, non-significant differences were observed when analysed by intention-to-treat analysis (online Supplementary Table S2).

Discussion

Main findings

Our meta-analysis of nine RCT with 2926 cases assessed the effect of Zn as an adjunct to antibiotics in children with severe pneumonia. The results suggested that adjunct treatment with Zn failed to reduce time to recovery from severe pneumonia, HLOS, treatment failure or change of antibiotics. In addition, adjunct treatment with Zn was not associated with reduced death rate, adverse events or time to recovery from severe pneumonia indicators, including tachypnoea, hypoxaemia, chest indrawing and fever. The continuous outcomes remained consistent when meta-analysed by pooling SMD and 95 % CI, and all outcomes remained stable in the intention-to-treat analysis.

Comparison with previous studies

A meta-analysis by Das *et al.*[27] indicated that no evidence supported the efficacy of Zn as an adjunct to antibiotic in the treatment of severe acute LRTI. The relative broad scope of LRTI could certainly contribute to substantial clinical heterogeneity, and it might be associated with the significant heterogeneity (time to recovery from severe illness: $I^2 = 82\,\%$, HLOS: $I^2 = 82\,\%$). As only a few studies assessed the effect of Zn as an adjunct to antibiotic for the treatment of LRTI, we defined our inclusion criteria as severe pneumonia rather than LRTI, to

Table 1. Baseline characteristics of the included randomised-controlled trials (RCT)
(Mean values and mean differences (MD); medians and interquartile ranges (IQR))

		Zn/control					
First author year	Country Period	Number of children Age (months) Serum Zn (μmmol/l)	Wheezing (%) Male (%)	Standard antibiotics therapy	Intervention of Zn	Control	Reported outcomes
Basnet 2012[12]	Nepal 8 January 2006– 30 June 2008	305/305 7·8 (MD 6·0)/7·1 (MD 5·6) NR	81·6/82·9 59·2/63·6	Benzyl penicillin + gentamicin intravenously until clinical improvement, and then oral amoxicillin for a total duration of 10 d	10 mg (2–11 months)/ 20 mg (>11 months)/d until discharge or for a maximum of 14 d	Placebo	Time to recovery from severe pneumonia, treatment failure and vomiting
Bose 2006[14]	India 15 September 2003– 31 August 2004	150/150 9·9 (MD 6·1)/9·1 (MD 5·7) 11·0 (MD 2·2)/10·9 (MD 2·4)	62·7/62·4 71·3/67·3	Benzylpenicillin + gentamicin/ cloxacillin and gentamicin (staphylococcal pneumonia) intravenously	20 mg/d until discharge or for a maximum of 14 d	Placebo	Time to recovery from severe pneumonia, tachypnoea, hypoxaemia, chest indrawing and fever, HLOS, treatment failure, death, change of antibiotics
