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The effect of case management on childhood pneumonia mortality in developing countries

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Background With the aim of populating the Lives Saved Tool (LiST) with parameters of effectiveness of existing interventions, we conducted a systematic review of the literature assessing the effect of pneumonia case management on mortality from childhood pneumonia.

Methods This review covered the following interventions: community case management with antibiotic treatment, and hospital treatment with antibiotics, oxygen, zinc and vitamin A. Pneumonia mortality outcomes were sought where available but data were also recorded on secondary outcomes. We summarized results from randomized controlled trials (RCTs), cluster RCTs, quasi-experimental studies and observational studies across outcome measures using standard meta-analysis methods and used a set of standardized rules developed for the purpose of populating the LiST with required parameters, which dealt with the issues of comparability of the studies in a uniform way across a spectrum of childhood conditions.

Results We estimate that community case management of pneumonia could result in a 70% reduction in mortality from pneumonia in 0–5-year-old children. In contrast treatment of pneumonia episodes with zinc and vitamin A is ineffective in reducing pneumonia mortality. There is insufficient evidence to make a quantitative estimate of the effect of hospital case management on pneumonia mortality based on the published data.

Conclusion The available evidence reinforces the effectiveness of community and hospital case management with World Health Organization-recommended antibiotics and the lack of effect of zinc and vitamin A supportive treatment for children with pneumonia. Evidence from one trial demonstrates the effectiveness of oxygen therapy but further research is required to give higher quality evidence so that an effect estimate can be incorporated into the LiST model. We identified no trials that separately evaluated the effectiveness of

other supportive care interventions. The summary estimates of effect on pneumonia mortality will inform the LiST model.

Keywords childhood pneumonia, case management, community, hospital, developing countries

Background

According to a UNICEF–World Health Organization (WHO) report from 2006, over 2 million children die from pneumonia each year, accounting for almost one in five under-5 deaths worldwide.[1] Globally, the estimated incidence of clinical pneumonia in children aged <5 years in developing countries is 0.28 episodes per child-year, whereas in developed countries it is 0.05 episodes per child-year.[2,3] Thus, ~155 million episodes of clinical pneumonia occur in children <5 years of age annually.

As part of the primary care approach, children with pneumonia require access to good-quality basic first-level care (community case management).[4] Based on current WHO guidelines it has been estimated that ~10% of children presenting with pneumonia, i.e. those with severe or very severe pneumonia, may require referral to a first referral or district hospital for hospital treatment. Since pneumonia is the leading cause of death in children <5 years of age, interventions to promote the prevention and treatment of pneumonia are an essential part of child survival efforts to achieve Millennium Development Goal 4.

Previous reviews by Sazawal and Black have studied the effect of community case management on pneumonia mortality and overall child mortality.[5,6] This article reviews a wider range of case management interventions and was conducted in a standard manner (adopted for a review of all child health interventions) following guidelines set by the Child Health Epidemiology reference Group (CHERG). The overall aim is to provide parameters needed for the Lives Saved Tool (LiST) software to model the preventable deaths childhood pneumonia and to document all steps of this process in a transparent manner, thus assisting the wider acceptance of the LiST tool.

Methods

Identification and selection of studies

We attempted to identify all randomized controlled trials (RCTs), cluster RCTs (cRCTs), quasi-experimental studies and observational studies investigating the effect of community and hospital case management on pneumonia mortality and other pneumonia-related outcomes in children <5 years old. Studies were identified from the following databases: Medline (1970 to August 2008), EMBASE (1970 to August 2008) and the Web of Knowledge (1970 to August 2008; only for the community case management review). Details of the exact search strategies used to identify relevant studies for (i) the community case management and (ii) hospital case management [including (a) antibiotic treatment for (very) severe pneumonia, (b) oxygen treatment, (c) treatment with zinc supplements and (d) treatment with vitamin A supplements are presented in Supplementary Tables S1 and S2]. In addition, relevant studies were identified by searching the references of the selected studies. Eligible studies were selected according to the pre-determined inclusion criteria.[7] In particular: (i) included studies (a) were RCTs, cRCTs, quasi-RCTs or observational studies and (b) had a control arm of placebo or no treatment; (ii) children of included studies were (a) <5 years old, (b) were followed up until ⩾2 years of age (in experimental studies; not applicable for the case–control studies) and (c) had a clear case definition consistent with pneumonia.[2]

Due to the nature of the hospital-based interventions under review, no RCTs were identified as it would not be ethical to conduct such studies. Therefore observational studies were sought according to the following inclusion criteria: developing country setting; clear case definition of pneumonia (severe or very severe as defined by WHO); children <5 years of age; sample size of 100 or more; intervention is well defined (in terms of dose, administration, frequency of delivery). The following exclusion criteria were applied: ambulatory treatment for non-severe pneumonia; no data on deaths available; selective groups of preschool children [e.g. malnourished, human immunodeficiency virus (HIV) positive, specific pneumonia pathogens isolated) studied (Supplementary Table S3)].

The main types of outcome measures for community case management were: pneumonia-specific mortality, all-cause mortality and incidence of moderate or severe episodes of acute lower respiratory infection (ALRI). The main outcomes for the hospital case management studies were (i) for antibiotic treatment studies: intervention case fatality ratios and treatment failure rates; (ii) for oxygen treatment study: all-cause mortality of children with pneumonia; (iii) for studies of zinc supplement treatment: length of hospitalization, time to resolution of severe illness, lethargy, inability to eat, low oxygen saturation, chest indrawing and tachypnoea; and (iv) for studies of vitamin A supplement treatment: all-cause mortality of children with pneumonia, length of hospitalization and time to resolution of low oxygen saturation and tachypnoea. There were no language or publication restrictions.

One original and one parallel review were conducted by independent investigators and results from the two searches and study selections were compared and merged.

Abstraction, quality assessment and meta-analyses

Data from all studies that met final inclusion and exclusion criteria were abstracted into a standardized form for each outcome of interest. We abstracted key variables with regard to the study identifiers and context, study design and limitations, intervention specifics and outcome effects. The quality of each study was assessed and graded according to the CHERG adaptation of the GRADE technique ('GRADE Profiler version 3.2' scoring system) (Supplementary Table a).

