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The status of community-acquired pneumonia in children under 5 years of age in India: A review

Dr. S Mohan Kumar[1], Dr. Preety Mohan Kumar[2]
[1] Associate Professor, Department of Pediatrics, MGM Medical College, Jamshedpur, Jharkhand, India
[2] Associate Professor, Department of Microbiology, MGM Medical College, Jamshedpur, Jharkhand, India

Abstract
Community-acquired pneumonia is currently a significant problem in developing countries. Annually, there are an estimated 120–160 million clinical pneumonia episodes worldwide, causing 14 million hospitalisations and about one million deaths in children aged <5 years. Although respiratory viruses are the most common pathogens associated with childhood pneumonia, most deaths are attributed to Streptococcus pneumoniae and Haemophilus influenzae type b. Hence, confirmation of microbial etiology is important for the individual, as well as for public health.

Keywords: community-aquired-pneumonia, microbiological agents, choice of antibiotics, low & middle income countries

Introduction

Consequently, antibiotics have reduced pneumonia-related morbidity and mortality. Nevertheless, several knowledge gaps exist with prescribing antibiotics for pneumonia, including the optimal duration of treatment required. These limitations are evident in both national and international guidelines, which have had to rely upon expert opinion and weak levels of evidence from a small number of clinical trials with substantial methodological limitations. A good example of these difficulties is the range of recommendations provided on treatment duration for uncomplicated childhood pneumonia, raising several questions for healthcare workers in developing countries, when determining how long they should be giving antibiotics to a child with pneumonia.

The key symptom of CAP is fast breathing. WHO [1994] has defined fast breathing as respiratory rate of >60 per minute for infants less than 2 months, >50 per minute for infants of 2–12 months, and >40 per minute for children more than 12–59 months. This is in the training content of the IMNCI (Integrated Management of Neonatal & Childhood Illnesses), which is predominantly meant for health workers at the peripheries, to recognize when a child with CAP needs to be referred to a facility higher up in the hierarchy. Fast breathing with chest in-drawing and grunting, along with any of the danger signs- namely inability to feed, drowsiness or altered consciousness, convulsions, cyanosis, is to be recognized as very severe disease, requiring referral.

The rationale of the present review is to assess the current status of management and prevention of CAP with the aim to identify knowledge gaps and implementation inefficiencies. This can help to reduce mortality due to CAP and to achieve the Sustainable Development Goal (SDG) of ⩽25 deaths of children under 5 years of age per 1000 live births by the year 2030 [UNO, 2015].

The treatment of CAP requires effective antibiotics in optimum dosage and duration, with the choice of antibiotics based on the bacterial aetiology. The commonest causative bacterial pathogens responsible for CAP vary according to the age of the patient. In paediatric patients, including the 2–59-month group, Streptococcus pneumoniae and Haemophilus influenzae are the leading and most commonly targeted organisms. However, empirical antibiotics after clinical diagnosis of CAP and not aetiology itself, is currently the most important basis of pneumonia treatment guidelines even in resource-rich Western countries. Microbiological diagnosis is still warranted in special circumstances such as in those children who have severe symptoms of pneumonia, those who become hospitalised, and in children with complicated clinical course.3 Strategies do exist to prevent pneumonia and are an essential component to reduce child mortality; these include immunisation against haemophilus influenzae type B vaccine, pneumococcus, measles and pertussis, exclusive breastfeeding for the first 6 months of life, and complementary feeding thereon with supplementation of zinc, and addressing environmental hygiene [4].

The high pneumonia burden and mortality, especially in children less than 59 months in Low and Medium Income Countries (LMICs), necessitates an updated review on the most suitable antibiotic therapy based on trials involving this age group and in LMIC setting. We found previous reviews5–8 and reports9–14 on this subject published in recent years (see online table 1). Evidence from Lodha *et al* [5] which also dealt purely with antibiotic therapy showed amoxicillin to be an effective alternative to co-trimoxazole for treating ambulatory patients with CAP. Lodha *et al* further recommend oral amoxicillin for children with severe pneumonia without hypoxaemia, and penicillin/ampicillin plus gentamicin for children hospitalised with severe and very severe CAP. he recommendations in the review by Lodha *et al*, [5] However, are for children under the age of 16 years, whereas, the current review focuses on children between 2 and 59 months of age. Also, while previous reviews,6 8 including that of Lodha *et al* focused purely on a single modality, such as the choice or duration of antibiotics for treating CAP, the present review updates evidence on the overall spectrum of anti- biotic recommendation for treating CAP in children, namely, the

choice, optimum dose, duration, route and combination of anti- biotics. This crucial information is presented with the aim of providing a targeted cure for the LMICs setting.

