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[Intervention Review]

Short-course versus long-course intravenous therapy with the same antibiotic for severe community-acquired pneumonia in children aged two months to 59 months

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ABSTRACT

Background

Pneumonia is a leading cause of childhood mortality from infectious disease, responsible for an estimated 1.3 million deaths annually in children under five years of age, many of which are in low-income countries. The World Health Organization recommends intravenous antibiotics for five days as first-line treatment for children with severe pneumonia. Although controversy exists regarding the specific clinical features used to diagnose pneumonia, the criteria for diagnosis of severe pneumonia are better defined and are widely used to triage children for referral and second-line therapy.

In 2011 it was estimated that approximately 120 million new cases of pneumonia occur globally each year in children under five years of age, of which 14 million become severe episodes. Hospitalisation for severe pneumonia in children places a significant burden on both patients and their families, including substantial expense, loss of routine, and decrease in quality of life. By reducing the duration of hospital treatment, healthcare burdens could potentially be reduced and treatment compliance may improve.

This is an update of a review published in 2015.

Objectives

To evaluate the efficacy of short-course (two to three days) versus long-course (five days) intravenous therapy (alone or in combination with oral antibiotics) with the same antibiotic for severe community-acquired pneumonia in children aged two months to 59 months.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 12), MEDLINE (1966 to December week 3, 2016), Embase (1974 to 22 December 2016), and four trials registers (23 August 2017), together with reference checking of all relevant trials and reviews.

Selection criteria

Randomised controlled trials evaluating the efficacy of short-course (two to three days) versus long-course (five days) intravenous antibiotic therapy (alone or in combination with oral antibiotics) for severe pneumonia in children aged two months to 59 months. We excluded children with any other debilitating disease, including those infected with HIV. We also excluded children who had developed

pneumonia during their hospital stay (i.e. with nosocomial infection). There was no restriction on the type of antibiotic used, the dose, or the frequency of dosing.

Data collection and analysis

We used standard methodological procedures expected by Cochrane.

Main results

Our searches identified 4295 records, however no studies met our predefined inclusion criteria.

Authors' conclusions

We identified no randomised controlled trials comparing a short course (two to three days) of intravenous antibiotics compared to a long course (five days) for severe pneumonia in children aged two months to 59 months that met our inclusion criteria.

PLAIN LANGUAGE SUMMARY

Short-course versus long-course intravenous therapy with the same antibiotic for severe community-acquired pneumonia in children aged two months to 59 months

Review question

We conducted this review to determine if there are any differences in treatment outcomes between short- (two to three days) and long-course (five days) intravenous antibiotics (alone or combined with oral antibiotics) for children aged two months to 59 months with severe pneumonia.

Background

Pneumonia is infection of the lungs (often caused by a virus or bacteria) that causes about 1.3 million deaths each year in children under five years of age. There are about 120 million new cases of pneumonia among children under five years of age globally each year, of which about 14 million become severe pneumonia. A significant proportion of these new cases of pneumonia occur among children in low-income countries.

The World Health Organization (WHO) recommends five days of intravenous antibiotic treatment for children with severe pneumonia. Treatment in hospital for children with severe pneumonia places significant burden on children and their families, including substantial expense, loss of routine, and decreased quality of life. Reducing time spent in hospital for treatment could potentially reduce the burden of disease and may lead to better treatment compliance.

Search date

We conducted our last search in 22 December 2016, and identified no studies that fulfilled the inclusion criteria.

Key results

We did not find any relevant studies to include in this review. Physicians should continue to treat children with severe pneumonia according to the WHO recommendations until further evidence becomes available.

BACKGROUND

Description of the condition

Pneumonia is an infection of the lungs (Gaston 2002). When a child who was previously healthy acquires this infection outside the hospital setting, it is called community-acquired pneumonia (CAP). Although non-severe pneumonia is more prevalent than severe pneumonia, most deaths occur in children with severe pneumonia (Graham 2008). The World Health Organization (WHO) bases its definition of severe pneumonia in children on clinical signs: lower chest indrawing (with or without fast breathing); unable to drink or breast-feed; vomiting; lethargy; unconsciousness; convulsions; central cyanosis; severe respiratory distress; or clinical severe malnutrition, which requires hospitalisation and administration of parenteral antibiotic therapy (WHO 2013).

The main bacterial causes of vaccine-preventable pneumonia in low-income countries are *Streptococcus pneumoniae* (*S pneumoniae*) and *Haemophilus influenzae* type b (*H influenzae*, Hib); the most common viral agent is respiratory syncytial virus (Marsh 2008). *S pneumoniae* is the most common pathogen in infants aged between three weeks and three months. In infants aged over four months and in preschool children, viruses are the most common cause of pneumonia overall, and *S pneumoniae* is the most common bacterial pathogen isolated in this age group (Ostapchuk 2004). It is very difficult to identify the causative organism in most cases of pneumonia. Blood cultures are used to isolate the causative organism. However, the yield from blood cultures is low for bacterial pathogens (approximately 25% to 33%) and cannot be relied upon (WHO 1991).

Data from 2010 to 2011 indicate that pneumonia is a leading cause of global childhood morbidity and mortality from infectious disease, causing an estimated 1.3 million deaths each year in children under five years of age (Walker 2013). The greater burden of disease is concentrated in low- and middle-income countries, where resources for medications and hospital-based management are poor (Zar 2013). Recent evidence suggests the use of oral antibiotics for effective management of severe pneumonia in children (Ashraf 2008; Chowdhury 2008).