Brooks 2004[9]	Bangladesh 23 August 1990– 19 August 2001	135/135 9·5 (MD 6·2)/9·6 (MD 6·0) 10·1 (MD 1·1)/10·1 (MD 1·0)	38·5/36·3 59·2/71·1	Ampicillin + gentamicin intravenously	20 mg/d until discharge	Placebo	Time to recovery from severe pneumonia, tachypnoea, hypoxaemia and chest indrawing, HLOS, treatment failure, death, change of antibiotics and vomiting
Sempertegui 2014[17]	Ecuador February 2008– April 2010	225/225 13·1 (MD 10·3)/13·0 (MD 11·3) 76·4 (MD 27·2)/74·2 (MD 24·9) (μg/dl)	16/15·1 53·3/55·1	Ampicillin (<2 years)/ penicillin (≥2 years) intravenously	20 mg/d until discharge	Placebo	Time to recovery from severe pneumonia, tachypnoea, hypoxaemia and chest indrawing, treatment failure, death, change of antibiotics and deterioration
Shah 2012[16]	Nepal June 2008– August 2009	64/53 9 (IQR 5·0–14·7)/10 (IQR 6·0–18·5) NR	67·2/74·5 67/62·3	Cefotaxime + gentamicin (age <1 year)/cefotaxime (>1 year) intravenously	20 mg/d for 7 d	Placebo	Time to recovery from severe pneumonia, hypoxaemia, HLOS, treatment failure and change of antibiotics
Srinivasan 2012[13]	Uganda September 2006– March 2007	176/176 17·9 (MD 12·2)/18·1 (MD 11·8) 4·4 (IQR 1·3–8·0)/4·8 (IQR 2·3–10·4)	NR/NR 55·7/56·8	Chloramphenicol or ceftriaxone intravenously for 7 d	10 mg (<12 months)/ 20 mg (≥12 months)/d for a maximum of 7 d	Placebo	Time to recovery from tachypnoea, hypoxaemia, fever and death
Valavi 2011[10]	Iran December 2008– January 2009	64/64 15·41/15·89 NR	NR/NR 54·1/51·6	Ampicillin/intravenous cefazolin (staphylococcal pneumonia) intravenously	2 mg/kg per d, maximum 20 mg/d for 5 d	Placebo	Time to recovery from severe pneumonia, tachypnoea, fever and HLOS
Valentiner-Branth 2010[15]	Nepal 1 January 2004– 30 June 2007	55/56 4 (IQR 3–6)/4 (IQR 3–6) 8·1 (MD 2·9)/8·9 (MD 2·2)	89/88 58/64	Benzylpenicillin intravenously for 3 d/oral amoxycillin for a total of 5 more days	10 mg/d for 14 d	Placebo	Time to recovery from severe pneumonia, HLOS, treatment failure
		19/19 16 (IQR 14–26)/16 (IQR 13–22) 13 (MD 13)/7·9 (MD 1·5)	84/84 42/68		20 mg/d for 14 d		
Wadhwa 2013[11]	India February 2007– March 2010	274/276 5·5 (IQR 3–10)/5 (IQR 3–10) 9·3 (MD 3·9)/9·2 (MD 3·6)	54·7/54·7 64·2/70·3	Ampicillin + aminoglycoside (severe)/third generation cephalosporin (very severe) intravenously	20 mg/d until recovery or for a maximum of 14 d	Placebo	Time to recovery from severe pneumonia, treatment failure, death, change of antibiotics and deterioration