Methods

We included randomised controlled trials (RCT) that assessed the route, dose, combination and duration of antibiotics in the management of WHO defined non-severe/severe/very severe CAP. Only those studies that used standard WHO definition and/or classification for CAP9 were included, irrespective of language or publication status. Study participants included children of 2–59 months of age with CAP. The review included studies that compared any intervention that either examined a single drug or a combination; or a different dose, duration and route of the same drug. We included studies that analysed outcomes including clinical cure rate (ie, symptomatic and clinical recovery by end of treatment), treatment failure (ie, developing worsening clinical signs at any point in time; a respiratory rate (RR) exceeding age-specific cut-off and/or <90% oxygen saturation on pulse oximetry after completion of treatment), relapse rate (developing disease recurrence after being declared 'cured'), change in antibiotic required and mortality rate. We grouped and analysed the outcomes according to very severe, severe and non-severe pneumonia. Standard extraction forms were used to extract data from included studies by two independent reviewers. Errors were corrected by comparison of the extracted data and any differences in interpretation of data were resolved by contacting the trial author, where possible. All data was entered and analysed using Review Manager 5 software.15 We used Cochrane methods for risk of bias assessment to assess the quality of included studies.16 For each study, the level of attrition was noted and its impact on overall assessment of treatment effect was explored via sensitivity analysis. Analysis for all outcomes was done, as far as possible, on an intention-to-treat basis; that is, all participants randomised to each group in the analysis were included irrespective of their adherence. Fixed-effect meta-analysis model was used for analysis. Where heterogeneity was high ($I2>30\%$, $\tau2>0$, $\chi2$ $p<0.1$), data was analysed in a random-effect model.

Results

The review identified 8122 studies on initial search, while 22 trials with 20593 enrolled children were included in meta-analyses (figure 1). Three studies were included for very severe pneumonia, six studies for severe pneumonia and 13 studies for non-severe pneumonia. Out of 22 included studies, 20 were free of selective reporting, 12 were double-blinded and 14 had adequate allocation concealment. Five studies included for very severe and severe pneumonia were free of other bias, while four studies in non-severe pneumonia mentioned their source of funding. The nuances of the included studies in the current review are discussed in the table of characteristics.

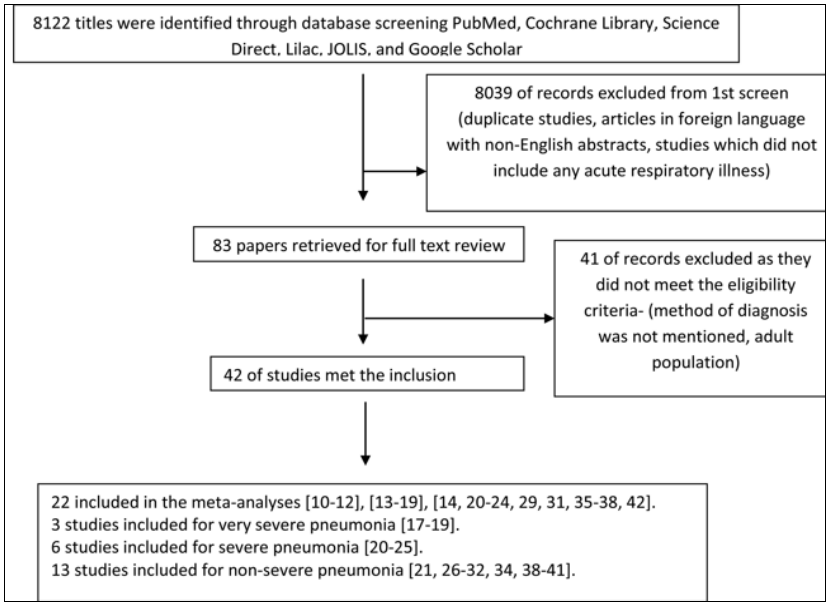

Fig 1: Search flow diagram

Very severe pneumonia (danger signs)

We found four studies17–20 for very severe pneumonia in children in LMICs, of which three17–19 met the review's criteria and were subject to meta-analysis. Two studies17 19 involved children 2–59months, and one study18 involved children of 1 month to 5 years of age; antibiotics in all these studies were administered parenterally (see online supplementary tables S2, S3, S6 and S7).

