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April 2008

Short-course versus long-course antibiotic therapy for non-severe community-acquired pneumonia in children aged 2 months to 59 months

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Short-course versus long-course antibiotic therapy for non-severe community-acquired pneumonia in children aged 2 months to 59 months (Review)

Haider BA, Lassi ZS, Bhutta ZA

Haider BA, Lassi ZS, Bhutta ZA.
Short-course versus long-course antibiotic therapy for non-severe community-acquired pneumonia in children aged 2 months to 59 months.
Cochrane Database of Systematic Reviews 2008, Issue 2. Art. No.: CD005976.
DOI: 10.1002/14651858.CD005976.pub2.

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[Intervention Review]

Short-course versus long-course antibiotic therapy for non-severe community-acquired pneumonia in children aged 2 months to 59 months

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Editorial group: Cochrane Acute Respiratory Infections Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 4, 2011.
Review content assessed as up-to-date: 1 September 2010.

Citation: Haider BA, Lassi ZS, Bhutta ZA. Short-course versus long-course antibiotic therapy for non-severe community-acquired pneumonia in children aged 2 months to 59 months. *Cochrane Database of Systematic Reviews* 2008, Issue 2. Art. No.: CD005976. DOI: 10.1002/14651858.CD005976.pub2.

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ABSTRACT

Background

Pneumonia is the leading cause of mortality in children under five years of age. Treatment of pneumonia requires an effective antibiotic used in adequate doses for an appropriate duration. Recommended duration of treatment ranges between 7 and 14 days, but this is not based on any empirical evidence. Shorter duration of therapy, if found to be effective, could be particularly important in resource-poor settings where there is a high risk of death, poor access to medicines and health care and limited budgets for medicines.

Objectives

To evaluate the efficacy of short-course versus long-course therapy with the same antibiotic for non-severe community-acquired pneumonia (CAP) in children aged 2 to 59 months.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2010, Issue 3) which contains the Cochrane Acute Respiratory Infections Group's Specialised Register and the Database of Abstracts of Reviews of Effects, MEDLINE (OVID) (January 1966 to August Week 4, 2010), EMBASE (Embase.com) (1974 to August 2010) and LILACS (1982 to August 2010).

Selection criteria

All randomised controlled trials (RCTs) evaluating the efficacy of short-course versus long-course therapy using the same antibiotic for non-severe CAP in children.

Data collection and analysis

Two review authors independently assessed trial quality and extracted the data.

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Main results

Four studies (6177 children) were included. Analysis of three days versus five days of treatment with the same antibiotic for non-severe CAP in children showed non-significant differences in rates of clinical cure at the end of treatment (risk ratio (RR) 0.99; 95% confidence interval (CI) 0.97 to 1.01), treatment failure at the end of treatment (RR 1.07; 95% CI 0.92 to 1.25), and relapse rate after seven days of clinical cure (RR 1.09; 95% CI 0.84 to 1.42), and we found no heterogeneity in the results. Subgroup analysis evaluating the impact of different antibiotics showed non-significant differences for these outcomes with different durations of therapy.

Authors' conclusions

The evidence of this review suggests that a short course (three days) of antibiotic therapy is as effective as a longer treatment (five days) for non-severe CAP in children under five years of age. However, there is a need for more well-designed RCTs to support our review findings.

PLAIN LANGUAGE SUMMARY

Comparing different durations of the same antibiotic therapy for non-severe community-acquired pneumonia in children under five years of age

Pneumonia is a major cause of mortality in children under five years of age. Treatment of pneumonia requires the use of an effective antibiotic in adequate doses for an appropriate duration. In most cases, treatment ranges between 7 and 14 days, but this is not based on any empirical evidence. Shorter duration of therapy, if found to be effective, would not only be beneficial in resource-poor settings but also result in improved adherence to therapy and reduced resistance to antibiotics and adverse effects. This review of four studies involving 6177 children found that a short course (three days) of antibiotic therapy is equally as effective as a longer treatment (five days) for non-severe pneumonia. We also found that different durations of either amoxicillin or cotrimoxazole give similar results in terms of clinical cure, failure of the treatment and rate of relapse.

BACKGROUND

Description of the condition

Pneumonia is an infection of the lungs (Gaston 2002). Pneumonia can be caused by organisms such as bacteria and viruses. In children, the organisms which cause pneumonia vary with the age of the child (McIntosh 2002; UNICEF 2006). Group B streptococcus and gram-negative enteric bacteria are the most common pathogens in neonates (from birth to 20 days after birth), whereas in infants aged between three weeks and three months *Streptococcus pneumoniae (S. pneumoniae)* is the most common pathogen. In infants older than four months and in preschool-aged children viruses are a frequent cause and *S. pneumoniae* is the most common bacterial pathogen (Ostapchuk 2004; Sinianiotis 2005). *Staphylococcus aureus (S. aureus)* and *Haemophilus influenzae (H. influenzae)*, including non-typable, are also common causes of childhood pneumonia in low-income countries (McIntosh 2002; UNICEF 2006).

Acute lower respiratory tract infections (LRTIs) are among the leading causes of mortality in children under five years of age (Bryce 2005; Rudan 2008); they account for nearly two million deaths each year with most of the deaths occurring in low-income countries. Pneumonia is the largest killer, accounting for 19% of all child deaths in low-income countries (Bryce 2005; Rudan 2008). Interventions that affect mortality due to pneumonia are therefore of great importance in an effort to improve child survival.

Description of the intervention

Definitions of pneumonia vary widely. Some require evidence of the presence of infiltrates on a chest radiograph, whereas others require certain respiratory signs or symptoms (McIntosh 2002). The World Health Organization (WHO) has defined pneumonia solely on the basis of clinical findings obtained by visual inspection and setting respiratory rate cut-offs (WHO 1981). According to the WHO guideline, a respiratory rate of > 50 per minute in infants aged two to 11 months and a respiratory rate of > 40 per

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minute in children younger than 12 to 59 months with no lower chest in-drawing, suggests non-severe pneumonia; while a respiratory rate of > 50 per minute in infants aged two to 11 months and a respiratory rate of > 40 per minute in children younger than 12 to 59 months plus lower chest in-drawing indicates severe pneumonia. Indicators for severe pneumonia plus convulsions, abnormal sleep and difficulty in waking up, stridor in a calm child and inability to drink, indicate very severe pneumonia. To reduce the number of people dying from pneumonia, the WHO developed standard guidelines for the management of acute respiratory tract infections (ARTIs) (WHO 1990). These guidelines were developed using evidence from studies on aetiology, clinical aspects and susceptibility (WHO 1991). As *S. pneumoniae* and *H. influenzae* are the most common causes of childhood pneumonia in low-income countries, the WHO recommends using oral cotrimoxazole or amoxicillin as first-line drugs for treatment of non-severe CAP at first-level health facilities (WHO 1990; WHO 1991). These guidelines have effectively reduced death from pneumonia in low-income countries (Sazawal 2003).