NR, not reported; HLOS, hospital length of stay.

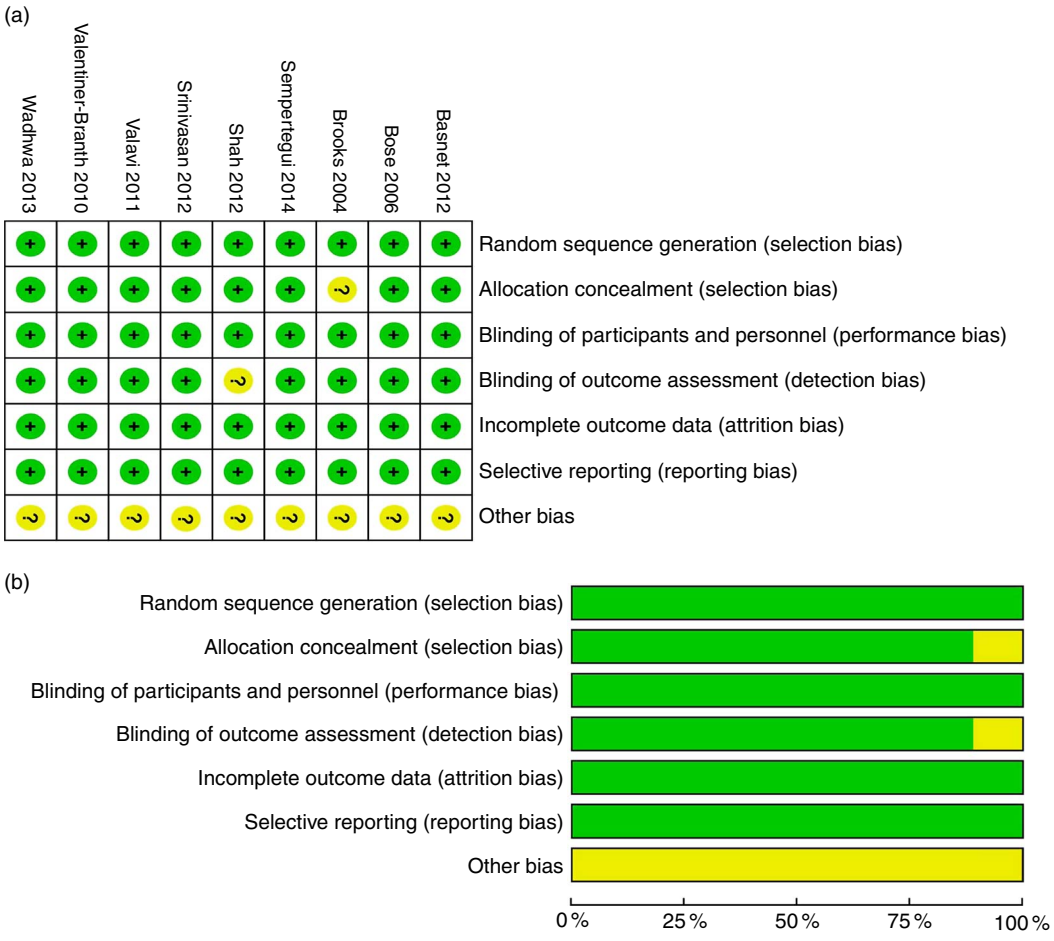

Fig. 2. Risk of bias of the included randomised-controlled trial (RCT). (a) Reviewers' judgments about each risk of bias item; (b) each risk of bias item presented as percentages. ■, Low risk of bias; ■, unclear risk of bias.

decrease potential heterogeneity. In addition, the heterogeneities in outcomes of time to recovery from tachypnoea ($I^2 = 77\%$), time to recovery from fever ($I^2 = 77\%$) and change of antibiotics ($I^2 = 52\%$) were statistically significant, and thus it was not appropriate to use a fixed-effects model for meta-analysis. Furthermore, the previous meta-analysis[27] used SMD and 95% CI for continuous outcomes (time to recovery), and it would be more appropriate to treat them as time-to-event data and calculate with HR and 95% CI. For dichotomous outcomes, RR, rather than OR, should be used, as the event rates were relatively high in the included RCT.

Another meta-analysis conducted by Theodoratou *et al.*[28] was praised to express intervention effect as HR with 95% CI. However, only two studies with 463 children were included. Moreover, it is unreasonable to exclude children with wheezing in the study by Brooks *et al.*[9], as wheezing is a common sign of severe pneumonia in children[29]. Furthermore, significant heterogeneity was observed in all outcomes. A Cochrane review was also performed to assess the adjunct effect of Zn in the treatment of severe pneumonia. Nevertheless, only four RCT were included, and three of them were involved in quantitative analysis[30]. The author found that adjunct treatment with Zn failed to reduce time to recovery from severe pneumonia (HR = 1·12; 95% CI 0·89, 1·41) by combining two studies with 408 children or HLOS (HR = 1·04; 95% CI 0·89, 1·22) by pooling three studies with 707 children. However, substantial heterogeneity was observed ($I^2 = 73\%$; $P_H = 0{\cdot}05$ and $I^2 = 56\%$; $P_H = 0{\cdot}1$, respectively) and inappropriate fixed-effect model was used. Considering the statistical heterogeneity, random-effects model should be used to give a wider CI. In both previous meta-analyses[28,30], clinical outcomes such as treatment failure, changes of antibiotics, death rate and adverse events were not analysed.