In 2005, the WHO provided guidance that hospitalised children with severe pneumonia receive at least three days of intravenous antibiotics followed by two days of oral antibiotics (WHO 2005). Revised WHO evidence summaries on the classification and treatment of childhood pneumonia recommend intravenous antibiotics for five days as first-line treatment for severe pneumonia (WHO 2014). Although controversy exists around the specificity of clinical features in the diagnosis of pneumonia (Fox 2015; Rambaud-Althaus 2015), diagnostic criteria for severe pneumonia are better defined and are widely used to triage children for referral and second-line therapy (Qazi 2015). Approximately 120 million new cases of pneumonia occur globally each year in children up to five years of age, and of these, 14 million progress to severe episodes (Walker 2013). Hospitalisation for severe pneumonia in children places a significant burden on both patients and their families, including substantial expense, loss of routine, and decrease in quality of life (Shoham 2005). By reducing the duration of hospital treatment, healthcare burdens could potentially be reduced and treatment compliance may improve.

Description of the intervention

Children diagnosed with severe CAP are hospitalised and require effective antibiotic treatment. The selection of the antibiotic for treatment is commonly empirical (Jadavji 1997). This is due to lack of rapid, accurate commercially available laboratory tests in low-income countries, which makes identifying the causative agent difficult (WHO 1991). Hence, the WHO standard case management guidelines for severe pneumonia are directed toward treatment of the two main bacterial aetiological pathogens in children, *S pneumoniae* and Hib. Inpatient management of children with severe pneumonia comprises serial examinations, basic supportive care (including supplemental oxygen, suctioning, intravenous fluids, analgesics, and antipyretics as required), and parenteral antibiotic therapy (Durbin 2008; WHO 1991; WHO 2005; WHO 2013; WHO 2014). Switching from parenteral to oral therapy is a key management issue. Most children receiving parenteral therapy for two to four days can be switched to oral therapy, provided they are clinically stable and can tolerate medication orally (Jadavji 1997; WHO 2005). Amoxycillin, ampicillin, co-trimoxazole, injectable penicillin G, and chloramphenicol are usually effective treatments for severe pneumonia (WHO 1991).

How the intervention might work

Of the millions diagnosed with pneumonia globally each year, up to 20 million children require hospitalisation (UNICEF/WHO 2006). The estimated inpatient cost for management of severe pneumonia (USD 235) is three times that for non-severe pneumonia treated in community settings (USD 71) (Hussain 2006). Beyond the financial considerations, hospitalised care may have an impact on the quality of life of children and their families in terms of daily family organisation, social activities, and stress and anxiety (Shoham 2005). Inpatient treatment thus imposes burdens on resources and children's quality of life. These burdens could potentially be reduced by early transition to oral antibiotics after an abbreviated course of intravenous therapy (Omidvari 1998).

Why it is important to do this review

Almost all (95%) new cases of pneumonia worldwide among children under five years occur in low-income countries, where there is a high risk of death, poor access to medication and health care, and limited budgets for medicines (UNICEF/WHO 2006). An optimum duration of antibiotic therapy for pneumonia is especially important in such resource-poor settings (Campbell 1995). Hence, there was a need to undertake a systematic review in order to establish whether a long course of intravenous antibiotics is any more advantageous than a short course. Our systematic review could provide a basis for rational decision-making, that is whether healthcare providers should shift to a shorter course of intravenous antibiotic therapy for the management of severe CAP.

OBJECTIVES

To evaluate the efficacy of short-course (two to three days) versus long-course (five days) intravenous therapy (alone or in combination with oral antibiotics) with the same antibiotic for severe community-acquired pneumonia (CAP) in children aged two months to 59 months.

METHODS

Criteria for considering studies for this review

Types of studies

We sought randomised controlled trials (RCTs) evaluating the efficacy of short-course versus long-course therapy using the same antibiotic for severe CAP in children. We assessed studies using the standard WHO algorithm for acute respiratory infections (WHO 2013). The algorithm defines severe pneumonia as the presence of lower chest indrawing (with or without cough or difficult and fast breathing (respiratory rate of 50 breaths per minute or more for children aged two months to 11 months, or respiratory rate of 40 breaths per minute or more for children aged 12 months to 59 months)) with a general danger sign (inability to breast-feed or drink, lethargy or reduced level of consciousness, convulsions). We planned to include studies irrespective of language or publication status. We excluded observational studies and non-RCTs (quasi-RCTs).

Types of participants

Eligible participants were children aged from two to 59 months with severe CAP, diagnosed according to the WHO acute respiratory infection guidelines (WHO 2013), chest examination by a physician, or on the basis of radiological evidence. We excluded children with any other debilitating disease, including those infected with HIV. We also excluded children who had developed pneumonia during their hospital stay (nosocomial infection).

Types of interventions

Children randomised to intervention groups receiving short course (two to three days) intravenous antibiotic therapy (Jadavji 1997; Omidvari 1998; WHO 2005) (alone or in combination with oral antibiotics), compared to children in control groups receiving intravenous antibiotic (alone or in combination with oral antibiotics) therapy for more than three days. There was no restriction on the type of antibiotic used, the dose, or the frequency of dosing.

Types of outcome measures

Primary outcomes

1. Clinical cure: defined as improvement in symptoms, such as return of respiratory rate to the normal age-specific range and disappearance of chest indrawing.
2. Duration of hospital stay: defined as the duration for which the patient was admitted due to severe CAP. This duration is not outcome-dependent and does not include time spent in the hospital for treatment for other conditions, if any.