We summarized the evidence by outcome including qualitative assessment of the quality of each specific outcome (Supplementary Table b). In addition, for any outcome with more than one study, a meta-analysis was conducted and pooled relative risk and corresponding 95% confidence interval (CI) reported using the fixed-effect model (Mantel–Haenszel method).[8] In the case of heterogeneity ($P < 0.1$), the random effect model (DerSimonian–Laird method) was applied (although it is recognized that due to the variation in precise interventions, study methods and outcome definitions, the meta-estimates should be interpreted cautiously). All analyses were conducted using STATA 10.0 statistical software.

For the outcome of interest, namely the effect of community case management with antibiotics, oxygen treatment, zinc treatment and vitamin A treatment on pneumonia mortality, we applied the CHERG Rules for Evidence Review to the collective pneumonia morbidity and mortality outcomes to generate a final estimate for the reduction in pneumonia mortality (Supplementary Table c).

Results

Community case management

We identified 154 titles from the search conducted in Medline, 87 from Embase and 62 from Web of Knowledge. After elimination of duplicates, studies with alternative outcome parameters, review articles and studies that did not fit the inclusion criteria, a total of 12 studies were extracted from the bibliographic databases[9–20] and two studies were identified from a published meta-analysis[21,22] (Supplementary Figure S1). The characteristics of the studies that were identified to estimate the effect of community case management on pneumonia mortality are presented in Supplementary Table S4. A summary of the identified outcomes as well as their exact definitions are presented in Supplementary Table S5. Two of the identified studies[10,20] did not report enough data, and therefore they were not included in the meta-analyses. In addition, although four studies reported data on the effect of community case management with antibiotics on incidence of moderate/severe episodes of ALRI, a morbidity analysis was not performed because the signs they used to identify ALRI were either reported by the child's mother,[12,15] or were not based on the WHO classification (mild, moderate, severe),[17] or were not specified.[9]

In Table 1, we report the quality assessment of studies by outcome, as well as results from corresponding meta-analyses for the effect of community case management with antibiotic treatment on pneumonia-related outcomes. The summary effect of community case management with antibiotic treatment on ALRI mortality for children (i) 0–1-month-old after summarizing four concurrent studies[11,13,16,18] was 42% (95% CI 23–54%); (ii) 0–1-year-old after summarizing eight concurrent[11,14,16,18,19,22] and one before/after study[17] was 42% (95% CI 33–55%); (iii) 1–4 years old after summarizing two before/after studies[17,19] was 49% (95% CI −7 to 76%); and (iv) 0–5 years old after summarizing seven concurrent[11,13,14,16,18,19,22] and two before/after studies[9,17] was 35% (95% CI 18–48%) (Figure 1a). In addition, the summary effect of community case management with antibiotic treatment on all-cause mortality for children: (i) 0–1 month old after summarizing five concurrent studies[11,13,14,16,18] was 27% (95% CI 18–35%); (ii) 0–1 years old after summarizing eight concurrent[11,14,16,18,19,22] and one before/after study[17] was 21% (95% CI 14–28%); (iii) 1–4 years old after summarizing two before/after studies was[17,19] 51% (95% CI 30–66%); and (iv) 0–5 years old after summarizing eight concurrent[11,13,14,16,18,19,21,22] and two before/after studies[9,17] was 21% (95% CI 12–30%) (Table 1). According to the CHERG Rules 2 for Evidence Review in order to estimate the effect on pneumonia mortality, we used the effect of community case management with antibiotic treatment on ALRI mortality of children 0–5 years old (Figure 1b).

Hospital case management

Antibiotic treatment for (very) severe pneumonia

We identified 476 titles from the search conducted in Medline and 1241 from Embase. After elimination of duplicates, studies with alternative outcome parameters, review articles and studies that did not fit the inclusion criteria, a total of ten studies were extracted from the bibliographic databases[23–32] (Supplementary Figure S2a). These studies included two before/after studies and observational data (large case series conducted in a structured manner often as one arm of a clinical trial) and reported mortality outcomes. The characteristics of these studies are presented in Supplementary Table S6. A summary of the identified outcomes as well as their exact definitions are presented in Supplementary Table S7. We have not reported observational studies that reported

Table 1 Quality assessment of studies of community case management with antibiotic treatment on pneumonia related outcomes

No. of studies (ref.)	Quality assessment					No. of events		RR (95% CI)
	Design	Limitations	Consistency	Directness		Intervention	Control	
				Generalizability to population of interest	Generalizability to intervention of interest			
ALRI-specific mortality								
ALRI mortality 0–1 months: moderate outcome specific quality of evidence								
4[11,13,16,18]	Concurrent	No major	3 of 4 studies show benefit	Africa and Asia	3 of 4 studies WHO case management by local health workers or traditional birth attendants; 1 study other ARI case management	384	636	0.58 (0.44–0.77)
ALRI specific mortality 0–1 year: moderate outcome specific quality of evidence								
6 [11,13,1416,18,22]*†	Concurrent	Mainly no major limitations; in 1 study differences between study populations	Heterogeneity from meta-analysis ($P = 0.03$); All studies show benefit	Africa and Asia	4 of 6 studies WHO case management by local health workers or traditional birth attendants; 2 studies other ARI case management	916	1510	0.59 (0.46–0.75)
2 [14,17]†	Before/after	High ALRI incidence and differences between study populations	Heterogeneity from meta-analysis ($P = 0.06$). Both studies show benefit	Asia	1 of 2 studies WHO case management by local health workers; 1 study other ARI case management	7	34	0.36 (0.16–0.82)
7[11,13,14,16–18, 22]a	Concurrent; before/after	See above	Heterogeneity from meta-analysis ($P = 0.02$). All studies show benefit	Africa and Asia	See above	917	1522	0.57 (0.44–0.75)
9[11–14,16–19,22]	Concurrent; before/after	See above	Heterogeneity from meta-analysis ($P = 0.04$); All studies show benefit	Africa and Asia	See above	938	1569	0.58 (0.50– 0.67)
ALRI-specific mortality 1–4 years: low outcome specific quality of evidence								
2[17,19]	Before/after	High ALRI incidence and intervention and control area different baseline mortality rates	Both studies show benefit	Only Asia	1 of 2 studies WHO case management by local health workers; 1 study other ARI case management	10	24	0.51 (0.24–1.07)
ALRI-specific mortality 0-4 years: moderate outcome specific quality of evidence								
6[11,13,1416,18,22]†	Concurrent	Mainly no major limitations; in one study differences between study populations	Heterogeneity from meta-analysis ($P = 0.004$); 5 of 6 studies show benefit	Africa and Asia	4 of 6 studies WHO case management by local health workers or traditional birth attendants; 2 studies other ARI case management	1632	2546	0.64 (0.49–0.85)
5[9,14,16,17,18]†	Before/after	Mainly no major limitations; in one study	All studies show benefit	Africa and Asia	2 of 5 studies WHO case management by local	190	253	0.68 (0.56–0.82)