Our study generally agreed with and further extended the previous meta-analyses[27,28,30] in several important aspects. We particularly appraised the effect of Zn as an adjunct to antibiotics in children with severe pneumonia and reinforced the earlier results[30] by adding six new RCT with 2207 cases. In our study, the outcomes of time to recovery were meta-analysed as time-to-event data (HR), and the results were consistent with the pooled estimates when analysed as continuous variables (SMD). The consistency undoubtedly consolidated our results. Moreover, sensitivity analysis was performed for the primary outcomes, and intention-to-treat analysis was used for all outcomes, and the null association still remained stable. Furthermore, other meaningful outcomes, such as treatment failure, change of antibiotics, death, vomiting and clinical deterioration, were also analysed.

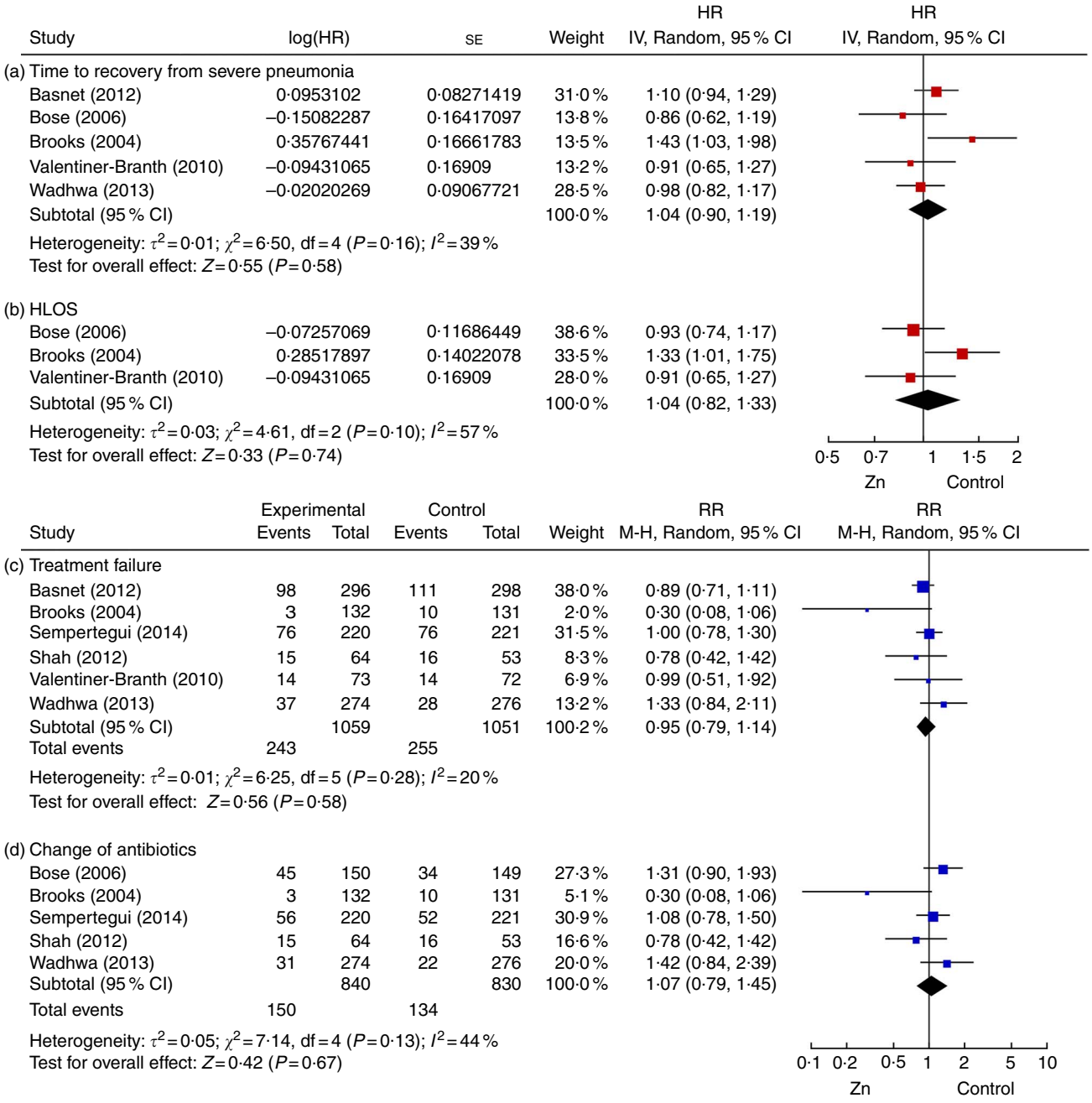

Fig. 3. Forest plots of the effects of zinc as an adjunct to antibiotics on outcomes of (a) time to recovery from severe pneumonia, (b) HLOS, (c) treatment failure and (d) change of antibiotics. HLOS, hospital length of stay; HR, hazard ratio.

Table 2. The pooled results of continuous variable as standard mean differences (SMD) (95 % confidence intervals)

Outcomes	Number of trials	Number of patients	I^2 (%)	P_H	SMD	95 % CI	*P*
Primary outcomes							
Time to recovery from severe pneumonia (9, 10, 12–17)	8	2447	81	<0·001	–0·02	–0·21, 0·17	0·82