How the intervention might work

Treatment of CAP requires the use of an effective antibiotic given in adequate doses and for an appropriate duration. Recommendations for antibiotic therapy for CAP are based, in general, on aetiological diagnosis (Prober 2000). Identification of the causative organism in routine clinical care is rare and is not usually attempted. Because of these diagnostic problems empirical antibiotic therapy is the commonly accepted practice worldwide (McIntosh 2002). In most cases the duration of treatment ranges between 7 and 14 days, but this is not based on any empirical evidence. Rather this treatment duration seems to be the result of initial treatment studies of tonsillo-pharyngitis, which was treated for 10 to 14 days (Pichichero 2000).

Why it is important to do this review

Optimum duration of therapy for CAP is especially important in resource-poor settings where there is a high risk of death, poor access to medicines and health care, and limited budgets for medicines (Campbell 1995). Important aspects of a shorter course of antibiotic therapy, if found to be effective and without an increase in morbidity and mortality, include improved adherence to therapy, reduced antimicrobial resistance and lowered cost.

OBJECTIVES

To evaluate the efficacy of short-course versus long-course therapy with the same antibiotic for non-severe CAP in children aged 2 to 59 months.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) evaluating the efficacy of short-course versus long-course therapy using the same antibiotic for non-severe CAP in children. We considered studies using a standard WHO algorithm for ARTIs (WHO 1991), which defines non-severe CAP as cough or difficult and fast breathing (respiratory rate of 50 breaths per minute or more for children aged 2 months to 11 months, or respiratory rate of 40 breaths per minute or more for children aged 12 months to 59 months). We also included trials published in languages other than English after translation. We excluded non-randomised (quasi-randomised) trials.

Types of participants

We included children aged 2 months to 59 months with non-severe CAP. We excluded studies including children with severe or very severe CAP (defined on the basis of chest in-drawing, inability to drink, convulsions, abnormal sleepiness or difficulty waking), any chronic illness, or those who had received antibiotics in the past 48 hours.

Types of interventions

Short-course versus long-course therapy using the same antibiotic for non-severe CAP in children. We performed a comparison of different durations of antibiotic therapies (durations between three to seven days).

Types of outcome measures

Primary outcomes

Clinical cure rate, defined as return of respiratory rate to the normal age-specific range.

Secondary outcomes

1. Treatment failure: defined as development of chest in-drawing, convulsions, drowsiness, or inability to drink at any time; respiratory rate above the age-specific cut-off on completion of treatment; or 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 CAP within seven days after fast breathing had returned to normal.

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3. Additional interventions used.
4. Mortality at one month.

Search methods for identification of studies

Electronic searches

For this update we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2010, Issue 3) which contains the Cochrane Acute Respiratory Infections Group's Specialised Register and the Database of Abstracts of Reviews of Effects, MEDLINE (OVID) (January 1966 to August Week 4, 2010), EMBASE (Embase.com) (1974 to August 2010) and LILACS (1982 to August 2010). See Appendix 1 for details of previous searches.

We used the following search terms to search MEDLINE and CENTRAL. We combined the MEDLINE search with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximising version (2008 revision) (Lefebvre 2008). The search strategy also incorporated the search strategy devised by Boluyt 2008 to identify child studies. We adapted the terms to search EMBASE (Appendix 2) and LILACS (Appendix 3).

MEDLINE (OVID)

1 exp Pneumonia/
2 (pneumon* or CAP).mp.
3 lower respiratory tract infection*.mp.
4 lower respiratory infection*.mp.
5 LRTI.mp.
6 or/1-5
7 exp Anti-Bacterial Agents/
8 antibiotic*.mp.
9 exp Anti-Infective Agents/
10 exp Amoxicillin/
11 exp Penicillins/
12 exp Ampicillin/
13 exp Trimethoprim-Sulfamethoxazole Combination/
14 exp Macrolides/
15 exp Erythromycin/
16 exp Azithromycin/
17 exp Clarithromycin/
18 (penicillin* or amoxicillin or ampicillin or cotrimoxazole or macrolide* or erythromycin or azithromycin or clarithromycin).mp.
19 or/7-18
20 6 and 19)
21 exp Infant/)
22 (infant* or infancy or newborn* or baby* or babies or neonat* or preterm* or prematur*).tw.
23 exp Child/
24 (child* or schoolchild* or school age* or preschool* or kid or kids or toddler*).tw.
25 Adolescent/
26 (adoles* or teen* or boy* or girl*).tw.
27 Minors/
28 Puberty/
29 (minor* or pubert* or pubescen*).tw.
30 exp Pediatrics/
31 (pediatric* or pediatric*).tw.
32 exp Schools/
33 (nursery school* or kindergar* or primary school* or secondary school* or elementary school* or high school* or highschool*).tw.
34 or/21-33
35 20 and 34 (12429)

Searching other resources

We limited searches to human studies and we imposed no language or publication restrictions. We also searched the related conference proceedings for relevant abstracts. We contacted organisations and researchers in the field and pharmaceutical companies for information on unpublished and ongoing trials. We also checked the reference lists of all trials identified by the above methods.

Data collection and analysis

Selection of studies

Two review authors (BAH, ZSL) independently assessed the eligibility of the trials. We selected studies as being potentially relevant by screening the titles and abstracts, if available. We retrieved and reviewed the full text of the article if we could not ascertain the relevance of studies by screening the title and the abstract. We retrieved full texts of all potentially relevant articles and independently assessed the eligibility by filling out eligibility forms designed in accordance with the specified inclusion criteria. We resolved disagreements by discussion and a consensus was reached.

Data extraction and management

We carried out data extraction using a data extraction form which was designed and pilot tested by the review authors. The form extracted information regarding:

1. study setting (for example, country, type of population and socioeconomic status);
2. description of antibiotic used (including type of drug, dose, duration and frequency);
3. sample size;
4. length of follow up;
5. randomisation procedure; and

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6. outcomes as listed above.

We extracted the total number of participants for each group for dichotomous outcomes and the number of participants experiencing an event. There were no continuous outcomes in our review.

Assessment of risk of bias in included studies

Two review authors (BAH, ZSL) independently assessed the 'Risk of bias' for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2009). A third review author (ZAB) resolved any disagreements by discussion.

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

We described 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 assessed the method as:

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

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

We described 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 assessed the methods as:

- adequate (for example, 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 described for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Studies were judged at low risk of bias if they were blinded, or if we judged that the lack of blinding could not have affected the results. Blinding was assessed separately for different outcomes or classes of outcomes. We assessed the methods as:

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

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

We described for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We stated 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. Where sufficient information was reported, or could be supplied by the trial authors, we re-included missing data in the analyses which we undertook. We assessed methods as:

- adequate;
- inadequate; or
- unclear.

(5) Selective reporting bias

We described for each included study how we investigated the possibility of selective outcome reporting bias and what we found. We assessed the methods as:

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

(6) Other sources of bias

We described for each included study any important concerns we have about other possible sources of bias. We assessed 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 made explicit judgements about whether studies are at high risk of bias, according to the criteria given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2009). With reference to (1) to (6) above, we assessed the likely magnitude and direction of the bias and whether we consider it is likely to impact on the findings. We also explored the impact of the level of bias through undertaking sensitivity analyses.