(continued)

Table 1 Continued

No. of studies (ref.)	Quality assessment					No. of events		RR (95% CI)
	Design	Limitations	Consistency	Directness: Generalizability to population of interest	Directness: Generalizability to intervention of interest	Intervention	Control	
		differences between study populations and in one study high ALRI incidence			health workers or traditional birth attendants; 3 studies other ARI case management			
8[9,11,13,14,16–18, 22]†	Concurrent; before/after	See above	Heterogeneity from meta-analysis ($P=0.003$); 7 of 8 studies show benefit	Africa and Asia	See above	1670	2584	0.64 (0.49–0.83)
9[9,16,17,11,14,18,19,13,22]	Concurrent; before/after	See above	Heterogeneity from meta-analysis ($P=0.006$); 8 of 9 studies show benefit	Africa and Asia	See above	1690	2630	0.65 (0.52–0.82)
All cause mortality								
All cause mortality 0–1months: moderate outcome specific quality of evidence								
5[11,13,14,16,18]	Concurrent	Mainly no major limitations; in 1 study differences between study populations	All studies show benefit	Africa and Asia	4 of 5 studies WHO case management by local health workers or traditional birth attendants; 1 study other ARI case management	925	957	0.73 (0.65– 0.82)
All-cause mortality 0–1 year: moderate outcome specific quality of evidence								
6[11,13,14,16,18,22]a,b	Concurrent	Mainly no major limitations; in 1 study differences between study populations	All studies show benefit	Africa and Asia	4 of 6 studies WHO case management by local health workers or traditional birth attendants; 2 studies other ARI case management	2095	2487	0.78 (0.71– 0.85)
2[17,19] b	Before/after	High ALRI incidence and differences between study populations	Both studies show benefit	Only Asia	1 of 2 studies WHO case management by local health workers; 1 study other ARI case management	41	100	0.60 (0.42–0.85)
7[11,13,14,16–18, 22]*a,b	Concurrent; before/after	See above	All studies show benefit	Africa and Asia	See above	2114	2524	0.77 (0.70– 0.85)
9[11–14,16–19,22]	Concurrent; before/after	See above	All studies show benefit	Africa and Asia	See above	2230	2703	0.79 (0.72–0.86)
All-cause mortality 1–4 years: low outcome specific quality of evidence								
2[17,19]	Before/after	High ALRI incidence and intervention and control area different baseline mortality rates	Both studies show benefit	Only Asia	1 of 2 studies WHO case management by local health workers; 1 study other ARI case management	43	82	0.49 (0.34–0.70)

(continued)

Table 1 Continued

No. of studies (ref.)	Quality assessment					No. of events		RR (95% CI)
	Design	Limitations	Consistency	Directness: Generalizability to population of interest	Directness: Generalizability to intervention of interest	Intervention	Control	
All-cause mortality 0–4 years: moderate outcome specific quality of evidence								
7[21,16,11,18,13,22]b	Concurrent	Mainly no major limitations; in 1 study differences between study populations	Heterogeneity from meta-analysis ($P=0.01$); All studies show benefit	Africa and Asia	4 of 7 studies WHO case management by local health workers; 3 studies other ARI case management	4558	5563	0.76 (0.67–0.86)
5[9,14,16–18]b	Before/after	Mainly no major limitations; in one study differences between study populations and in one study high ALRI incidence	All studies show benefit	Africa and Asia	2 of 5 studies WHO case management by local health workers or traditional birth attendants; 3 studies other ARI case management	984	919	0.75 (0.69–0.82)
9[9,11,13,14, 16–18, 21,22]b	Concurrent; before/after	See above	Heterogeneity from meta-analysis ($P=0.004$); 8 of 9 studies show benefit	Partly (Africa, Asia)	See above	4833	5760	0.77 (0.72–0.82)
10[21,16,17,11,14,18,19,13,9,22]	Concurrent; before/after	See above	Heterogeneity from meta-analysis ($P=0.001$); 9 of 10 studies show benefit	Africa and Asia	See above	4934	5932	0.79 (0.70–0.88)

[a]Datta *et al.*[12] excluded due to restriction in children of low birth weight.
[b]Reddaiah[19] excluded because intervention and control area different baseline mortality rates.