HLOS (9, 10, 14–16)	5	947	75	0·001	–0·14	–0·42, 0·13	0·31
Secondary outcomes							
Time to recovery from tachypnoea (9–11, 14, 17)	5	1439	75	0·003	–0·11	–0·33, 0·10	0·3
Time to recovery from hypoxaemia (9, 11, 14, 16, 17)	5	1414	0	0·41	0·03	–0·07, 0·14	0·53
Time to recovery from chest indrawing (9, 14, 17)	3	961	14	0·31	–0·07	–0·20, 0·07	0·33
Time to recovery from fever (10, 11, 14)	3	774	68	0·05	–0·14	–0·40, 0·12	0·29

P_H, *P* for heterogeneity.

Table 3. The results of sensitivity analysis for the primary outcomes (Hazard ratios (HR), standard mean difference (SMD), relative risk (RR) and 95 % confidence intervals)

Outcome	ES (min)	95 % CI	I^2 (%)	*P*	ES (max)	95 % CI	I^2(%)	*P*
Time-to-event data				HR (95 % CI)				
Time to recovery from severe pneumonia (9, 12–15)	1·01	0·91, 1·12	0	0·89	1·07	0·92, 1·24	40	0·36
HLOS (9, 14, 15)	0·92	0·76, 1·11	0	0·41	1·11	0·77, 1·61	66	0·57
Continuous variables				SMD (95 % CI)				
Time to recovery from severe pneumonia (9, 10, 12–17)	−0·08	−0·27, 0·10	77	0·36	0·05	−0·10, 0·21	68	0·48
HLOS (9, 10, 14–16)	−0·18	−0·51, 0·14	79	0·26	−0·00	−0·14, 0·14	0	1
Dichotomous variables				RR (95 % CI)				
Treatment failure (9, 12, 13, 15–17)	0·91	0·78, 1·06	0	0·24	0·97	0·74, 1·28	29	0·85
Change of antibiotics (9, 12, 14, 16, 17)	0·96	0·64, 1·45	51	0·86	1·15	0·93, 1·42	0	0·19

ES, effect size; min, minimum; max, maximum; HR, hazard ratios; HLOS, hospital length of stay; SMD, standard mean difference; RR, relative risk.