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Measures of treatment effect

We extracted the total number of participants for each group and the number of participants experiencing an event for dichotomous outcomes. We used the risk ratio (RR) and 95% confidence intervals (CIs).

Dealing with missing data

We noted levels of attrition for included studies. For all outcomes, analysis was carried out, as far as possible, on an intention-to-treat (ITT) basis, i.e. we attempted to include all participants randomised to each group in the analyses.

Assessment of heterogeneity

We measured heterogeneity among the trials by calculating the I^2 statistic, Chi^2 test P value and by visual inspection of the forest plots. If the I^2 statistic exceeded 30%, Chi^2 test P value was less than 0.1, and visual inspection of the forest plots was indicative of heterogeneity in effect size, then heterogeneity would have been considered to be substantial. We did not find any heterogeneity, therefore subgroup analyses based on differences in dosage, frequency, bacterial or viral aetiology, baseline infant mortality, half-lives of antibiotic used and differences in the techniques for diagnosing CAP were not sought. However, we attempted to look for the use of different antibiotics.

Data synthesis

We carried out statistical analysis using the Review Manager software (RevMan 2008). We used fixed-effect inverse variance meta-analysis for combining data because trials were examining the same intervention, and the trials' populations and methods were judged sufficiently similar.

Subgroup analysis and investigation of heterogeneity

We pre-specified the following subgroup analysis to investigate heterogeneity.

1. Dosage and frequency of antibiotics used.
2. High baseline infant mortality.
3. Bacterial or viral aetiology.
4. Differences in the half-lives of the antibiotics used.
5. Characteristics of the study population.
6. Differences in the technique for diagnosing CAP.

Sensitivity analysis

We undertook sensitivity analysis to study the effect of a short course versus a long course of antibiotic therapy on clinical cure, treatment failure and relapse rates of non-severe CAP by excluding the Kartasasmita 2002 study, for which we did not have information regarding allocation concealment, blinding and loss to follow up. However, the overall effect estimates and CIs were not sensitive to this change.

RESULTS

Description of studies

Results of the search

In this update a total of 296 records were retrieved during the search.

Included studies

We identified only four studies (Agarwal 2004; Kartasasmita 2002; Lupison 1999; MASCOT 2002) as potentially eligible for inclusion in our review. The trial by the ISCAP study group (Agarwal 2004) was conducted in India. The trial by the MASCOT pneumonia study group (MASCOT 2002) was conducted in Pakistan. The trial by Lupison (Lupison 1999) was conducted in Pasay City, Philippines. The trial by the Cotrimoxazole Study Group was conducted in Indonesia and Bangladesh (Kartasasmita 2002). All studies were double-blind and placebo-controlled with individual randomisation of the treatment groups. Participants included children aged 2 to 59 months diagnosed with non-severe CAP which was defined as respiratory rate of more than or equal to 50 breaths per minute for children aged 2 to 11 months, or more than or equal to 40 breaths per minute for children aged 12 to 59 months. Children with severe CAP, any chronic illness and those who had received antibiotics in the previous two days were excluded from the Agarwal 2004 and MASCOT 2002 studies. In Lupison 1999 children were excluded if they presented with ongoing antibiotic treatment for the present illness, chest in-drawing, cyanosis, inability to drink, lethargy, convulsion, severe malnutrition, severe complicating illness, chronic disease, chronic otitis media with acute exacerbation and allergy to cotrimoxazole. There was no significant difference in the baseline characteristics of the study groups (Agarwal 2004; Lupison 1999; MASCOT 2002). We cannot comment on the exclusion criteria used for the participants in the Kartasasmita 2002 study as it is still in its abstract form.

The Agarwal 2004 and MASCOT 2002 studies compared three days versus five days of treatment with oral amoxicillin, given three times daily. In Agarwal 2004 participants received scored dispersible tablets of amoxicillin 125 mg dissolved in 5 ml of water containing an approximate effective dose per kg body weight of 31 to 54 mg/day for the first three days. The dose in the MASCOT 2002 was 15 mg/kg every eight hours for the initial three days. This was followed by either active medicine or a placebo for the next two days. The Kartasasmita 2002 study evaluated three days

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of oral cotrimoxazole against five days of therapy. In Lupison 1999 children older than 12 months were given cotrimoxazole 80 mg BID (twice a day) and children 2 to 12 months old were given cotrimoxazole 40 mg BID.
Please refer to the Characteristics of included studies table for more details.

Excluded studies

We excluded six studies (El Moussaoui 2006; Ficnar 1997; Harris 1998; Leophonte 2002; Peltola 2001; Siegal 1999) as they did not satisfy the inclusion criteria of the review. The study by Harris (Harris 1998) included children aged 6 months to 16 years, Peltola (Peltola 2001) included children aged 3 months to 15 years, and Ficnar (Ficnar 1997) included children of 6 months to 12 years. These studies did not report their outcomes separately for children younger than five years of age. Also Ficnar (Ficnar 1997) was not a RCT. On the other hand, three studies (El Moussaoui 2006; Leophonte 2002; Siegal 1999) only included adult populations.
Please refer to the Characteristics of excluded studies table for more details.

Risk of bias in included studies

Figure 1 and Figure 2 summarise the risk of bias in the included studies. Methodological details for each trial can be found in the Characteristics of included studies table.