Secondary outcomes

1. Treatment failure, defined as: deterioration or failure to improve; evidence of persistent pneumonia despite receiving intravenous antibiotic therapy for 48 hours (such as persistence of chest indrawing with or without rapid breathing on completion of treatment, convulsions, drowsiness, or inability to drink at any time); oxygen saturation measured by pulse oximetry of less than 90% after completion of the treatment; loss to follow-up or withdrawal from the study.

2. Relapse rate, defined as: development of any sign of pneumonia within seven days after chest indrawing and fast breathing have returned to normal.
3. Complications of the disease, including incidence of needle-associated diseases, and sepsis.
4. Mortality.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 12) via the Cochrane Library (22 December 2016), which includes the Cochrane Acute Respiratory Infections Group's and Cochrane Infectious Diseases Group's Specialised Registers; MEDLINE (Ovid) (1966 to December week 3, 2016), and Embase (Elsevier) (1974 to 22 December 2016). Details of previous searches are presented in Appendix 1.

We used the search strategy described in Appendix 2 to search CENTRAL and MEDLINE. We combined the MEDLINE search strategy with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximising version (2008 revision); Ovid format (Lefebvre 2011) and a filter for identifying 'child' studies (Boluyt 2008). We adapted the strategy to search Embase (Appendix 3).

Searching other resources

We checked the reference lists of all relevant trials and reviews identified by the above methods. We also searched the online clinical trial registers ClinicalTrials.gov (www.clinicaltrials.gov/) (Appendix 4), Australian New Zealand Clinical Trials Registry (www.anzctr.org.au/) (Appendix 5), Current Controlled Trials Register (ISRCTN) (www.controlled-trials.com/isrctn/) (Appendix 6), and WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictip/en/) (Appendix 7) on 23 August 2017 to identify any ongoing trials.

Data collection and analysis

We followed standard review methods as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* and by the Cochrane Acute Respiratory Infections Group (Higgins 2011).

Selection of studies

Two review authors (ZSL, AI) independently assessed trial eligibility and screened all available titles and abstracts for inclusion. Two review authors (ZSL, AI) retrieved the full texts of all potentially relevant articles and independently assessed eligibility by completing eligibility forms designed in accordance with the specified inclusion criteria. We resolved any disagreements by discussion or, if required, consulted a third review author (ZAB). We excluded quasi-RCTs.

Data extraction and management

We had planned to independently assess extracted data from the included studies using standardised data extraction forms. We had planned to use Review Manager 5 software for analysis (Review Manager 2014).

Assessment of risk of bias in included studies

We had planned to independently assess the risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We had planned to resolve any disagreements by discussion with the third review author (ZAB).

(1) Sequence generation (checking for possible selection bias)

We had planned to describe for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups. We had planned to assess the method as:

- adequate (any truly random process, e.g. random number table, computer random number generator);
- inadequate (any non-random process, e.g. odd or even date of birth, hospital or clinic record number); or
- unclear.

(2) Allocation concealment (checking for possible selection bias)

We had planned to describe for each included study the method used to conceal the allocation sequence in sufficient detail and determine whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment. We had planned to assess the methods as:

- adequate (e.g. telephone or central randomisation; consecutively numbered, sealed, opaque envelopes);
- inadequate (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth); or
- unclear.

(3) Blinding (checking for possible performance bias)

We had planned to describe for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We had planned to judge studies as at low risk of bias if they were blinded. We had planned to assess blinding separately for different outcomes or classes of outcomes. We had planned to assess the methods as:

- adequate, inadequate, or unclear for participants;
- adequate, inadequate, or unclear for personnel; or
- adequate, inadequate, or unclear for outcome assessors.

(4) Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations)

We had planned to describe for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We had planned to state whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. We had planned to assess methods as:

- adequate;
- inadequate; or
- unclear.

(5) Selective reporting bias

We had planned to describe for each included study how we investigated the possibility of selective outcome reporting bias and what we found. We had planned to assess the methods as:

- adequate (where it was clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review have been reported);
- inadequate (where not all of the study's prespecified outcomes have been reported; one or more reported primary outcomes were not prespecified; outcomes of interest were reported incompletely and so could not be used; study failed to include results of a key outcome that would have been expected to have been reported); or
- unclear.

(6) Other sources of bias

We had planned to describe for each included study any important concerns we had about other possible sources of bias. We had planned to assess whether each study was free of other problems that could put it at risk of bias:

- yes;
- no; or
- unclear.

(7) Overall risk of bias

We had planned to make explicit judgements about whether studies were at high risk of bias, according to the criteria provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). With reference to (1) to (6) above, we had planned to assess the likely magnitude and direction of the bias and whether we considered it likely to have impacted the findings. We had also planned to explore the impact of the level of bias through undertaking sensitivity analyses.

Measures of treatment effect

For dichotomous data, we had planned to present our results as summary risk ratios (RR) with 95% confidence intervals (CI). For continuous data, we had planned to use the mean difference (MD) if outcomes were measured in the same way between trials and the standardised mean difference (SMD) to combine trials that measured the same outcome with different methods/units.

Unit of analysis issues

We had planned to deal with cluster-RCTs and cross-over trials as specified in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Dealing with missing data

We had planned to contact trial authors to retrieve missing data. We had planned to perform a sensitivity analysis to evaluate the impact of our assumption on the results.