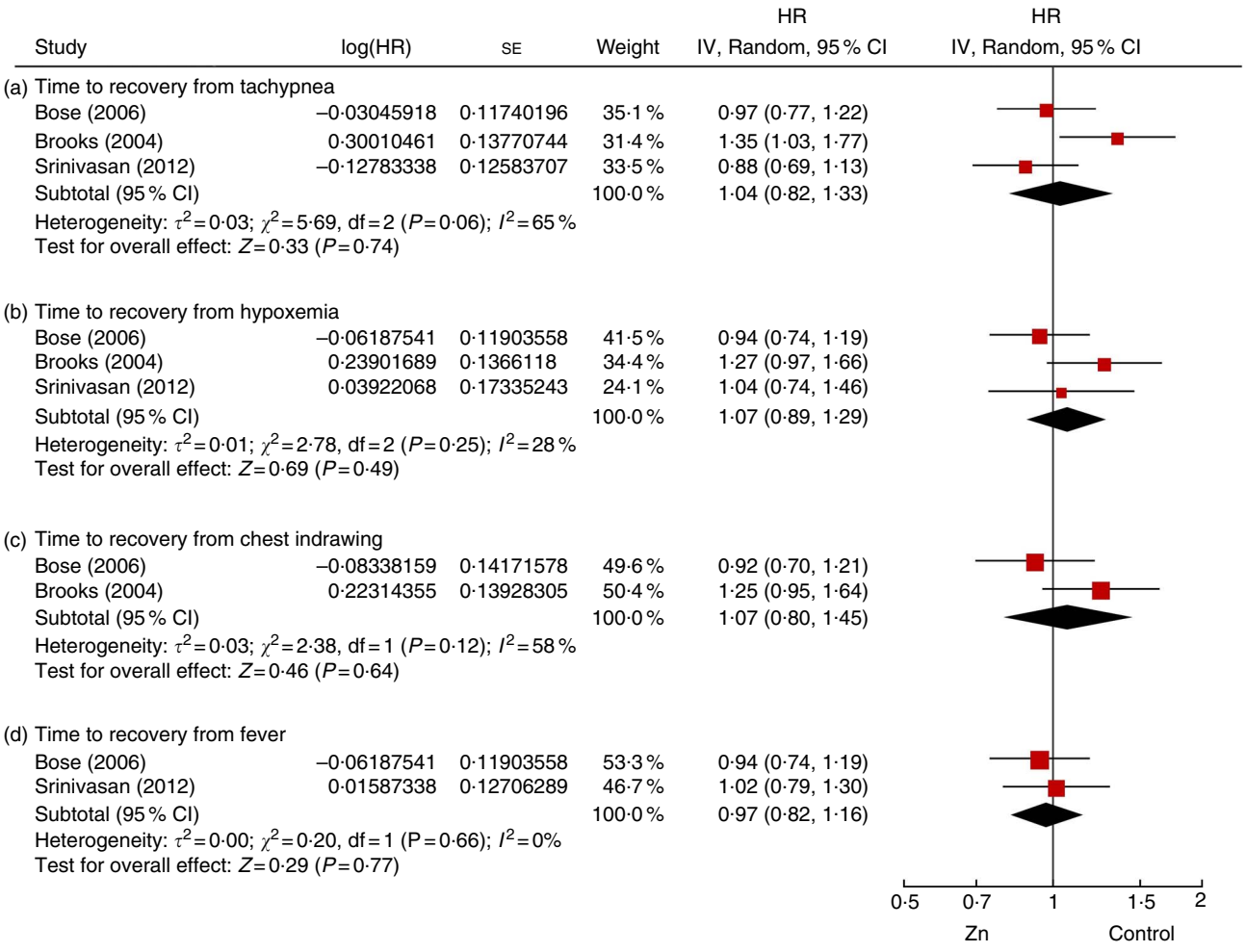

Fig. 4. Forest plots of the effects of zinc as an adjunct to antibiotics on outcomes of (a) time to recovery from tachypnoea, (b) hypoxaemia, (c) chest indrawing and (d) fever. HR, hazard ratio.