Figure 1. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

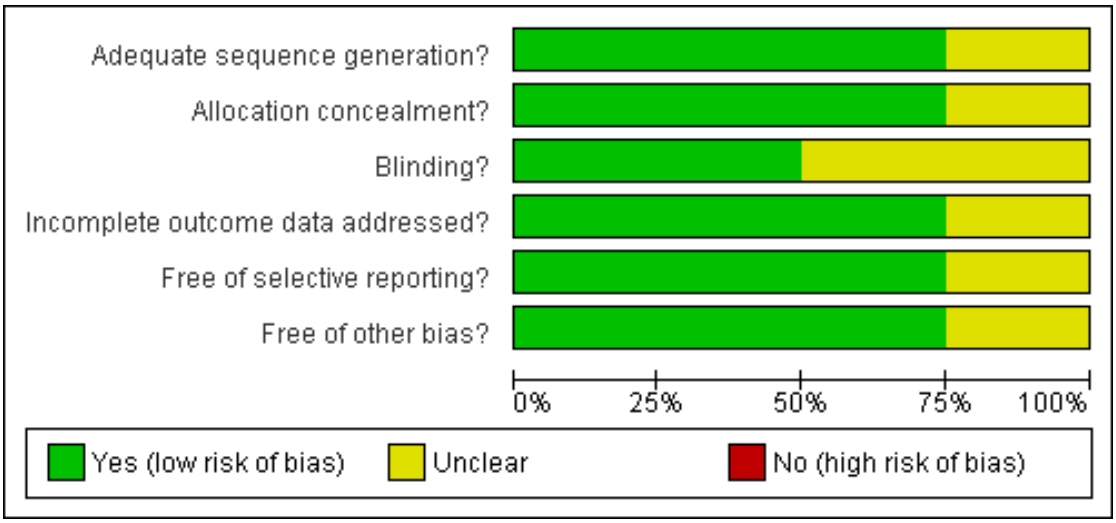

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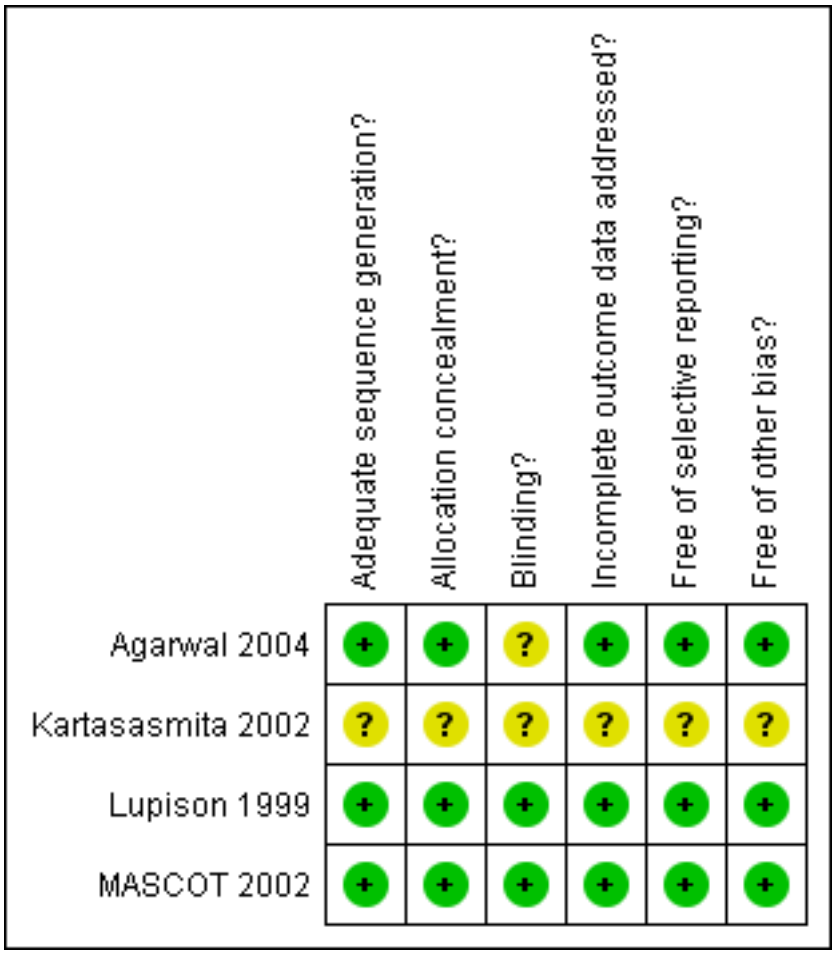
Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Allocation

The Agarwal 2004 and MASCOT 2002 studies were of adequate methodological quality. Participants were individually randomised to the treatment groups with adequate allocation concealment in both studies. In Lupison 1999 numbers were computer-generated and were only known to the programmer. Block randomisation with uneven block sizes was used. Participants were also individually randomised in the Kartasasmita 2002 study but information regarding allocation concealment was not available.

Blinding

Two studies (Agarwal 2004; MASCOT 2002) showed adequate blinding of the participants, caregivers and outcome assessors. In Lupison 1999 caregivers were blinded to the treatment and placebo assignment. Block randomisation with uneven block sizes was used. Information regarding blinding was not available in Kartasasmita 2002.

Incomplete outcome data

Loss to follow up was around 5% at first follow up in three studies (Agarwal 2004; Lupison 1999; MASCOT 2002). However insufficient information in Kartasasmita 2002 did not allow us to make any judgement.

Selective reporting

Agarwal 2004, MASCOT 2002 and Lupison 1999 appeared to be free from selective reporting, while insufficient information from Kartasasmita 2002 did not permit any conclusion regarding selective reporting.

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Other potential sources of bias

Agarwal 2004, MASCOT 2002 and Lupison 1999 appeared to be free from other bias, while insufficient information from Kartasasmita 2002 did not permit us to draw any conclusions from it.

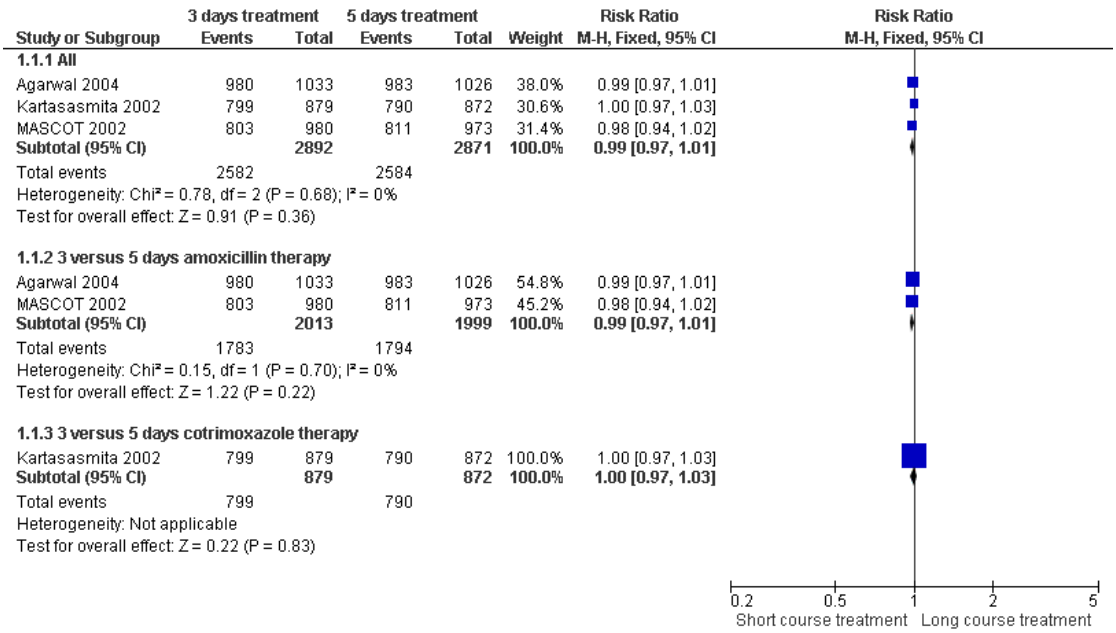
Effects of interventions

The analysis includes data of 6177 children from four included studies.

Primary outcome measure

Analysis of three days versus five days of treatment with the same antibiotic for non-severe CAP in children showed non-significant differences in clinical cure at first follow up at the end of treatment (RR 0.99; 95% CI 0.97 to 1.01, three studies (fixed-effect, n = 5763)) and there was no heterogeneity (Chi² test, P value 0.68; I² statistic = 0%) (Analysis 1.1; Figure 3). When data were disaggregated on the basis of antibiotic used, which included amoxicillin and cotrimoxazole, summary estimates and the CIs remained non-significant.