Assessment of heterogeneity

We had planned to apply tests for heterogeneity among trials, if appropriate, using the I^2 statistic. In the case of high levels of heterogeneity among trials (greater than 50%), we had planned to explore sources of the heterogeneity by subgroup analysis (see

[Subgroup analysis and investigation of heterogeneity](#)). We had planned to use a random-effects meta-analysis model as an overall summary where we considered this to be appropriate.

Assessment of reporting biases

We had planned to assess reporting bias by comparing the published article with the study protocol.

Data synthesis

We had planned to carry out statistical analysis using Review Manager 5 software ([Review Manager 2014](#)). In the absence of significant heterogeneity, where trials were sufficiently similar, we had planned to use a fixed-effect meta-analysis model for combining data.

GRADE and 'Summary of findings' table

We had planned to create a 'Summary of findings' table. However, because no studies met inclusion criteria, this was not possible. We planned to use the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of the evidence ([Atkins 2004](#)). We had planned to use methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions*, [Higgins 2011](#), and GRADEpro GDT software ([GRADEpro GDT 2015](#)). We would have justified all decisions to down- or upgrade the evidence quality of studies in

footnotes, and made comments to aid readers' understanding of the review where necessary.

Subgroup analysis and investigation of heterogeneity

We had planned to subgroup participants on the basis of the antibiotics used to treat severe CAP; any prior antibiotic treatment administered to children; children receiving intramuscular antibiotics prior to hospitalisation and intravenous antibiotic therapy; and any concomitant respiratory disease the child had (asthma, bronchiolitis, etc.).

Sensitivity analysis

We had planned to carry out a sensitivity analysis to explore the effect of trial quality (assessed by concealment of allocation) by excluding studies with clearly inadequate allocation concealment.

RESULTS

Description of studies

We conducted the electronic searches on 22 December 2016 and identified a total of 2762 studies were identified after removing duplicates. However, none met the eligibility criteria.

Results of the search

We assessed only one study in detail ([Greenberg 2014](#)), but it was excluded (see [Excluded studies](#); [Figure 1](#)).

Figure 1. Study flow diagram

Included studies

No studies fulfilled our inclusion criteria.

Excluded studies

We excluded one study conducted in Israel, which studied short-course versus long-course oral amoxicillin for CAP ([Greenberg 2014](#)). This trial was conducted in two phases and enrolled 140 children: 12, 56, and 72 children were enrolled in the three-day, five-day and 10-day treatment groups, respectively. The first phase studied a three-day versus 10-day course of oral amoxicillin. During this phase the study randomised 22 children: 40% of children in the three-day antibiotics group experienced treatment failure (e.g. required a rescue treatment or hospitalisation) compared to none in the 10-day course group. Children were then randomised to a five-day versus 10-day course of oral amoxicillin; there was no statistically significant difference between the groups. The study concluded that five days of high-dose oral amoxicillin was highly effective and equivalent to a 10-day treatment, while a three-day treatment may be associated with unacceptable failure rates.

However, we excluded this study from the review because the antibiotics were given orally rather than intravenously and it was not clear if all of the children had severe pneumonia.

Risk of bias in included studies

No studies fulfilled the inclusion criteria, therefore we did not assess risk of bias.

Effects of interventions

No studies fulfilled the inclusion criteria.

DISCUSSION

Summary of main results

We did not identify any studies for inclusion. The one excluded study from Israel compared short-course versus long-course oral antibiotic (amoxicillin) for CAP ([Greenberg 2014](#)). The study concluded that five days of high-dose oral amoxicillin was highly effective and equivalent to a 10-day treatment, while a three-day treatment may be associated with unacceptable failure rates.

However, we excluded this study because the antibiotics were given orally and it was not clear if all the participants had severe pneumonia.

Overall completeness and applicability of evidence

No studies fulfilled the inclusion criteria.

Quality of the evidence

There is no evidence to support a short course (two to three days) of intravenous antibiotics for severe pneumonia as there are no RCTs that have studied this question.

Potential biases in the review process

We were aware of the possibility of introducing bias in the selection of studies, therefore two review authors independently assessed eligibility for inclusion.

Agreements and disagreements with other studies or reviews

No studies fulfilled the inclusion criteria.

AUTHORS' CONCLUSIONS

Implications for practice

There are no randomised controlled trials that have studied a shorter course (two to three days) of intravenous antibiotics (alone or in combination with oral antibiotics) compared to a longer course (five days) for severe community-acquired pneumonia in children aged two months to 59 months.

Implications for research

There are currently no studies addressing the primary question of this review. However, this is an important question as

severe pneumonia is a major problem in low- and middle-income countries and requires significant financial expenditure at secondary and tertiary health service levels. The 2013 World Health Organization guidelines recommend five days of intravenous antibiotics for severe pneumonia ([WHO 2014](#)). Since we did not identify any studies for inclusion, there is no evidence to indicate whether a shorter course of antibiotics is better than a longer course.

An earlier Cochrane Review that compared oral antibiotics with intravenous antibiotics for hospitalised children (aged three months to five years) with severe pneumonia concluded that oral antibiotics are a safe and effective alternative to parenteral antibiotics when there are no associated complications ([Rojas-Reyes 2006](#)). However, those results were based on two studies (1836 children) that could not be pooled.