Evidence from Asghar *et al* [17] showed that a combination of ampicillin and gentamicin led to a significant decrease in failure rates on day 5 by 30% (RR 0.70; 95% CI 0.51 to 0.97), day 10 by 27% (RR 0.73; 95% CI 0.55 to 0.97), and day 21 by 25% (RR 0.75; 95% CI 0.57 to 0.98) compared to chloramphenicol group. Duke *et al*, [18] however, reported no impact in overall adverse effects and death rates with a combination of penicillin and gentamicin compared with chloramphenicol alone. The pooled estimate of the two studies17 18 showed a non-significant decrease in mortality

by 29% (RR 0.71; 95% CI 0.51 to 1.00), and a significant lower failure rate by 21% (RR 0.79; 95% CI 0.66 to 0.94) in the penicillin and gentamicin group compared to the chloramphenicol group (figure 2). Bansal *et al* [19] found no differences in failure rates on comparing the combination of penicillin and gentamicin with amoxicillin-clavulanic acid (table 1).

Severe pneumonia (chest indrawing pneumonia)

There were seven eligible studies21–27 for severe pneumonia, however, six20–25 met our criteria and were subject to meta-analysis. Four other studies28–31 which made a diagnosis of pneumonia radiologically were not included because the review's criteria was to include only those studies which diagnosed pneumonia according to WHO's definition of pneumonia.7 All 7 studies were conducted in LMIC settings, and children included were between 2 and 59 months of age (see online tables S4, S5, S6 and S7). Different routes were also employed for comparing antibiotics, and these routes are mentioned with their respective findings in this section (table 2).

Evidence from Cetinkaya *et al* [21] showed a combination of parenteral penicillin and chloramphenicol versus parenteral ceftriaxone to be equally efficacious in cure rates by day 10 (RR 1.05; 95% CI 0.88 to 1.27). Straus *et al* [22] compared oral antibiotics for severe pneumonia and reported a significant increase by 79% (RR 1.79; 95% CI 1.13 to 2.84) in treatment failure with co-trimoxazole compared to amoxicillin at 48 h.

For severe pneumonia, availability of parenteral treatment is sometimes a challenge in LMICs where a safe and equally effective alternative is warranted. This review found oral amoxicillin to have similar failure rates when compared to: combination of intravenous penicillin and oral amoxicillin, 23 combination of intravenous ampicillin plus oral amoxicillin by 66%,24 or intra- venous benzyl penicillin (P 0.031).25 Campbell *et al* [26] showed similar rates of treatment failure with oral co-trimoxazole when compared to a combination of intramuscular procaine penicillin and oral ampicillin: −0.01% (95% CI −0.11 to 0.09%). Due to paucity of studies, however, the current review's objective of comparing various dosages or duration of antibiotics for the treatment of severe pneumonia in children of age 2–59 months could not be met.

Non-severe pneumonia (fast breathing pneumonia)

There were 26 eligible studies32–57 on children with non-severe pneumonia, however 13 were subject to meta-analysis (table 3).22 32–38 40 44–47 Most of these studies met the review's target age group of 2–59 months, and were conducted in LMIC setting (see online tables S8 and S9).

Pooled estimates of evidence from Straus *et al*, [22] CATCHUP,32 and Awasthi *et al* [33] which compared oral co-trimoxazole versus oral amoxicillin showed failure rate to be similar between the two groups (RR 1.09; 95% CI 0.93 to 1.27) (figure 3). Also, cure rates in two of these studies 32 33 were similar (RR 0.99; 95% CI 0.96 to 1.01).

Levofloxacin is highly effective for adult pneumonia, but its efficacy or safety profile has not been widely explored in children less than 5 years of age. Bradley *et al* [34] compared oral levofloxacin versus oral co-amoxiclav and showed a similar effect in cure rate. Pooled estimates from two other trials 35 36 which assessed efficacy of oral azithromycin with co-amoxiclav for children with non-severe pneumonia showed no difference in rates of treatment failure (RR 1.20; 95% CI 0.45 to 3.21).