Potential mechanism

Zn has a crucial role in immune response, including the activation of polymorphonuclear cells, macrophages, natural killer cells, T cell, antibody production, the balance of T helper lymphocyte and immune defence-specific protein synthesis[9,31]. Plasma Zn decreases during the acute phase response because of the mobilisation and sequestration of Zn to metallothionein[32], and hence Zn supplementation in the treatment of severe pneumonia might be associated with a robust immune response and consequently a better prognosis. However, no effect of Zn in the treatment of severe pneumonia was observed in current meta-analysis. It might be explained by the following hypotheses. First, respiratory system, different from the digestive system, is sterile below the larynx in normal circumstance, and tissue damage could be caused by Zn-induced robust host response[33].

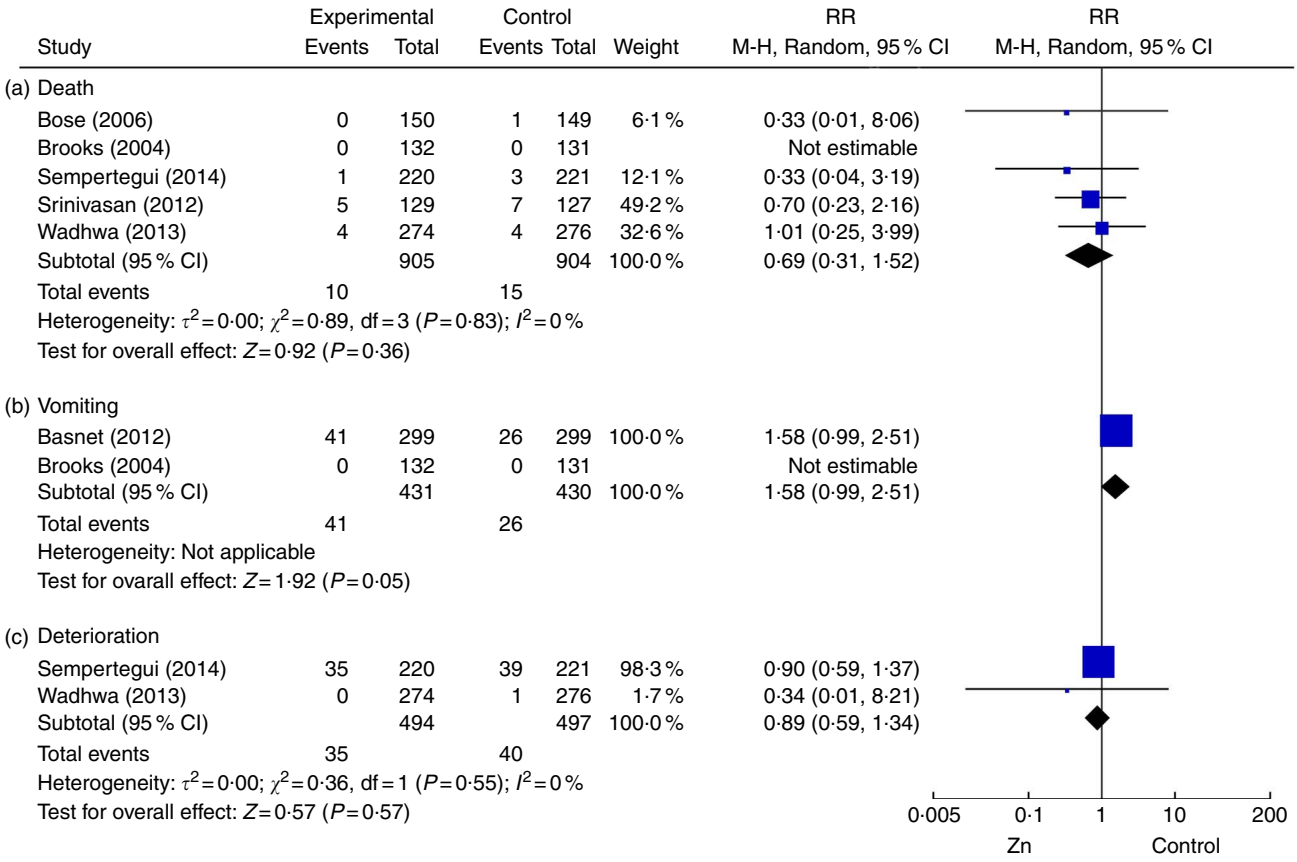

Fig. 5. Forest plots of the effects of zinc as an adjunct to antibiotics on outcomes of (a) death rate, (b) vomiting and (c) deterioration. RR, relative risk.