Based on recent evidence of the effectiveness of oral amoxicillin for the treatment of fast breathing in newborn infants and the uncertainty around the diagnostic criteria for pneumonia, future studies of antibiotic therapy will need better characterisation of patient populations and objective criteria for the diagnosis of severe pneumonia (such as radiologically proven pneumonia) ([AFRINEST 2015a](#); [AFRINEST 2015b](#); [Baqui 2015](#)).

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REFERENCES

References to studies excluded from this review

Greenberg 2014 {published and unpublished data}

Greenberg D, Ben-Shimol S, Zdaka Y, Givon-Lavi N, Dagan R. Short antibiotic treatment (Rx) for community-acquired alveolar pneumonia (CAAP) in children - a double blinded, randomized trial. 48th Annual Meeting of Infectious Disease Society of America (IDSA), 2010 October 21-24. Vancouver, Canada. 2010. [Abstract No 514]

* Greenberg D, Givon-Lavi N, Sadaka Y, Ben-Shimol S, Bar-Ziv J, Dagan R. Short-course antibiotic treatment for community-acquired alveolar pneumonia in ambulatory children: a double-blind, randomized, placebo-controlled trial. *Pediatric Infectious Disease Journal* 2014;**33**(2):136-42.

Additional references

AFRINEST 2015a

African Neonatal Sepsis Trial (AFRINEST) group, Tshetu A, Lokangaka A, Ngaima S, Engmann C, Esamai F, et al. Oral amoxicillin compared with injectable procaine benzylpenicillin plus gentamicin for treatment of neonates and young infants with fast breathing when referral is not possible: a randomised, open-label, equivalence trial. *Lancet* 2015; Vol. 385, issue 9979:1758-66. [DOI: [10.1016/S0140-6736\(14\)62285-6](https://doi.org/10.1016/S0140-6736(14)62285-6)]

AFRINEST 2015b

African Neonatal Sepsis Trial (AFRINEST) group, Tshetu A, Lokangaka A, Ngaima S, Engmann C, Esamai F, et al. Simplified antibiotic regimens compared with injectable procaine benzylpenicillin plus gentamicin for treatment of neonates and young infants with clinical signs of possible serious bacterial infection when referral is not possible: a randomised, open-label, equivalence trial. *Lancet* 2015; Vol. 385, issue 9979:1767-76. [DOI: [10.1016/S0140-6736\(14\)62284-4](https://doi.org/10.1016/S0140-6736(14)62284-4)]

Ashraf 2008

Ashraf H, Jahan SA, Alam NH, Mahmud R, Kamal SM, Salam MA, et al. Day-care management of severe and very severe pneumonia, without associated co-morbidities such as severe malnutrition, in an urban health clinic in Dhaka, Bangladesh. *Archives of Disease in Childhood* 2008;**93**(6):490-4.

Atkins 2004

Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. GRADE Working Group. Grading quality of evidence and strength of recommendations. *BMJ* 2004;**328**(7454):1490.

Baqui 2015

Baqui AH, Saha SK, Ahmed AS, Shahidullah M, Quasem I, Roth DE, et al. Projahnmo Study Group in Bangladesh. Safety and efficacy of alternative antibiotic regimens compared with 7 day injectable procaine benzylpenicillin and gentamicin for outpatient treatment of neonates and young infants with clinical signs of severe infection when referral is not possible: a randomised, open-label, equivalence trial. *Lancet Global Health* 2015; Vol. 3, issue 5:e279-87. [DOI: [10.1016/S2214-109X\(14\)70347-X](https://doi.org/10.1016/S2214-109X(14)70347-X)]

Boluyt 2008

Boluyt N, Tjosvold L, Lefebvre C, Klassen TP, Offringa M. Usefulness of systematic review search strategies in finding child health systematic reviews in MEDLINE. *Archives of Pediatrics and Adolescent Medicine* 2008;**162**(2):111-6.

Campbell 1995

Campbell H. Acute respiratory infection: a global challenge. *Archives of Disease in Childhood* 1995;**73**(4):281-6.

Chowdhury 2008

Chowdhury EK, El Arifeen S, Rahman M, Hoque DE, Hossain MA, Begum K, et al. Care at first-level facilities for children with severe pneumonia in Bangladesh: a cohort study. *Lancet* 2008;**372**(9641):822-30.

Durbin 2008

Durbin WJ, Stille C. Pneumonia. *Pediatrics in Review* 2008;**29**(5):147-58.

Fox 2015

Fox MP, Baqui AH, Hibberd PL, Black RE, Santosham M, Bhutta Z, et al. Antibiotic trials for community-acquired pneumonia. *Lancet Respiratory Medicine* 2015;**3**(3):e4-5.

Gaston 2002

Gaston B. Pneumonia. *Pediatric Reviews* 2002;**23**(4):132-40.

GRADEpro GDT 2015 [Computer program]

McMaster University (developed by Evidence Prime). GRADEpro GDT. Version (accessed prior to 27 July 2017). Hamilton (ON): McMaster University (developed by Evidence Prime), 2015.

Graham 2008

Graham SM, English M, Hazir T, Enarson P, Duke T. Challenges to improving case management of childhood pneumonia at health facilities in resource-limited settings. *Bulletin of the World Health Organization* 2008;**86**(5):349-55.

Higgins 2011

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available at handbook.cochrane.org.

Hussain 2006

Hussain H, Waters H, Omer SB, Khan A, Baig IY, Mistry R, et al. The cost of treatment for child pneumonias and meningitis in the northern areas of Pakistan. *International Journal of Health Planning and Management* 2006;**21**(3):229-38.