Figure 3. Forest plot of comparison: 1 3 days versus 5 days treatment with the same antibiotic, outcome: 1.1 Clinical cure.



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Secondary outcome measures

When three days of treatment was compared against five days of treatment with the same antibiotic, non-significant differences were found for rates of treatment failure at the end of treatment (RR 1.07; 95% CI 0.92 to 1.25, three studies (fixed-effect, n = 5763)) and there was no heterogeneity (Chi² test, P value 0.63; I² statistic = 0%) (Analysis 1.2; Figure 4) and relapse rate after seven days of clinical cure (RR 1.09; 95% CI 0.84 to 1.42, four studies (fixed-effect, n = 5469)) and there was no heterogeneity (Chi² test, P value 0.97; I² statistic = 0%) (Analysis 1.3; Figure 5). When a subgroup analysis was undertaken on the basis of whether amoxicillin or cotrimoxazole was used, non-significant differences were found for the outcomes of treatment failure and relapse rate with the different durations of the therapy used.

Figure 4. Forest plot of comparison: 1 3 days versus 5 days treatment with the same antibiotic, outcome: 1.2 Treatment failure.

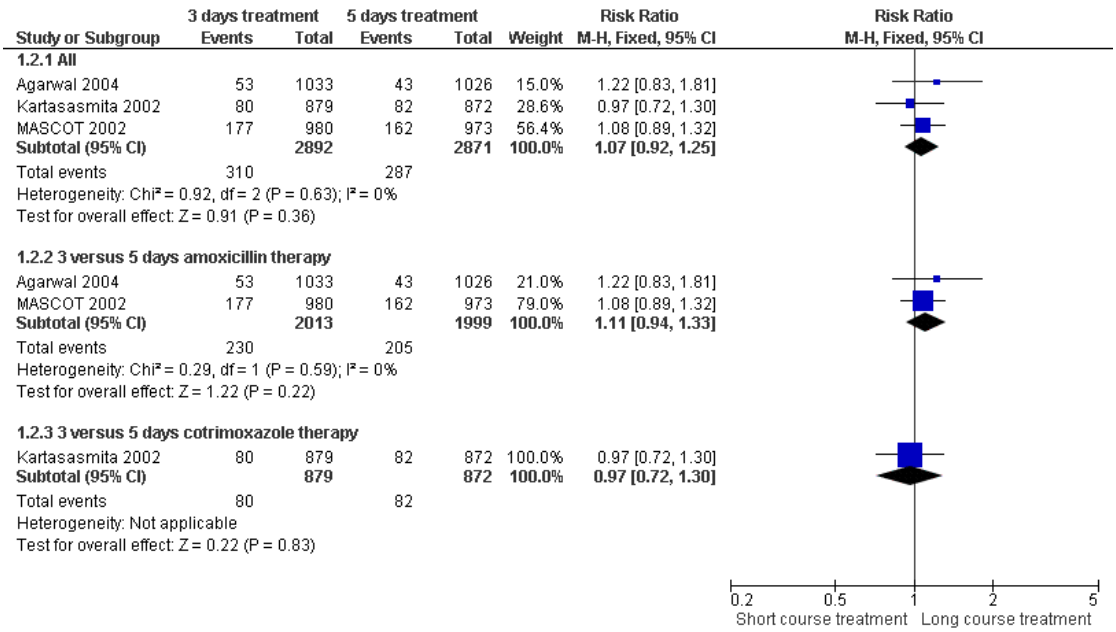

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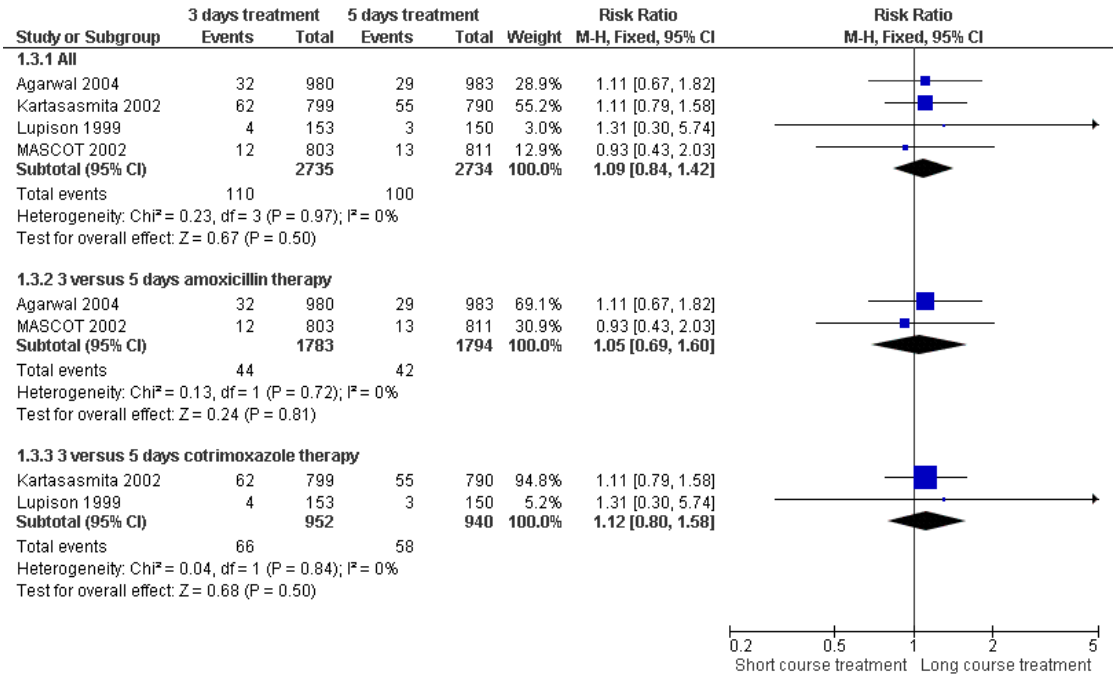
Figure 5. Forest plot of comparison: 1 3 days versus 5 days treatment with the same antibiotic, outcome: 1.3 Relapse rate.



Outcomes of mortality at one month and additional interventions used could not be evaluated in this review due to non-availability of data from the included studies. There was no significant heterogeneity among the trials assessed on the basis of visual inspection of forest plots and the I^2 statistic, hence the following a priori subgroup analyses were not undertaken.