Thus, the decreased inflammatory signs might actually favour the clinical recovery of severe pneumonia[34]. Second, Zn might exacerbate the situation by the increased pro-inflammation while eradicating infection. Consistently, it was reported that Zn could decrease the case fatality and treatment failure without improving clinical recovery[11,35], indicating that the benefit of Zn might be counteracted or alleviated by the detrimental effect from increased pro-inflammation. Third, the duration of Zn supplementation was relatively short, and the impaired immune response could not be reversed by such a short-time supplementation[17]. Finally, the varied results from studies and subgroup analyses[9–17] could be attributed to the differences in population characteristics, intervention of Zn supplementation, outcome measures and location and period of the study, all of which could confound the effect of Zn in the treatment of severe pneumonia.

Limitations

Several limitations should be taken into account. First, several studies expressed the primary outcomes of time to recovery from severe pneumonia and HLOS as continuous variables. Although corresponding authors were contacted repeatedly, results from time-to-event analysis were not obtained in several RCT. The missing data might also induce bias, but the results obtained by pooling HR with 95 % CI were consistent with that obtained from pooling SMD with 95 % CI. Second, significant heterogeneity was found in HLOS and secondary outcomes. To test the robustness of results, sensitivity analysis and intention-to-treat analysis were used, and all the results remained consistent. Third, age, sex and nutrition status of children[9,10,17], the aetiology, definition, severity and recovery criteria of severe pneumonia[9,12,13], the dose, timing and duration of Zn supplementation and the location and season of study[10,14] have been reported to influence the effect of Zn in treatment of severe pneumonia. However, subgroup analysis was not performed because of the limited number of included studies.

Future direction

Some valuable evidence could be obtained from our meta-analysis. Both previous researches and our results demonstrated that Zn supplementation could increase the incidence of vomiting. However, it is usually limited and slight, and thus proper dose of Zn should be recommended without much concern about the increasing incidence of vomiting. Although there was a reduction of 31 % case-fatality rate in the Zn group, no statistical significance was observed. As only twenty-five deaths were involved, low statistical power might be attributed to, and high-quality and large-scale RCT are still needed. In addition, future studies should take nutrition status of children, breast-feeding time, aetiology of pneumonia, the dose, timing and duration of Zn supplementation into consideration. Moreover, clinical outcomes of vomiting, feeding difficulty, clinical

deterioration and need for intensive care should also be evaluated.

Conclusion

In conclusion, our meta-analysis suggested that adjunct treatment with Zn failed to show beneficial effect for the treatment of severe pneumonia in children <5 years old. However, this conclusion should be interpreted cautiously because of clinical heterogeneity across studies, and high-quality and large-scale RCT are still needed before making any definite conclusion. In addition, some confounding factors and valuable clinical outcomes should also be considered.

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The authors' responsibilities were as follows: H.-T. T. designed the conception, conducted the search, collected the data, assessed the quality of included studies, analysed and interpreted the data and drafted the manuscript. Q. T. conducted the search, assessed the quality of included studies, analysed and interpreted the data and revised the intellectual content. M.-Z. L. collected the data, assessed the quality of included studies and conducted the statistical analysis. Q. L. collected the data and revised the intellectual content. J.-L. Y. designed the conception, analysed and interpreted the data and revised the intellectual content. Q.-C. W designed the conception, analysed and interpreted the data and revised the intellectual content. All authors read and approved the final manuscript.

The authors declare that there are no conflicts of interest.

Supplementary material

For supplementary material/s referred to in this article, please visit http://dx.doi.org/doi:10.1017/S0007114515005449

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