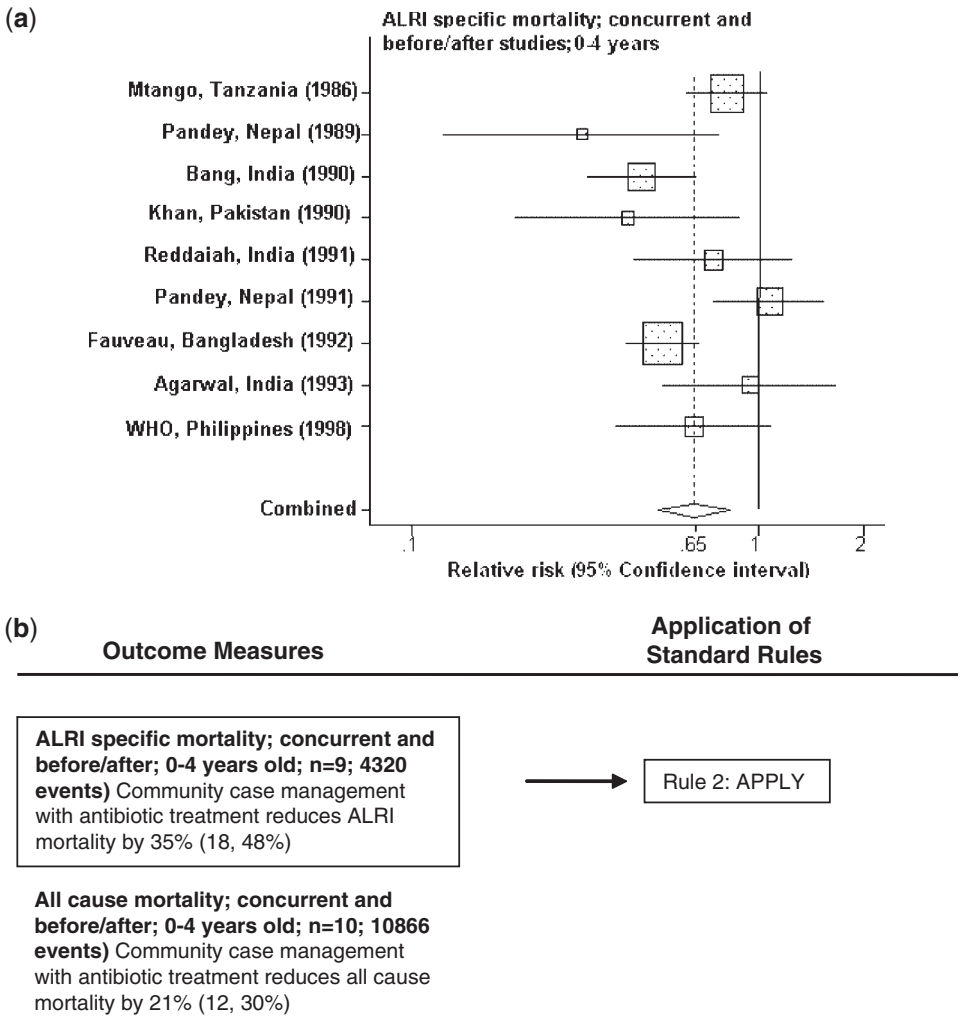

Figure 1 (a) Forrest plot for the effect of community case management with antibiotic treatment on ALRI mortality (concurrent and before/after studies; children 0–5 years old). (**b**) Application of standardized rules for choice of final outcome to estimate effect of community case management with antibiotic treatment for pneumonia.

other treatment outcomes such as failure to improve, need for change in antibiotic treatment or time to reduction in respiratory rate since these were applied in a non-standard manner that varied widely and had not a clear relationship to risk of mortality.

The reduction of the case fatality rate after the implementation of the WHO's standard acute respiratory infection (ARI) case management guidelines was 23% (–100%, 70%) based on the results of two before/after study.[26,32] The summary case fatality rate of antibiotics on severe pneumonia after summarizing four studies (3945 episodes)[28–31] was 0.6% (95% CI 0.4–0.9%) (Table 2 and Figure 2). These studies were conducted in developing countries including Columbia, Ghana, India, Mexico, Pakistan, South Africa, Vietnam, Uruguay and Zambia (between 1991 and 2006). The reported case fatality rates ranged from 0 to 1% and the antimicrobial agents used to manage these children included oral amoxicillin, oral co-trimoxazole, parenteral ampicillin, parenteral penicillin and macrolides (Supplementary Table S6). Some studies did not contain information on co-interventions; however, where specified, these included oxygen therapy, bronchodilators and antipyretics when indicated (Supplementary Table S6).

The summary case fatality rates of antibiotics on very severe pneumonia after summarizing four studies (5376 episodes)[23–27] were 6.5% (95% CI 4.3–9.6%) (Table 2 and Figure 2). These studies were conducted in developing countries including Bangladesh, Ecuador, India, Pakistan, Papua New Guinea, Mexico, South Africa, Yemen and Zambia (between 1979 and 2004). The reported case fatality rates ranged from 2 to 19% and it is evident that case fatality rates were higher in children <12 months old than in older children (Supplementary Table S6).

Oxygen treatment

We identified 213 titles from the search conducted in Medline and 172 from Embase. After elimination of

Table 2 Quality assessment of studies of hospital case management on pneumonia related outcomes: (i) Antibiotic treatment for (very) severe pneumonia, (ii) oxygen systems for treatment of pneumonia, (iii) zinc supplementation for treatment of pneumonia and (iv) vitamin A supplementation for treatment of pneumonia

No. of studies (ref.)	Quality assessment					No. of events		CFR (%)
	Design	Limitations	Consistency	Directness: Generalizability to population of interest	Directness: Generalizability to intervention of interest	After application of WHO ARI standard case management	Before application of WHO ARI standard case management	
(i) Antibiotic treatment for (very) severe pneumonia								
Deaths among ARI admissions: very low outcome specific quality								
2[26,32]	Before/after	No major	Heterogeneity from meta-analysis ($P < 0.0005$)	Asia	Benzyl penicillin or ampicillin (severe pneumonia), chloramphenicol (very severe pneumonia)	126	123	0.77 (0.30–2.00)

No. of studies (ref.)	Quality assessment					No. of events		CFR (%) (95% CI)
	Design	Limitations	Consistency	Directness: Generalizability to population of interest	Directness: Generalizability to intervention of interest	Episodes	Control	
Case fatality ratio of severe pneumonia: very low outcome specific quality								
5[28,29,30,31]		Mainly no major; in 1 study many cases treated as bacterial; in 1 study potential for outcome misclassification		Africa, Asia, S.America, C.America	Amoxicillin, ampicillin/ macrolides, penicillin,	19	n/a	0.6% (0.4–0.9%)
Case fatality ratio of very severe pneumonia: very low outcome specific quality								
10[23b,25,26a,27a]		In 1 study 28% were lost to follow up; In 1 study management protocol changed during course of study; in 1 study potential for misclassification of bacterial pneumonia	Heterogeneity from meta-analysis ($P < 0.0005$)	Africa, Asia, S.America, C.America	Chloramphenicol sodium succinate, benzylpenicillin, ampicillin, gentamicin, chloramphenicol	420	n/a	6.5% (4.3–9.6%)

(Continued)

Table 2 Continued

No. of studies (ref.)	Quality assessment					No. of events Median hours (95% CI)		RR (95% CI)
	Design	Limitations	Consistency	Directness: Generalizability to population of interest	Directness: Generalizability to intervention of interest	Intervention	Control	
(ii) Oxygen systems for treatment of pneumonia								
Risk of mortality of children with pneumonia: very low outcome specific quality								
1[33]	Before/after	Possibility of secular trends in mortality rate over time; ascertainment bias and altered thresholds for hospital admission	n/a	Only 1 study	Oxygen concentrators and pulse oximeters	133	356	0.65 (0.52–0.78)