DISCUSSION

Summary of main results

Pneumonia in children under five years of age accounts for the highest number of deaths in low-income countries. This review addressed an important aspect of treatment, which is the optimal duration of antibiotic therapy. Short durations of antibiotic therapy have been found to be effective in upper respiratory tract infections (Pichichero 2000). Evidence for efficacy in acute lower respiratory tract infections (LRTIs) is limited. Effective shortened durations of antibiotic therapy for community-acquired pneumonia (CAP) would be especially beneficial for low-income countries and resource-poor settings as it would lead to a reduction in the overall cost of treatment, improved compliance and tolerance of treatment and reduced antimicrobial resistance. We found only four studies evaluating the efficacy of short-course versus long-course therapy using the same antibiotic for non-severe CAP in children under five years of age, and these were all from low-income countries such as Pakistan, India, Bangladesh and the Philippines. All the included studies evaluated the same durations of short and long courses of therapy, which were three days versus five days. Analysis showed that treatment with an oral antibiotic for either three days or five days was equally efficacious in treating non-severe CAP in children. Three days of treatment failed to show significant differences in clinical cure, treatment failure or relapse rates compared to five days of treatment with the same antibiotic. There was no significant heterogeneity among the included studies but we undertook subgroup analyses to evaluate the impact of the use of different antibiotics in the treatment of non-severe pneumonia. Subgroup analyses also showed that a short course versus a long course of either oral amoxicillin or cotrimoxazole was equally effective in terms of clinical cure, treatment failure and relapse rates.

Overall completeness and applicability of evidence

These findings are very important but they should be interpreted with caution as they are limited by the small number of studies

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available on the topic. Although only four studies were included in this analyses, all included studies had a good number of participants contributing to its results. The impact of a short duration of antibiotic therapy on other secondary outcomes, that is, mortality at one month and additional interventions used, could not be assessed in this review due to the non-availability of data.

Quality of the evidence

The World Health Organization (WHO) definition of CAP focuses on the clinical findings and respiratory cut-offs. This simplified syndromic diagnosis of childhood CAP poses a challenge in the accurate diagnosis of CAP cases as shown by a study conducted in Pakistan. This study (Hazir 2006) showed that only 14% of children diagnosed with pneumonia by the WHO criteria had radiological evidence of pneumonia. These findings have also been supported by other community-based studies in Pakistan (Nizami 2005). This raises concerns as to the robustness of the clinical criteria being used for pneumonia diagnosis. Also, once diagnosed with non-severe CAP, children are treated with oral cotrimoxazole or amoxicillin and are followed up at home after 48 hours. Identification of the true cause (bacterial or viral) of CAP is limited and in such a scenario treatment of a non-bacterial CAP with inexpensive antibacterial agents therefore significantly increases the risk of development of antimicrobial resistance. This poses a significant public health problem and needs attention in the form of modification of clinical diagnostic criteria and management guidelines.

Potential biases in the review process

We undertook a systematic, thorough search of the literature to identify all studies meeting the inclusion criteria for this review and we are confident that all trials meeting the inclusion criteria are included in this review. We independently and in duplicate selected studies and extracted data and we reached consensus by discussing any discrepancies. A protocol was published for this review.

Agreements and disagreements with other studies or reviews

We found no significant differences between three and five days of the same antibiotics for non-severe pneumonia. A recent study from India (Awasthi 2008) compared three days of oral amoxicillin with placebo in 1671 children aged 2 to 59 months with non-severe pneumonia who also had a wheeze. The investigators of this trial used WHO criteria and found that placebo treatment was associated with clinical failure (odds ratio (OR) 1.28; 95% CI 1.01 to 1.62) and they concluded that three days of oral antibiotics should be the current treatment standard for patients with non-severe pneumonia in low-income countries.

AUTHORS' CONCLUSIONS

Implications for practice

Evidence provided in this review suggests that a short-course (three days) of antibiotic therapy is equally as effective as a longer treatment (five days) for non-severe CAP in children under five years of age. No difference was found in terms of clinical cure rates at the end of treatment, rates of treatment failure or relapse rates within seven days of clinical cure, with the different durations of antibiotic therapy. Therefore a shorter course of antibiotic therapy should benefit both the individual, family and the public.

Implications for research

This review only allowed a comparison of three days of treatment against five days. More well designed randomised controlled trials comparing different durations of short and long courses of antibiotic therapies are needed to support our review findings.

ACKNOWLEDGEMENTS

The authors wish to thank the following people for commenting on the draft protocol: Janet Yarrow, Feyzullah Cetinkaya, Philippe Ovetchkine, Nelcy Rodriguez and Allen Cheng. The authors would also like to thank the following people for commenting on the draft review: Chanpen Choprapawon, Feyzullah Cetinkaya, Wen Chin Chiang, Rob Ware and Allen Cheng. The authors would also like to thank the following people for commenting on the updated draft review Amy Zelmer, Feyzullah Cetinkaya, Max Bulsara, and Allen Cheng. The authors would also like to thank Amina Zaidi, who helped in writing the protocol of this review and Ammad Saeed, who helped in data extraction.

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* *Indicates the major publication for the study*

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Agarwal 2004

Methods	Double-blind, placebo-controlled, randomised trial. Block randomisation was done with variable block sizes. The allocation concealment was adequate. For both treatment groups, tablets were placed in serially numbered opaque white envelopes, each of which contained a green envelope containing 11 doses of amoxicillin for 3 days and a blue envelope containing 8 doses of either amoxicillin or placebo for the next 2 days. Blinding of participants, caregiver and outcome assessor was done adequately. The loss to follow up was 5.4% by day 5, and 6.8% by day 14
Participants	Children aged 2 to 59 months with cough, rapid respiration, or difficulty in breathing. Non-severe CAP was defined as respiratory rate of more than or equal to 50 breaths per minute for children aged 2 to 11 months, or more than or equal to 40 breaths per minute for children aged 12 to 59 months Children having signs of severe CAP or disease (cyanosis, convulsions, inability to drink, difficulty waking, severe malnutrition, stridor), other conditions requiring antibiotic treatment, clinically recognised congenital heart disease, chronic systemic disorders, a history of repeated wheezing or asthma, who had been hospitalised in the previous 2 weeks, taken antibiotics in the previous 2 days, had measles within the previous month, or a history of penicillin allergy were excluded. Patients with fever or wheeze received symptomatic treatment before enrolment Those whose fast-breathing persisted were enrolled after their parents or guardian had consented There were no substantial differences in the baseline characteristics of the treatment groups. In all, 2188 patients were recruited, 1095 in the 3 days of amoxicillin treatment group and 1093 in the 5 days of treatment group
Interventions	All participants received scored dispersible tablets of amoxicillin (125 mg) for the first 3 days. Amoxicillin was given 3 times daily dissolved in 5 ml of water. Effective dose per kilogram body weight varied from 31 to 54 mg/day. For the next 2 days participants received either amoxicillin or placebo There were 1095 subjects in the 3 days of amoxicillin treatment group and 1093 in the 5 days of treatment group
Outcomes	Primary outcome: proportions of children recovering after 3 days and 5 days of treatment Secondary outcomes: treatment failure defined as development of chest in-drawing, convulsions, drowsiness or inability to drink at any time; respiratory rate above age-specific cut-off points on day 3 or later; or oxygen saturation by pulse oximetry < 90% on day 3; proportions relapsed within the next 6 to 14 days, proportions with resistant strains of *S. pneumoniae* or *H. influenzae* in nasopharyngeal cultures at enrolment and at 14-day follow up, direct medical costs of treating clinical failures and relapses, and proportion of participants with nasopharyngeal aspirates positive for respiratory syncytial virus at enrolment
Notes	Study was conducted in the outpatient departments of 7 referral hospitals in India
Risk of bias	