Jadavji 1997

Jadavji T, Law B, Lebel MH, Kennedy WA, Gold E, Wang EE. A practical guide for the diagnosis and treatment of pneumonia. *CMAJ: Canadian Medical Association Journal* 1997;**156**(5):S703-11.

Lefebvre 2011

Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Marsh 2008

Marsh DR, Gilroy KE, van de Weerd R, Wansi E, Qazi S. Community case management of pneumonia: at a tipping point? *Bulletin of the World Health Organization* 2008;**86**(5):321-416.

Omidvari 1998

Omidvari K, de Boisblanc BP, Karam G, Nelson S, Haponik E, Summer W. Early transition to oral antibiotic therapy for community-acquired pneumonia: duration of therapy, clinical outcomes, and cost analysis. *Respiratory Medicine* 1998;**92**(8):1032-9.

Ostapchuk 2004

Ostapchuk M, Roberts DM, Haddy R. Community-acquired pneumonia in infants and children. *American Family Physician* 2004;**70**:899-908.

Qazi 2015

Qazi S, Were W. Improving diagnosis of childhood pneumonia. *Lancet Infectious Diseases* 2015;**15**(4):372-3.

Rambaud-Althaus 2015

Rambaud-Althaus C, Althaus F, Genton B, D'Acremont V. Clinical features for diagnosis of pneumonia in children younger than 5 years: a systematic review and meta-analysis. *Lancet Infectious Diseases* 2015;**15**(4):439-50.

Review Manager 2014 [Computer program]

Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Rojas-Reyes 2006

Rojas-Reyes MX, Granados Rugeles C. Oral antibiotics versus parenteral antibiotics for severe pneumonia in children. *Cochrane Database of Systematic Reviews* 2006, Issue 2. [DOI: [10.1002/14651858.CD004979.pub2](https://doi.org/10.1002/14651858.CD004979.pub2)]

Shoham 2005

Shoham Y, Dagan R, Givon-Lavi N, Liss Z, Shagan T, Zamir O, et al. Community-acquired pneumonia in children: quantifying the burden on patients and their families including decrease in quality of life. *Pediatrics* 2005;**115**(5):1213-9.

UNICEF/WHO 2006

UNICEF/WHO. Pneumonia: the forgotten killer of children. apps.who.int/iris/bitstream/10665/43640/1/9280640489_eng.pdf. (accessed prior to 27 July 2017) 2006.

Walker 2013

Walker CL, Rudan I, Liu L, Nair H, Theodoratou E, Bhutta ZA, et al. Global burden of childhood pneumonia and diarrhoea. *Lancet* 2013;**381**(9875):1405-16.

WHO 1991

World Health Organization. Programme of Acute Respiratory Infections. Technical bases for the WHO recommendations on the management of pneumonia in children at first-level health facilities (1991). apps.who.int/iris/handle/10665/61199 (accessed prior to 27 July 2017).

WHO 2005

World Health Organization. Pocket book of hospital care for children: guidelines for the management of common illnesses with limited resources (2005). apps.who.int/iris/bitstream/10665/43206/1/9241546700.pdf. Geneva, Switzerland: World Health Organization, (accessed prior to 27 July 2017).

WHO 2013

World Health Organization. Pocket book of hospital care for children: guidelines for the management of common childhood illnesses (2nd edition, 2013). apps.who.int/iris/bitstream/10665/81170/1/9789241548373_eng.pdf (accessed prior to 27 July 2017).

WHO 2014

World Health Organization. Revised WHO classification and treatment of childhood pneumonia at health facilities: evidence summaries (2014). apps.who.int/iris/bitstream/10665/137319/1/9789241507813_eng.pdf. Geneva, Switzerland: World Health Organization, (accessed prior to 27 July 2017).

Zar 2013

Zar HJ, Madhi SA, Aston SJ, Gordon SB. Pneumonia in low and middle income countries: progress and challenges. *Thorax* 2013;**68**:1052-6.

References to other published versions of this review

Lassi 2015

Lassi ZS, Imdad A, Bhutta ZA. Short-course versus long-course intravenous therapy with the same antibiotic for severe community-acquired pneumonia in children aged two months to 59 months. *Cochrane Database of Systematic Reviews* 2015, Issue 6. [DOI: [10.1002/14651858.CD008032.pub2](https://doi.org/10.1002/14651858.CD008032.pub2)]

Zaidi 2009

Zaidi A, Haider BA, Bhutta ZA. Short course versus long course intravenous therapy of the same antibiotic for severe community-acquired pneumonia in children aged two months to 59 months. *Cochrane Database of Systematic Reviews* 2009, Issue 4. [DOI: [10.1002/14651858.CD008032](https://doi.org/10.1002/14651858.CD008032)]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Greenberg 2014	Antibiotics were given orally, and it was not clear if all participants had severe pneumonia.

APPENDICES

Appendix 1. Previous search strategy

7 March 2010

We searched *The Cochrane Library*, Cochrane Central Register of Controlled Trials (CENTRAL 2010, Issue 1), which includes the ARI Group's and Infectious Diseases Group's Specialised Registers; MEDLINE (1966 to February Week 4, 2010) and Embase (1974 to March 2010).

We used the following search strategy to search MEDLINE and CENTRAL. We combined the MEDLINE search strategy with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximising version (2008 revision); Ovid format (Lefebvre 2009) and a filter for identifying 'child' studies ([Boluyt 2008](#)). We adapted the search strategy to search Embase.