No. of studies (ref.)	Quality assessment					No of events Median hours (95% CI)		Relative Risk (95% CI)
	Design	Limitations	Consistency	Directness: Generalizability to population of interest	Directness: Generalizability to intervention of interest	Intervention	Control	
(iii) Zinc supplementation for treatment of pneumonia								
Duration of hospitalization (hours): low outcome specific quality								
2[34,35]	RCT	No major	Heterogeneity from meta-analysis ($P=0.03$)	Only Asia; both studies 2–23 months	Zinc sulphate and acetate	23089.3 (57.2, 139.4)	23096.0 (54.8, 168.0)	0.87 (0.55–1.37)
Duration of severe illness (hours to resolution; inability to feed, O2 saturation <93%, and respiratory rate >50 breaths/min): low outcome specific quality								
2[34,35]	RCT	No major	Heterogeneity from meta-analysis ($P=0.02$)	Only Asia; both studies 2–23 months	Zinc sulphate and acetate	23085.5 (77.1, 94.8)	23082.9 (66.7, 103.1)	0.83 (0.48–1.44)
Duration of hypoxia (hours to resolution): low outcome specific quality								
2[34,35]	RCT	No major	Heterogeneity from meta-analysis ($P=0.08$)	Only Asia; both studies 2–23 months	Zinc sulphate and acetate	230 78.2 (63.2, 96.9)	230 82.6 (62.6, 109.0)	0.91 (0.64–1.29)
Duration of tachypnoea (hours to resolution; >50 breaths/min): low outcome specific quality								
4[34,35,37,38]	RCT	No major; 1 study more loss to follow-up in placebo	Heterogeneity from meta-analysis ($P=0.002$)	Only Asia; 3 of 4 studies 2–23 months; 1 study 9 months to 15 years	Zinc sulphate and acetate	309 68.9 (59.5, 79.7) 269[c] 68.2 (57.8, 80.5)	306 64.9 (51.4, 81.9) 268 64,1 (49,0, 83,7)	0.98 (0.70–1.37) 0.92 (0.62–1.37)

(Continued)

Table 2 Continued

No of studies (ref.)	Quality Assessment					No of events		RR (95% CI)
	Design	Limitations	Consistency	Directness		Intervention	Control	
				Generalizability to population of interest	Generalizability to intervention of interest			
(iv) Vitamin A supplementation for treatment of pneumonia								
Mortality: very low outcome specific quality								
6[40–45]	RCT	Mainly no major; in 1 study initial vitamin A status of children was unknown	3 of 6 studies show benefit, 2 show no effect and 1 show risk	Asia, Africa, S. America)	2 of 6 studies vitamin E in the vitamin A supplement	22	21	1.09 (0.59–2.04)
Duration of hospitalization (days): low outcome specific quality								
3[40,45,46]	RCT	Mainly no major; in 1 study initial vitamin A status of children was unknown	All studies show no effect	Asia, Africa, S.America; 1 study 3–119 months		6725.70 (5.37–6.05)	6955.67 (5.35–6.01)	0.04 (−0.40 to 0.48)
Duration of hypoxia (days to resolution): low outcome specific quality								
4[40,42–44]	RCT	No major	All studies show no effect	Africa, S. America	1 of 4 studies vitamin E in the vitamin A supplement	7131.75 (0.70–4.38)	7091.81 (0.77–4.27)	−0.02 (−0.16 to 0.12)
Duration of tachypnoea (hours to resolution; >50 breaths/min): low outcome specific quality								
5[40,42–45]	RCT	Mainly no major; in 1 study initial vitamin A status of children was unknown	All studies show no effect	Asia, Africa, S. America	1 of 5 studies vitamin E in the vitamin A supplement	10264.28 (4.08–4.49)	10374.15 (3.96–4.34)	0.05 (−0.21 to 0.31)

[a]Include both severe and very severe cases.
[b]The Zambia site of this multi-centre study was withdrawn from the study after 23 enrolments (2.4% of total) due to high mortality.
[c]Results after excluding the Mahalanabis *et al.*[37] study (due to the age range: 9 months to 15 years).