Deivanayagam *et al* [38] examined the use of parenteral ampicillin versus combination of benzyl penicillin and chloramphenicol for non-severe pneumonia, and reported no difference in cure rate and treatment failure rate. Other trials comparing parenteral versus parenteral antibiotics were found in the current review, including evidence from Camargos *et al*, [39] which showed relapse of pneumonia within 24h to significantly increase with single shot group of intravenous benzathine penicillin (75.3%) versus 7 days of intramuscular procaine penicillin (66.3%); In the same study, relapse rate was significantly lower after 24–48 hours of treatment with benzathine penicillin (8.6%) compared to treatment with IM procaine penicillin (16.9%).

To examine the ideal dose of antibiotic to manage non-severe pneumonia, evidence from Rasmussen *et al* [40] showed no difference in clinical cure rate with a double dose of co-trimoxazole (trimethoprim plus sulfamethoxazole) compared to standard dose. Two other trials 41 42 reported amoxicillin twice a day to be a reasonable alternative to dosing three times a day. A similar finding was reported by Cook RC *et al* [43] in that clinical cure rate with amoxicillin/clavulanate was not different in the thrice a day versus twice a day group (difference 3.2%; 95% CI 4.36 to 10.80).

For the duration of antibiotic treatment for non-severe pneumonia, evidence from four studies 44–47 was analysed; a 3-day therapy with either amoxicillin or co-trimoxazole was equivalent to a 5-day therapy for relapse rate (RR 0.99; 95% CI 0.98 to 1.01). A similar finding was reported by Ficnar *et al* [48] which reported no difference in cure rate in the 5-day versus 3-day group (p=0.82) of azithromycin. To determine the ideal route of antibiotic therapy for non-severe pneumonia, the current review identified two studies, 49 50 but which could not be analysed as the study did not specifically include children who were between 2–59 months of age.

Global child health

What factors influence decisions on antibiotic duration? Several factors are considered when both choosing an antibiotic to treat a suspected case of bacterial pneumonia and determining how long it should be given. These include: (i) clinical presentation and severity; (ii) assumed bacterial aetiology based upon the child's age, vaccination status, underlying co-morbidities and the local pathogen antibiotic susceptibility profiles; and (iii) cost, availability, tolerability, and ease of administration (e.g. frequency and palatability) of the chosen agent that may influence treatment adherence.

In clinical practice, the optimal duration of antibiotic treatment depends upon whether the pneumonia is straightforward or complicated (e.g. empyema or systemic infection involving other organs); if underlying medical disorders are present (e.g. malnutrition, human immuno-deficiency virus infection, or chronic cardiopulmonary dis-ease); the nature of the causative pathogen, adequacy of source control, and the patient's response to treatment.

In uncomplicated pneumonia the advantages of a short-treatment course include a lower risk of develop- ing

antibiotic resistance, improved adherence, fewer ad- verse effects, and decreased costs [6, 8]. The main danger though of shortened therapy in young children is treatment failure from delayed or incomplete eradication of the infecting pathogen(s), risking additional morbidity and injury to the developing lungs and possibly a greater chance of impaired lung function, chronic obstructive pulmonary disease and bronchiectasis later in life [9].

It is really bacterial pneumonia?

Most studies on antibiotic duration were undertaken in low- and low-to-middle-income countries where the burden of pneumonia is greatest. Unfortunately, the diagnosis of bacterial pneumonia in these settings is also the most uncertain as it relies upon healthcare workers following clinical algorithms without adequate laboratory and radiographic support. Furthermore, no diagnostic gold standard for pneumonia exists, and there are major difficulties differentiating between viral and bacterial pneumonia clinically and radiographically, l *et al* one obtaining an accurate microbiological cause [10].

What are the current recommendations and what are their limitations?

As most childhood pneumonia deaths occur out of hospital in the low-resource settings of sub-Saharan Africa and Southern Asia, the diagnostic algorithms used by the World Health Organization (WHO) are designed to reduce mortality, sacrificing specificity for sensitivity [4]. Otherwise healthy children with suspected clinical pneumonia are managed as outpatients and receive either 3 days of high-dose oral amoxicillin (80–90 mg/kg/day) if tachypnoeic alone, or 5 days if subcostal recession is also present [4]. Those with severe clinical pneumonia accompanied by danger signs (e.g. dehydration, seizures, or altered consciousness) receive parenteral penicillin (or ampicillin) and gentamicin as first-line agents for at least 5 days. These recommendations are based upon several large randomised controlled trials (RCTs) of oral vs. parenteral antibiotics and 3 vs. 5 days of oral anti-biotic treatment in children from developing countries [7, 11]. A recent systematic review published in the journal [7] found three RCTs from developing countries comparing short (3 days) vs. standard (5 days) oral anti- biotic treatments in children with non-severe (tachypnoea alone) pneumonia. These studies were conducted in either India or Pakistan and each involved >2000