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Agarwal 2004 (*Continued*)

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Quote: "Randomised; Block randomisation, with variable sized blocks, was done for each participating site to avoid unblinding." Comment: adequately done
Allocation concealment?	Low risk	Quote: "For both treatment groups, tablets were placed in serially numbered opaque white envelopes, each of which contained a green envelope containing 11 doses of amoxicillin for three days and a blue envelope containing eight doses of either amoxicillin or placebo for the next two days." Comment: adequately done
Blinding? All outcomes	Unclear risk	Quote: "Double blind"
Incomplete outcome data addressed? All outcomes	Low risk	Loss to follow up was 5.4% by day 5, and 6.8% by day 14
Free of selective reporting?	Low risk	Study appears to be free from other bias
Free of other bias?	Low risk	Study appears to be free from other bias

Kartasasmita 2002

Methods	Double-blind, randomised, placebo-controlled, multi-centre equivalence trial. Trial was carried out in 2 sites in Indonesia and Bangladesh
Participants	Children aged 2 to 59 months with non-severe CAP
Interventions	Participants received oral cotrimoxazole either for 3 days or for 5 days. There were 1008 children in the 3 days cotrimoxazole group and 1014 in the 5 days group. Effective dose per kilogram body weight varied from 30 to 45 mg/kg/day
Outcomes	Clinical cure, treatment failure, relapse rates and effect on antimicrobial resistance in nasopharyngeal *S. pneumoniae* and *H. influenzae* isolates
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement

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Kartasasmita 2002 (*Continued*)

Adequate sequence generation?	Unclear risk	Quote: "Randomised" Comment: insufficient information to permit judgement
Allocation concealment?	Unclear risk	Insufficient information to permit judgement
Blinding? All outcomes	Unclear risk	Quote: "double-blind" Comment: insufficient information to permit judgement
Incomplete outcome data addressed? All outcomes	Unclear risk	Insufficient information to permit judgement
Free of selective reporting?	Unclear risk	Insufficient information to permit judgement
Free of other bias?	Unclear risk	Insufficient information to permit judgement

Lupison 1999

Methods	The study was conducted from December 1991 to December 1992 in Pasay City, Metro Manila, Philippines where the ARI case management strategy was implemented as part of a feasibility study of ARI control programme implementation
Participants	Children of 2 to 59 months (with cough and fast breathing) were recruited and enrolled in the outpatient section of Pasay City General Hospital. Participants were assessed and recruited consecutively from 5 health centres in the catchment area by trained nurses and referred to the project physician based at the hospital outpatient section for final assessment and enrolment
Interventions	Antibiotic treatment was supervised for the initial dose by the hospital project nurse and the subsequent doses in the respective homes by the field nurses for Days 1 to 3. Children > 12 month old were given cotrimoxazole 80 mg BID and children 2 to 12 months old were given cotrimoxazole 40 mg BID
Outcomes	Relapse and re-infection rates after the 3- and the 5-day courses of cotrimoxazole
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	Quote: "The numbers were computer generated and known only to the programmer. "

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Lupison 1999 (*Continued*)

		Comment: adequately done
Allocation concealment?	Low risk	Quote: "Randomisation was done on Day 4 of treatment for those assessed to have treatment success by picking out a numbered bottle of identical drugs from a box kept at the hospital and appropriate numbers were tagged to the respective patient charts." Comment: adequately done
Blinding? All outcomes	Low risk	Quote: "double-blind"; "nurses were blinded to treatment regimen for patient" Comment: adequately done
Incomplete outcome data addressed? All outcomes	Low risk	5% attrition reported along with their reasons
Free of selective reporting?	Low risk	Study seems free from any selective bias
Free of other bias?	Low risk	Study seems to be free from any other bias

MASCOT 2002

Methods	Double-blind, randomised, placebo-controlled trial. The randomisation scheme was generated by a computer programme at WHO, Geneva, with uneven blocks of 4, 6 and 8. The allocation concealment was adequate. Participant, caregiver and the outcome assessor were blinded to the intervention assignment. Loss to follow up was less than 5%
Participants	Children aged 2 to 59 months with non-severe CAP. Children were classified using the standard WHO algorithm for ARI as having non-severe pneumonia-cough or difficulty breathing with fast breathing (respiratory rate of more than or equal to 50 breaths per minute for children aged 2 to 11 months, or more than or equal to 40 breaths per minute for children aged 12 to 59 months) Excluded children include those who had underlying chronic illness, a history of 3 or more episodes of wheeze or acute bronchial asthma, and who had used any antibiotic in appropriate doses during the previous 48 hours. The baseline characteristics were almost similar and showed that 1051 (54%) of children were younger than 1 year old
Interventions	All children received 15 mg/kg oral amoxicillin every 8 hours for 3 days. In the next 2 days, children were given either active medicine or placebo. Oral salbutamol and paracetamol were given when needed
Outcomes	Primary outcome: treatment failure, which included any patient who had the study drug changed by study staff up to 5 days after enrolment, developed severe pneumonia/disease, did not improve, or who died Secondary outcome: relapse of disease defined as development of any sign of pneumonia between days 6 and 14 after fast breathing had initially returned to normal, clinical

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	resolution defined as return of respiratory rate to the normal age-specific range	
Notes	This study was done in 7 sites in 5 cities of Pakistan (Gilgit, Islamabad, Lahore, Multan and Rawalpindi)	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	Quote: "randomized; The randomisation scheme was generated by a computer program at WHO, Geneva, with uneven blocks of four, six, and eight." Comment: adequately done
Allocation concealment?	Low risk	Quote: "Self-adhesive sticking labels with unique identification numbers were prepared in Geneva. A copy of the randomisation list with unique identification numbers was given to a health professional not associated with the study, who randomized the study drugs." Comment: adequately done
Blinding? All outcomes	Low risk	Quote: "double-blind; drug assignment was concealed from patients, parents, and study personnel."
Incomplete outcome data addressed? All outcomes	Low risk	2% excluded from intervention group and 3% from control arm. Their reason for exclusions were described in the text and flow diagram
Free of selective reporting?	Low risk	Study seems to be free from selective bias
Free of other bias?	Low risk	Study appears to be free from other bias

CAP: community-acquired pneumonia
ARI: acute respiratory infection
BID: twice daily

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Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
El Moussaoui 2006	Age of participants was > 18 years
Ficnar 1997	Age of participants 6 months to 12 years; outcomes of interest in population of 6 to 59 months of age children are not separately reported; quasi-randomised trial
Harris 1998	Age of participants was 6 months to 16 years
Leophonte 2002	Age of participants was > 18 years
Peltola 2001	Age of participants was 3 months to 15 years; outcomes of interest in population of 6 to 59 months of age children are not separately reported
Siegal 1999	Age of participants was > 18 years