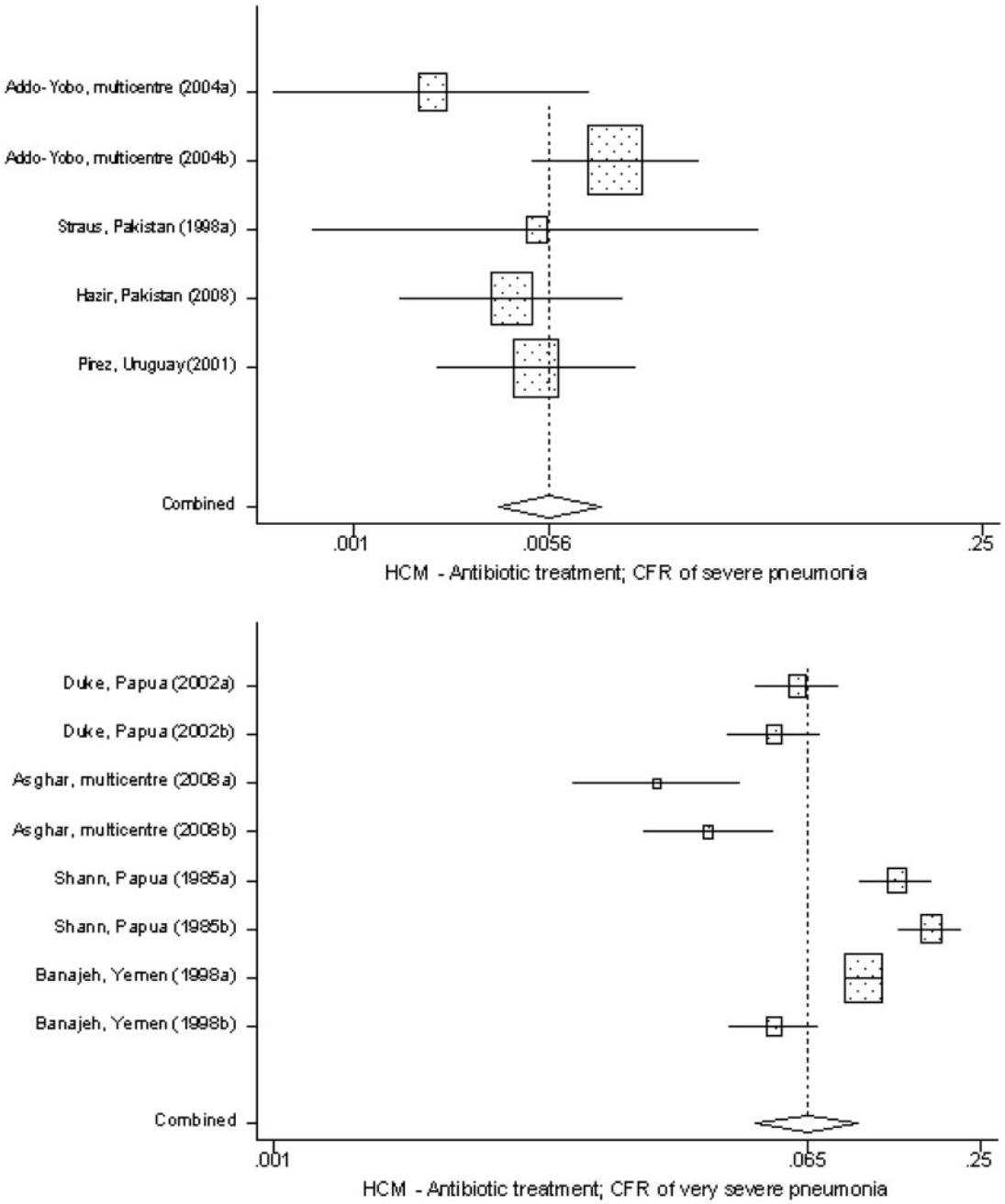

Figure 2 Forrest plot of case fatality rates of antibiotic treatment for (very) severe pneumonia.

duplicates, studies with alternative outcome parameters, review articles and studies that did not fit the inclusion criteria, one study was extracted from the bibliographic databases (Supplementary Figure S2b). The characteristics of this study[33] that were identified to estimate the effect of oxygen therapy on pneumonia mortality is presented in Supplementary Table S6. The exact definition of the outcome is presented in Supplementary Table S7. In Table 2, we report the quality assessment of the study as well as the effect of oxygen treatment on mortality for children with pneumonia (35%, 95% CI 22–48%).

Treatment with zinc supplements

We identified 55 titles from the search conducted in Medline and 153 from Embase. After elimination of duplicates, studies with alternative outcome parameters, review articles and studies that did not fit the inclusion criteria, a total of five studies were extracted

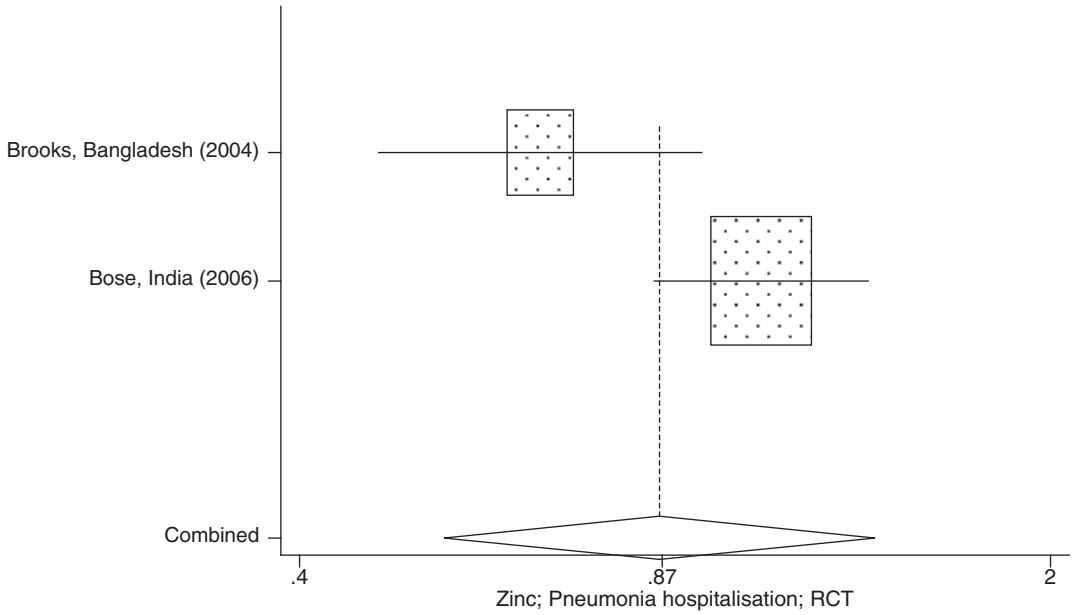

Figure 3 Forest plot for the effect of zinc supplementation for the treatment of pneumonia on the hours of hospitalization.

from the bibliographic databases[34–38] (Supplementary Figure S2c). The characteristics of the studies that were identified to estimate the effect of zinc supplementation on pneumonia-related outcomes are presented in Supplementary Table S6. A summary of the identified outcomes as well as their exact definitions are presented in Supplementary Table S7.

In Table 2, we report the quality assessment of studies by outcome, as well as results from corresponding meta-analyses for the effect of zinc supplementation treatment on pneumonia-related outcomes. Of the four outcomes related to the duration of pneumonia symptoms, the effect size ranged from 17% for hours to severe disease resolution (based on two RCTs[34,35]) to 2% for hours to tachypnoea resolution (based on four RCTs[34,35,37,38]). Since there were no mortality data in order to estimate the effect on pneumonia mortality, we used the hours of hospitalization effect based on the summary analysis of two RCTs[34,35] [13% (−37, 45%)] (according to the CHERG Rules for Evidence Review. Since there is not clear evidence of effect on pneumonia mortality this intervention against pneumonia will not be included in the LiST model) (Figure 3).

Treatment with vitamin A supplements

We identified 614 titles from the search conducted in Medline and 1099 from Embase. After elimination of duplicates, studies with alternative outcome parameters, review articles and studies that did not fit the inclusion criteria, a total of nine studies were extracted from the bibliographic databases[39–47] (Supplementary Figure S2d). The characteristics of the studies that were identified to estimate the effect of oxygen therapy on pneumonia mortality are presented in Supplementary Table S6. A summary of the identified outcomes as well as their exact definitions are presented in Supplementary Table S7.