children aged 2–59 months [12–14]. Each reported that 3 days was either equivalent [12] or not statistically different [13, 14] to 5 days treatment. However, the validity of these three studies is questionable. The follow-up was limited to only 14 days and although failure rates ranged from 9.5 % to 21 %, just a single death occurred in a 3- month old infant amongst the 6197 trial subjects, a much lower case fatality than expected for pneumonia in these settings [2, 3]. Almost half the subjects were infants, as many as 22 % had wheeze, and pneumonia was diagnosed following the WHO clinical algorithm [4]. Only one study included chest radiographs [12], where just one in seven children with clinical pneumonia had abnormal radio- graphic findings. Consequently, these studies of treating non-severe pneumonia in developing countries are limited by inherent biases towards equivalence of varying treatment durations, since many (if not most) participating sub- jects were unlikely to benefit from antibiotics as they had bronchiolitis, viral pneumonia, or virus-associated wheeze. Indeed, a recent double-blind RCT in 900 children aged 2–59 months from Pakistan with WHO-diagnosed non- severe pneumonia found equivalent clinical outcomes in those receiving either 3 days of oral amoxicillin or placebo with cumulative treatment failure rates by day 5 of 13.5 % and 17.6 %, respectively, while once again no deaths were reported [15].

In contrast to developing countries, criteria for diagnosing childhood pneumonia in developed nations often re- quire chest radiographic confirmation, especially for hospitalised cases [5]. Nevertheless, little information is available guiding treatment duration [6, 7], although a re- cent small, single-centre, three-arm RCT from Israel of 140 non-hospitalised children aged <5 years with likely bacterial pneumonia (based on clinical criteria, chest radio- graphic consolidation, and raised white blood cell counts) found that the 40 % failure rate of a 3 day course of amoxicillin was unacceptably high, while no failures were re- ported in those receiving either a 5 or 10 days course of the antibiotic [16]. These data help support current national guidelines from developed countries recommending at least 5 days of antibiotics for children suspected of bacterial pneumonia [5, 6].

So, what is required?

The guidelines for the treatment duration of pneumonia are based upon limited and often weak evidence [4–7]. The situation is not helped by the important knowledge gaps that still remain regarding how to best identify children with pneumonia, including how to reliably differentiate between bacterial and non-bacterial causes [10]. Healthcare workers in resource poor settings in particular need access to validated, simple, and inexpensive point-of-care diagnostic tests. Unfortunately, none are likely to be available soon. While new technologies such as gene expression signatures show considerable promise for identifying aetiological pathogens in pneumonia, these and other molecular-based platforms are unlikely to be made available in the foreseeable future to low- and middle-income countries where the burden of pneumonia is greatest. Meanwhile, although there is mounting global concern over rising rates of antibiotic resistance resulting in increased calls for shorter treatment courses, it is important to remember that an ineffective short antibiotic treatment course for pneumonia is still the worst strategy when either it is not needed (e.g. for viral respiratory infections) or when it results in treatment failure, risking death, increased morbidity and/or long-term sequelae [8–10].

Clearly, more robust evidence for antibiotic treatment duration for pneumonia is needed. A good start would be to undertake additional RCTs in sub-Saharan Africa and Asia (where feasible sample sizes are possible), recruiting subjects with a greater probability of bacterial infection (based on clinical severity or radiographic criteria). Mean- while, healthcare workers should recognise the limitations of current “one size fits all” pneumonia treatment guidelines and remember that the duration of antibiotic therapy is also determined by individual host and pathogen factors and how the child responds to treatment.

Discussion

With the last meta-analysis on the subject by Lodha *et al* [5] and Lassi *et al* [7] published in 2013 and 2011, respectively, the current review reanalysed pre-existing studies to look for new evidence on antibiotic therapy in children less than the age of five (table 4). The current review, however, analysed trials addressing additional components in antibiotic therapy (ie, dose, duration, route) compared to previous reviews 5 6 8 that dealt only with single modality, such as the choice or route. The evidence derived from the current review further focuses on children between 2 and 59 months of age in LMIC settings, which is an age group and setting where the highest pneumonia mortality burden is witnessed.