13 March 2014

We searched *The Cochrane Library*, Cochrane Central Register of Controlled Trials (CENTRAL 2014, Issue 1, limited to year published 2009 to 2014), which includes the ARI Group's and Infectious Diseases Group's Specialised Registers; MEDLINE (from 1 January 2010 to March week 1 2014) and Embase (from 1 January 2010 to March 2014).

4 February 2015

We searched *The Cochrane Library*, Cochrane Central Register of Controlled Trials (CENTRAL 2015, Issue 1, limited to years published 2013 to 2015), which includes the ARI Group's and Infectious Diseases Group's Specialised Registers; MEDLINE (1 January 2014 to January week 4 2015) and Embase (1 March 2014 to February 2015).

MEDLINE (Ovid)

```

1 exp Pneumonia/
2 pneumon*.tw.
3 cap.tw.
4 or/1-3
5 exp Anti-Bacterial Agents/
6 antibiotic*.tw.
7 amoxicillin*.tw.
8 penicillin*.tw.
9 ampicillin*.tw.
10 cotrimoxazole*.tw.
11 chloramphenicol*.tw.
12 trimethoprim*.tw.
13 sulphamethoxazole*.tw.
14 tmp smx.tw.
15 or/5-14
16 4 and 15
17 exp Infant/
18 (infant* or infancy or newborn* or baby* or babies or neonat* or preterm* or prematur*).tw.
19 exp Child/
20 (child* or schoolchild* or school age* or preschool* or kid or kids or toddler*).tw.
21 Adolescent/
22 (adoles* or teen* or boy* or girl*).tw.
23 Minors/

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24 Puberty/
25 (minor* or pubert* or pubescen*).tw.
26 exp Pediatrics/
27 (pediatric* or paediatric*).tw.
28 exp Schools/
29 (nursery school* or kindergar* or primary school* or secondary school* or elementary school* or high school* or highschool*).tw.
30 or/17-29
31 16 and 30

Appendix 2. MEDLINE (Ovid) search strategy

1 exp Pneumonia/
2 pneumon*.tw.
3 (bronchopneumon* or pleuropneumon*).tw.
4 cap.tw.
5 or/1-4
6 exp Anti-Bacterial Agents/
7 antibiotic*.tw.
8 (antibacteria* or anti-bacteria*).tw.
9 (amoxicillin* or amoxycillin*).tw,nm.
10 penicillin*.tw,nm.
11 ampicillin*.tw,nm.
12 cotrimoxazole*.tw,nm.
13 chloramphenicol*.tw,nm.
14 trimethoprim*.tw,nm.
15 sulphamethoxazole*.tw,nm.
16 tmp smx.tw,nm.
17 or/6-16
18 5 and 17

Appendix 3. Embase (Elsevier) search strategy

#17. #11 AND #16
#16. #12 OR #13 OR #14 OR #15
#15. random*:ab,ti OR placebo*:ab,ti OR factorial*:ab,ti OR crossover*:ab,ti OR 'cross over':ab,ti OR 'cross-over':ab,ti OR volunteer*:ab,ti OR assign*:ab,ti OR allocat*:ab,ti
#14. ((singl* OR doubl*) NEAR/2 (mask* OR blind*)):ab,ti
#13. 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp
#12. 'randomized controlled trial'/exp
#11. #7 AND #10
#10. #8 OR #9
#9. infant*:ab,ti OR infancy*:ab,ti OR newborn*:ab,ti OR baby*:ab,ti OR babies*:ab,ti OR neonat*:ab,ti OR preterm*:ab,ti OR prematur*:ab,ti OR
child*:ab,ti OR schoolchild*:ab,ti OR preschool*:ab,ti OR kid*:ab,ti OR kids*:ab,ti OR toddler*:ab,ti OR adoles*:ab,ti OR teen*:ab,ti OR boy*:ab,ti OR girl*:ab,ti OR minor*:ab,ti OR pubert*:ab,ti OR pubescen*:ab,ti OR pediatric*:ab,ti OR paediatric*:ab,ti OR kindergar*:ab,ti OR highschool*:ab,ti OR ((age* OR nursery OR primary OR secondary OR elementary OR high) NEAR/2 school*):ab,ti
#8. 'child'/exp OR 'adolescent'/exp OR 'puberty'/exp OR 'pediatrics'/exp OR 'school'/exp
#7. #3 AND #6
#6. #4 OR #5
#5. antibiotic*:ab,ti OR amoxicillin*:ab,ti OR penicillin*:ab,ti OR ampicillin*:ab,ti OR cotrimoxazole*:ab,ti OR chloramphenicol*:ab,ti OR trimethoprim*:ab,ti OR sulphamethoxazole*:ab,ti OR tmp smx*:ab,ti
#4. 'antibiotic agent'/exp
#3. #1 OR #2
#2. pneumon*:ab,ti OR cap:ab,ti
#1. 'pneumonia'/exp

Appendix 4. ClinicalTrials.gov

(pneumonia OR pneumonias OR bronchopneumonia OR bronchopneumonias OR pleuropneumonia OR pleuropneumonias OR cap) AND (antibiotic OR antibiotics OR antibacterial OR anti-bacterial OR amoxicillin OR amoxicillins OR amoxycillin OR amoxycillins)

(pneumonia OR pneumonias OR bronchopneumonia OR bronchopneumonias OR pleuropneumonia OR pleuropneumonias OR cap) AND (penicillin OR penicillins OR ampicillin OR ampicillins OR cotrimoxazole OR cotrimoxazoles)

(pneumonia OR pneumonias OR bronchopneumonia OR bronchopneumonias OR pleuropneumonia OR pleuropneumonias OR cap) AND (chloramphenicol OR chloramphenicols OR trimethoprim OR trimethoprim)