In Table 2, we report the quality assessment of studies by outcome, as well as results from corresponding meta-analyses for the effect of vitamin A supplementation treatment on pneumonia-related outcomes. Although there was an estimate of mortality based on six studies[39,41–45] [−9% (95% CI − 104 to 41%)], the specific outcome quality was very low (since there were <50 total events) (Table 2). Therefore, according to the CHERG Rules 0 and 5 for Evidence Review in order to estimate the effect on pneumonia mortality, we used the summary effect of vitamin A on days of hospitalization, which was based on three studies[39,45,46] (weighted mean difference 0.04 (95% CI − 0.40 to 0.48). Since there is not clear evidence of the effect on pneumonia mortality, this intervention against pneumonia will not be included in the LiST model) (Figure 4). Regarding the other pneumonia-related outcomes, vitamin A supplementation had no effect on either duration of hypoxia resolution (weighted mean difference based on four studies[39,42–44] −0.02 (95% CI − 0.16 to 0.12)) or duration of tachypnoea resolution [weighted mean difference based on five studies[39,42–45] 0.05 (95% CI − 0.21 to 0.31)] (Table 2).

Other supportive care

We were unable to identify controlled trials or quasi-experimental studies or observational studies that met our study criteria, which are reported on the separate effect of supportive care interventions

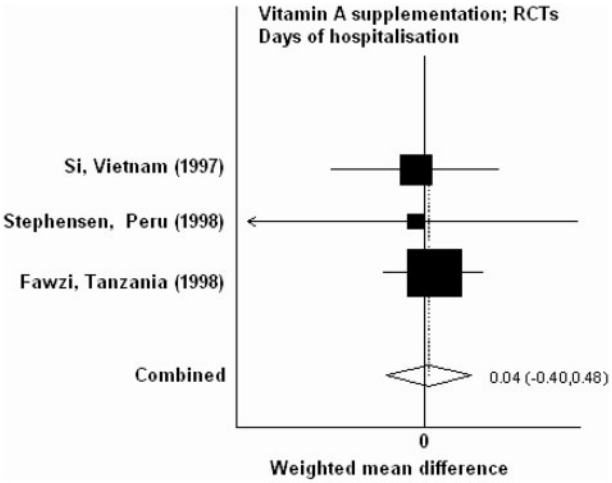

Figure 4 Forest plot for the effect of vitamin A supplementation for the treatment of pneumonia on the days of hospitalization.

such as fluid therapy, temperature control or clinical monitoring on pneumonia mortality.

DISCUSSION

The estimates presented in this article represent a systematic and structured review of the published evidence of effectiveness of case management interventions for childhood pneumonia in developing countries. The aim of this review was to inform the LiST model and to make explicit the available evidence.

The effect of case management in areas where HIV is a major problem may substantially differ from the estimates in regions where HIV is not such a problem. The evidence presented in this review was generally reported from areas in which HIV Acquired Immuno Deficiency Syndrome (AIDS) was not a major public health problem so this should be borne in mind when interpreting the results. Further research is required to provide data to model the effect in HIV-affected regions, since there are data showing that HIV has an impact on case fatality ratios (CFRs) in hospital management and that pneumocystis pneumonia (mainly found in HIV/AIDS patients) accounts for a large proportion of these deaths.[48]

Another important issue is the rapidly changing coverage with the new protein-polysaccharide conjugate vaccines against Hib and pneumococcal disease. The direct and indirect (herd immunity) effects of these vaccines at moderate to high coverage are likely to have a substantial impact on the major bacterial pathogens causing pneumonia mortality and this will necessitate a change in antibiotic treatment policies and will have an impact on the effect of case management strategies on pneumonia mortality impact. The studies reviewed in this report were conducted in settings where these vaccines were not used at all or not at a significant level of coverage.

Community case management with antibiotic treatment

The effect of community case management on pneumonia mortality has been established by previous reviews. However, there has been no previous attempt to estimate the effect of the major child health interventions using a common approach or to consider a wider range of case management interventions against pneumonia.

This systematic review clearly highlights again the effectiveness of community case management with antibiotic treatment in reducing mortality from childhood pneumonia and reinforces the findings of previous reviews.[5,6] A majority of these studies have been carried out in Asia. This approach was effective even in rural areas with very limited access to health services and severely limited resources. However, it is notable that despite the clear evidence in favour of the effectiveness of this strategy first reviewed by Sazawal *et al.*,[5] community case management is still not readily accessible in many populations with high levels of child mortality.

Community case management models differ. On the one hand, it might mean a proper assessment using the Integrated Management of Childhood Illness guidelines and antibiotics given by a nurse with 2–3 years of training in a well-setup primary government or mission-run health clinic. On the other hand, it might mean antibiotics given by a volunteer health worker with as little as 2–6 weeks of training in a village setting, with limited connection with the formal health system.[9,11,19,21,22] Recent programs considered are considering antibiotic treatment given at home by a health worker for children with severe pneumonia.[28,49]

Several studies emphasized the importance of active case finding in reducing mortality levels although once community awareness has been generated and as maternal education develops within the community, the use of active case finding may become gradually less essential. It is suggested by these studies that maternal education is an important factor in the long-term success of the case management approach. It is clear that good levels of health worker supervision are needed for community case management. Most of the trials evaluated community case management in conjunction with other interventions suggesting that integration of case management into existing health systems will be essential to achieve the greatest impact on childhood pneumonia mortality. Ideally there should be a health system continuum from community to primary care to hospitals.

There are certain patient groups in which community case management for pneumonia is more

complex and may not be appropriate. These groups include children with very severe pneumonia, hypoxaemia, neonates, malnourished children and children with HIV. This systematic review is limited in that it does not report studies that addressed these contextual issues or high-risk groups.