Based on trials addressing the important issue of choosing the most effective antibiotic for managing WHO-defined pneumonia with danger signs (old classification very severe pneumonia) in the 2–59-month age group, the current review favours a com- bination of penicillin/ampicillin and gentamicin.17–19 These trials were conducted in facilities in LMICs. An important issue in LMICs is that referral is often difficult and injection is not available, which makes it crucial to seek an equally effective oral drug as an alternative. We found oral amoxicillin to be equally efficacious as parenteral antibiotics for WHO-defined chest indrawing pneumonia (old WHO-defined severe pneumonia), and thus recommend it for treatment in LMICs.23 24 26 The 2005 WHO guidelines recommended IV/IM benzyl penicillin/ ampicillin for chest indrawing pneumonia, and a switch over to oral amoxicillin once improvement was witnessed.58 There weren't sufficient studies to address the issue of the optimum dose and duration of parenteral antibiotic for treating severe and very severe pneumonia in children of age 2–59 months; this is an area where more trials are warranted. WHO's Integrated Management of Childhood Infections (IMCI) 2006 guidelines however recommend that a prereferral dose of 7.5 mg/kg intra- muscular injection of gentamicin, and 50 mg/kg injection of ampicillin be used for very severe pneumonia.10 An important consideration in drafting guidelines for high-mortality diseases like pneumonia is the prevalence of HIV in a region, as it can alter pneumonia-related management of children in HIV-endemic regions. Without sufficient evidence from HIV patients in this review, we recommend WHO treatment guidelines that were developed for HIV-infected children with pneumonia in LMICs.10 59

For the management of fast breathing pneumonia, WHO recommended treatment with co-trimoxazole as a first-line empirical agent in countries with an infant mortality greater than 40 per 1000 live births.10 Evidence derived from our review did not favour use of co-trimoxazole over amoxicillin in managing non-severe pneumonia in children between 2 and 59 months of age, which is consistent with findings from the review by Lodha *et al* [5] Thus, amoxicillin is a better alternative to co-trimoxazole in managing non-severe pneumonia in this age group as it is also effective against chest indrawing. The review also concludes that a 3 day course of antibiotics is as effective as 5 day therapy for managing non-severe pneumonia, which is beneficial for low-income settings where cost is an issue. It further has the added benefit of decreased antibiotic resistance and improved compliance.35–38 But this switch over from 5-day to 3-day therapy is not recommended for HIV-endemic countries. Where the optimum dose of antibiotic for non-severe pneumonia is concerned, the current review prefers a twice a day to three times a day dosing which is also favoured by the American Academy of Paediatrics.60 We further found oral antibiotic to be a safe and cost-effective alternative to injectable antibiotic for fast breathing pneumonia in children aged between 2 and 59 months.49 50

In this review, we used 'clinical failure' to demonstrate difference between antibiotics, as this outcome was consistently mentioned in included trials. But Dagan *et al* [61] have previously argued that bacterial eradication is a more accurate determinant of antimicrobial efficacy than clinical outcome. While research gaps do exist in treatment of CAP in children, as noted in the present review, some useful interventions, besides antibiotics, to reduce childhood pneumonia mortality have also been examined. An important intervention is the early identification of pneumonia and referral of the sick child which is recommended by the IMCI. A study also demonstrated that provision of assured supply of oxygen via oxygen concentrators for children with severe pneumonia resulted in 35% mortality reduction.62 Other important interventions related to treatment of CAP warrant further exploration, such as the management of fast breathing pneumonia with potential supportive therapy sans antibiotics, role of hypoxaemia detection and management, identifying comorbidities in children with pneumonia and man- aging them, and community management of chest indrawing and pneumonia with danger signs in resource-poor settings. Further studies are also warranted to explore second-line anti-biotics. It is important to note here that while cephalosporins are used widely in high-resource countries, there is paucity of literature about their success in LMICs. Ceftriaxone is one cephalosporin that has the additional benefit of being a once-daily drug. Thus, if its success is established in trials conducted for LMICs, its usage could potentially simplify management of CAP in such settings as well.

Finally, the need for future research should not take away from the expediency of implementing what we know. As the recent global action plan for pneumonia and diarrhoea indicates, 63 we know enough in terms of key interventions for us to implement these at scale. This review supports that we know enough about the management of pneumonia among children in greatest need to implement strategies among those who need them most. This is imperative to save 1.2 million pneumonia-associated deaths annually, but affords no complacence in working concurrently on refining and improving existing interventions.

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