(pneumonia OR pneumonias OR bronchopneumonia OR bronchopneumonias OR pleuropneumonia OR pleuropneumonias OR cap) AND (sulphamethoxazole OR sulphamethoxazoles OR tmp smx)

Appendix 5. Australian New Zealand Clinical Trials Registry (anzctr.org.au)

(pneumon* OR bronchopneumon* OR pleuropneumon* OR cap) AND (antibiotic* OR antibacteria*)

(pneumon* OR bronchopneumon* OR pleuropneumon* OR cap) AND (anti-bacteria* OR amoxicillin*)

(pneumon* OR bronchopneumon* OR pleuropneumon* OR cap) AND (amoxycillin* OR penicillin*)

(pneumon* OR bronchopneumon* OR pleuropneumon* OR cap) AND (ampicillin* OR cotrimoxazole*)

(pneumon* OR bronchopneumon* OR pleuropneumon* OR cap) AND (chloramphenicol* OR trimethoprim*)

(pneumon* OR bronchopneumon* OR pleuropneumon* OR cap) AND (sulphamethoxazole* OR tmp smx)

Appendix 6. Current Controlled Trials Register (ISRCTN) (controlled-trials.com/isrctn)

(pneumonia OR bronchopneumonia OR pleuropneumonia OR cap) AND (antibiotic OR antibiotics OR antibacterial OR anti-bacterial OR amoxicillin OR amoxicillins OR amoxycillin OR amoxycillins OR penicillin OR penicillins OR ampicillin OR ampicillins OR cotrimoxazole OR cotrimoxazoles OR chloramphenicol OR chloramphenicols OR trimethoprim OR trimethoprim OR sulphamethoxazole OR "tmp smx")

Appendix 7. WHO ICTRP (apps.who.int/trialsearch)

pneumon* AND antibiotic* OR pneumon* AND antibacteria* OR pneumon* AND anti-bacteria* OR pneumon* AND amoxicillin* OR pneumon* AND amoxycillin* OR pneumon* AND penicillin* OR pneumon* AND ampicillin* OR pneumon* AND cotrimoxazole* OR pneumon* AND chloramphenicol* OR pneumon* AND trimethoprim* OR pneumon* AND sulphamethoxazole* OR pneumon* AND tmp smx

bronchopneumon* AND antibiotic* OR bronchopneumon* AND antibacteria* OR bronchopneumon* AND anti-bacteria* OR bronchopneumon* AND amoxicillin* OR bronchopneumon* AND amoxycillin* OR bronchopneumon* AND penicillin* OR bronchopneumon* AND ampicillin* OR bronchopneumon* AND cotrimoxazole* OR bronchopneumon* AND chloramphenicol* OR bronchopneumon* AND trimethoprim* OR bronchopneumon* AND sulphamethoxazole* OR bronchopneumon* AND tmp smx

pleuropneumon* AND antibiotic* OR pleuropneumon* AND antibacteria* OR pleuropneumon* AND anti-bacteria* OR pleuropneumon* AND amoxicillin* OR pleuropneumon* AND amoxycillin* OR pleuropneumon* AND penicillin* OR pleuropneumon* AND ampicillin* OR pleuropneumon* AND cotrimoxazole* OR pleuropneumon* AND chloramphenicol* OR pleuropneumon* AND trimethoprim* OR pleuropneumon* AND sulphamethoxazole* OR pleuropneumon* AND tmp smx

cap AND antibiotic* OR cap AND antibacteria* OR cap AND anti-bacteria* OR cap AND amoxicillin* OR cap AND amoxycillin* OR cap AND penicillin* OR cap AND ampicillin* OR cap AND cotrimoxazole* OR cap AND chloramphenicol* OR cap AND trimethoprim* OR cap AND sulphamethoxazole* OR cap AND tmp smx

WHAT'S NEW

Date	Event	Description
22 December 2016	New search has been performed	We updated the searches to 22 December 2016.
22 December 2016	New citation required but conclusions have not changed	Our searches identified 4295 records, however no studies met our predefined inclusion criteria.

CONTRIBUTIONS OF AUTHORS

Dr Zohra S Lassi (ZRL) updated the review. ZRL and Dr Aamer Imdad (AI) wrote the earlier review. Professor Zulfiqar Ahmed Bhutta (ZAB) was the overall supervisor and guarantor of the review.

DECLARATIONS OF INTEREST

Zohra S Lassi: None known.
Aamer Imdad: None known.
Zulfiqar A Bhutta: None known.

SOURCES OF SUPPORT

Internal sources

- Aga Khan University, Pakistan.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We added the phrase "(alone or in combination with oral antibiotics)" to the Objectives: To evaluate the efficacy of short-course (two to three days) versus long-course (five days) intravenous therapy (alone or in combination with oral antibiotics) with the same antibiotic for severe community-acquired pneumonia (CAP) in children aged two months to 59 months.

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Bacterial Agents [*administration & dosage]; Community-Acquired Infections [drug therapy]; Drug Administration Schedule; Injections, Intravenous; Pneumonia [*drug therapy]; Time Factors

MeSH check words

Child, Preschool; Humans