One issue for the effectiveness of the community case management intervention is the coverage of the antibiotic treatment, since not all children with pneumonia in these trials were identified and given antibiotic treatment. In the recent meta-analysis in 2003 by Sazawal *et al.*,[6] the authors in corporation with the principal investigators (PIs) of the trials conducted a structured assessment of a number of aspects related to the intervention intensity (intervention score), including antibiotic availability, percentage of detected cases, case treatment rates and treatment compliance. They then conducted a meta-regression that examined the correlation between intervention effectiveness and intervention score and they reported that community case management was more effective against pneumonia in higher intervention intensity studies.[6] Although, the data used to construct the intervention score represent qualitative rather than quantitative views of the study PIs, they are consistent with ~50% of children with pneumonia receiving the intervention as planned. It is therefore probable that the impact on pneumonia mortality could have been higher than that reported in the current and previously published meta-analyses[5,6] had a higher proportion of children with pneumonia received the intervention. Since the LiST tool is designed to provide the effectiveness of an intervention on an individual level, the meta-analysis estimate effect of community case management will be adjusted to take into consideration the 50% coverage of antibiotic treatment (adjusted effectiveness 70%).

Other issues such as the emergence of antibiotic resistance to simple oral antibiotics that can be prescribed by community health workers, increasing prevalence of HIV in a country or region and a change in the main causes of pneumonia deaths following high coverage with Hib and pneumococcal conjugate vaccines (discussed below) may necessitate a re-appraisal of the effectiveness of the specific antibiotics recommended or, more widely, of how this strategy is implemented.

Hospital antibiotic treatment

The current WHO guidelines for the acute management of very severe pneumonia in resource-limited settings recommend ampicillin and gentamicin for up to 10 days, or alternatively, chloramphenicol until improvement is seen. For pneumonia classified as severe, amoxicillin or benzylpenicillin is recommended for $\geqslant 5$ days. This review was unable to identify any controlled trials, quasi-experimental studies or observational studies from which treatment effectiveness in reducing pneumonia mortality could be estimated. The main reason for this is that WHO (and other national paediatric and Ministry of Health) treatment recommendations are widely accepted and such studies would not be considered ethical. One before/after study was identified that reported a 52% reduction in case fatality rate in children admitted with ARI after the implementation of WHO's standard ARI case management guidelines.[32] In contrast, there were no significant differences in CFR in another study before and after implementation of ARI case management guidelines.[26] Reports of very low CFRs for severe pneumonia and relatively low CFR for very severe pneumonia are consistent with a high level of effectiveness of hospital treatment. However, it is not possible from published data to quantify the precise effectiveness of hospital treatment with antibiotics since there is no control data available.

There is good general evidence that hospital care is often deficient in many countries, including a study of 21 hospitals across seven countries in Asia and Africa.[50] Similar observations were made in a study in Kenya, Tanzania, Solomon Islands, Kazakhstan, Brazil, Angola and elsewhere.[51–54] Attention to improving quality of hospital care is therefore required to ensure the appropriate, effective and timely treatment is given.

Oxygen therapy

Hypoxaemia is a major complication and cause of deterioration in pneumonia and is associated with a significantly increased mortality risk. It is estimated that $\geqslant 13\%$ of children with severe pneumonia requiring admission to health facilities have hypoxaemia, and the prevalence rates are as high as 50% in some hospitals.[55] There are 11–20 million children each year presenting to hospitals with pneumonia.[3] This corresponds to 1.5–2.7 million annual cases of hypoxaemic pneumonia (13% prevalence).[55]

WHO-recommended treatment of severe pneumonia includes oxygen therapy where oxygen saturation is $<90\%$ (where pulse oximetry is available).[56] This review shows that there is now evidence that ensuring ample supplies of oxygen and promoting a routine and systematic approach of screening for hypoxaemia using pulse oximetry is associated with reduced mortality, and suggests that the technology required to do so is sustainable and affordable in district hospitals in developing countries. These findings are in accordance with the results of a pilot study that was conducted in one hospital (Goroka) and reported a 35–40% reduction in mortality with oxygen therapy.[57] Regarding the oxygen delivery methods, a recent Cochrane review that summarized studies comparing oxygen delivery methods (nasal prongs, nasopharyngeal

catheters, nasal catheter, face mask, head box) found no difference in treatment failure.[58] However, more research is required on the impact, cost and correct implementation of effective technology in different contexts, and on how to overcome barriers to access, particularly in remote regions where power supplies are unreliable. Further quasi-experimental studies, e.g. with a stepped wedge introduction design would provide more precise estimates of pneumonia mortality reduction in different settings.

Supportive care

This review was unable to identify any controlled trials, quasi-experimental studies or observational studies that reported separately the effectiveness of discrete supportive care interventions (a review of the effectiveness of breastfeeding will be published separately). Many supportive care interventions are recommended by WHO, national paediatric associations and Ministries of Health in paediatric treatment guidelines and are widely accepted but further research is required to better define effective supportive care.

General issues related to case management interventions

Any consideration of case management interventions for pneumonia should recognize that weak infrastructure, shortage of essential supplies and, most of all, the human resource crisis amongst health staff, especially in sub-Saharan Africa, are major factors limiting the achievement of the mortality reduction effects reported in these studies. In addition, risk factors that are likely to affect pneumonia mortality such as prevalence of bacterial aetiology, hypoxia, zinc deficiency and measles prevalence, will differ between different regions of the globe and therefore this will affect the effectiveness of the interventions aiming to the mentioned risk factors. Finally, community health workers that are likely to deliver the community case management interventions are most of the times not linked to the formal health system of the country and they are expected to work as volunteers. Addressing issues such as drug supplies, equipment issues and other supportive technology (such as oxygen systems), human resources, health financing, physical facilities and infrastructure are essential elements underlying the successful delivery of the interventions reviewed here.

Conclusions

Following the CHERG guidelines we estimate that community case management of pneumonia could result in a 70% reduction in mortality from pneumonia. In contrast, it is difficult to quantify the effectiveness of hospital case management of severe and very severe pneumonia with antibiotics due to the lack of studies with a comparison group and therefore any estimate will require a review of the available observational data coupled to expert opinion gathered through a Delphi or a similar process. A single trial of oxygen therapy suggests that this is effective in reducing pneumonia mortality but further research is required to give higher quality evidence so that an effect estimate can be incorporated into the LiST model. Finally, treatment of pneumonia episodes with zinc and vitamin A were found to be ineffective in reducing pneumonia mortality.

Supplementary Data

Supplementary data are available at *IJE* online.

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KEY MESSAGES

- Results of the current review reinforce the evidence of the effectiveness of community and hospital case management.
- Zinc and vitamin A supportive treatment does not affect pneumonia related outcomes in children.
- There is some evidence of an effect of oxygen therapy on pneumonia related outcomes but further research is required.

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