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DATA AND ANALYSES

Comparison 1. 3 days versus 5 days treatment with the same antibiotic

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical cure	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 All	3	5763	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.97, 1.01]
1.2 3 versus 5 days amoxicillin therapy	2	4012	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.97, 1.01]
1.3 3 versus 5 days cotrimoxazole therapy	1	1751	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.97, 1.03]
2 Treatment failure	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 All	3	5763	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.92, 1.25]
2.2 3 versus 5 days amoxicillin therapy	2	4012	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.94, 1.33]
2.3 3 versus 5 days cotrimoxazole therapy	1	1751	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.72, 1.30]
3 Relapse rate	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 All	4	5469	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.84, 1.42]
3.2 3 versus 5 days amoxicillin therapy	2	3577	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.69, 1.60]
3.3 3 versus 5 days cotrimoxazole therapy	2	1892	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.80, 1.58]

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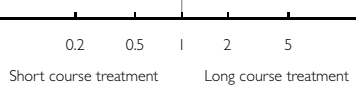
Analysis 1.1. Comparison 1 3 days versus 5 days treatment with the same antibiotic, Outcome 1 Clinical cure.

Review: Short-course versus long-course antibiotic therapy for non-severe community-acquired pneumonia in children aged 2 months to 59 months

Comparison: 1 3 days versus 5 days treatment with the same antibiotic

Outcome: 1 Clinical cure

Study or subgroup	3 days treatment n/N	5 days treatment n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 All					
Agarwal 2004	980/1033	983/1026		38.0 %	0.99 [0.97, 1.01]
Kartasasmita 2002	799/879	790/872		30.6 %	1.00 [0.97, 1.03]
MASCOT 2002	803/980	811/973		31.4 %	0.98 [0.94, 1.02]
Subtotal (95% CI)	**2892**	**2871**		**100.0 %**	**0.99 [0.97, 1.01]**
Total events: 2582 (3 days treatment), 2584 (5 days treatment)					
Heterogeneity: Chi^2 = 0.78, df = 2 (P = 0.68); I^2 =0.0%					
Test for overall effect: Z = 0.91 (P = 0.36)					
2 3 versus 5 days amoxicillin therapy					
Agarwal 2004	980/1033	983/1026		54.8 %	0.99 [0.97, 1.01]
MASCOT 2002	803/980	811/973		45.2 %	0.98 [0.94, 1.02]
Subtotal (95% CI)	**2013**	**1999**		**100.0 %**	**0.99 [0.97, 1.01]**
Total events: 1783 (3 days treatment), 1794 (5 days treatment)					
Heterogeneity: Chi^2 = 0.15, df = 1 (P = 0.70); I^2 =0.0%					
Test for overall effect: Z = 1.22 (P = 0.22)					
3 3 versus 5 days cotrimoxazole therapy					
Kartasasmita 2002	799/879	790/872		100.0 %	1.00 [0.97, 1.03]
Subtotal (95% CI)	**879**	**872**		**100.0 %**	**1.00 [0.97, 1.03]**
Total events: 799 (3 days treatment), 790 (5 days treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.22 (P = 0.83)					



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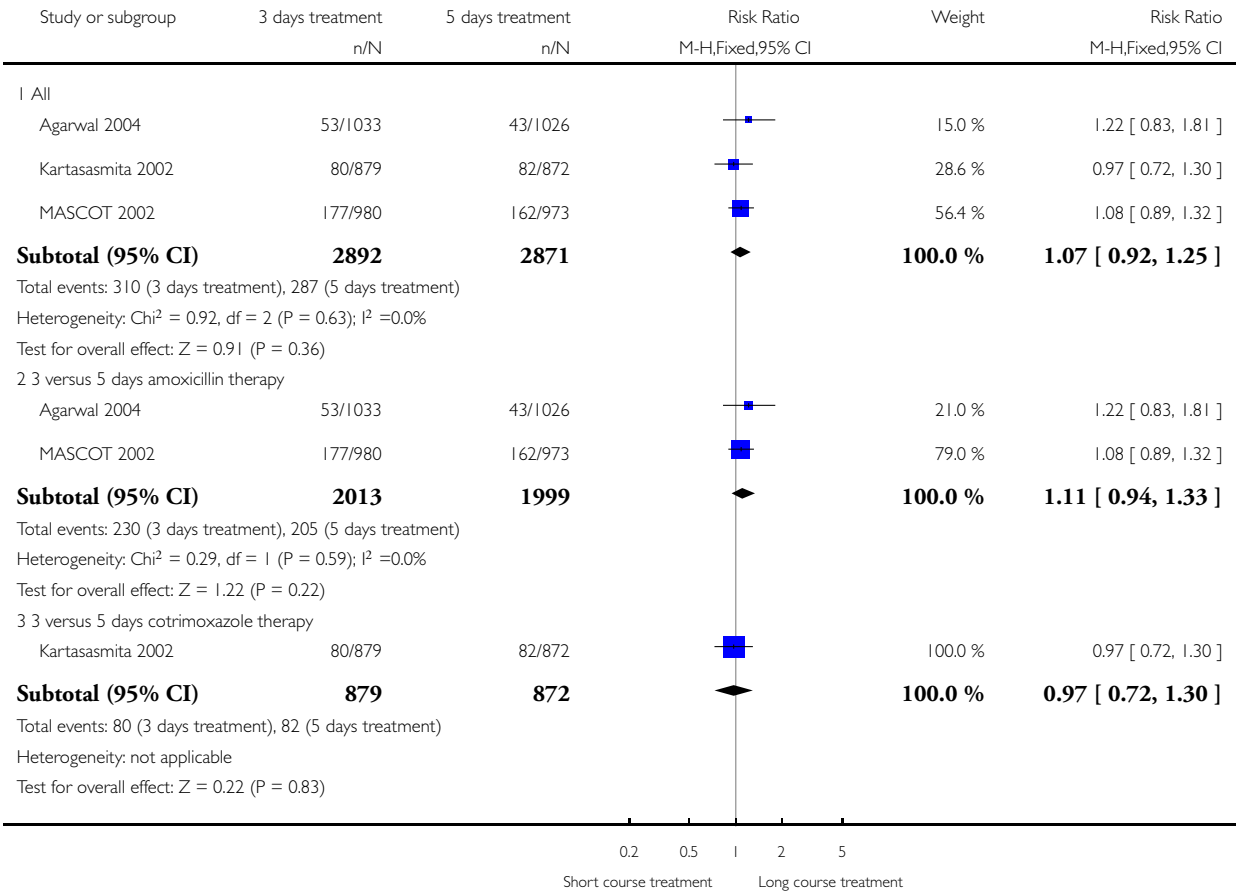
Analysis 1.2. Comparison 1 3 days versus 5 days treatment with the same antibiotic, Outcome 2 Treatment failure.

Review: Short-course versus long-course antibiotic therapy for non-severe community-acquired pneumonia in children aged 2 months to 59 months

Comparison: 1 3 days versus 5 days treatment with the same antibiotic

Outcome: 2 Treatment failure



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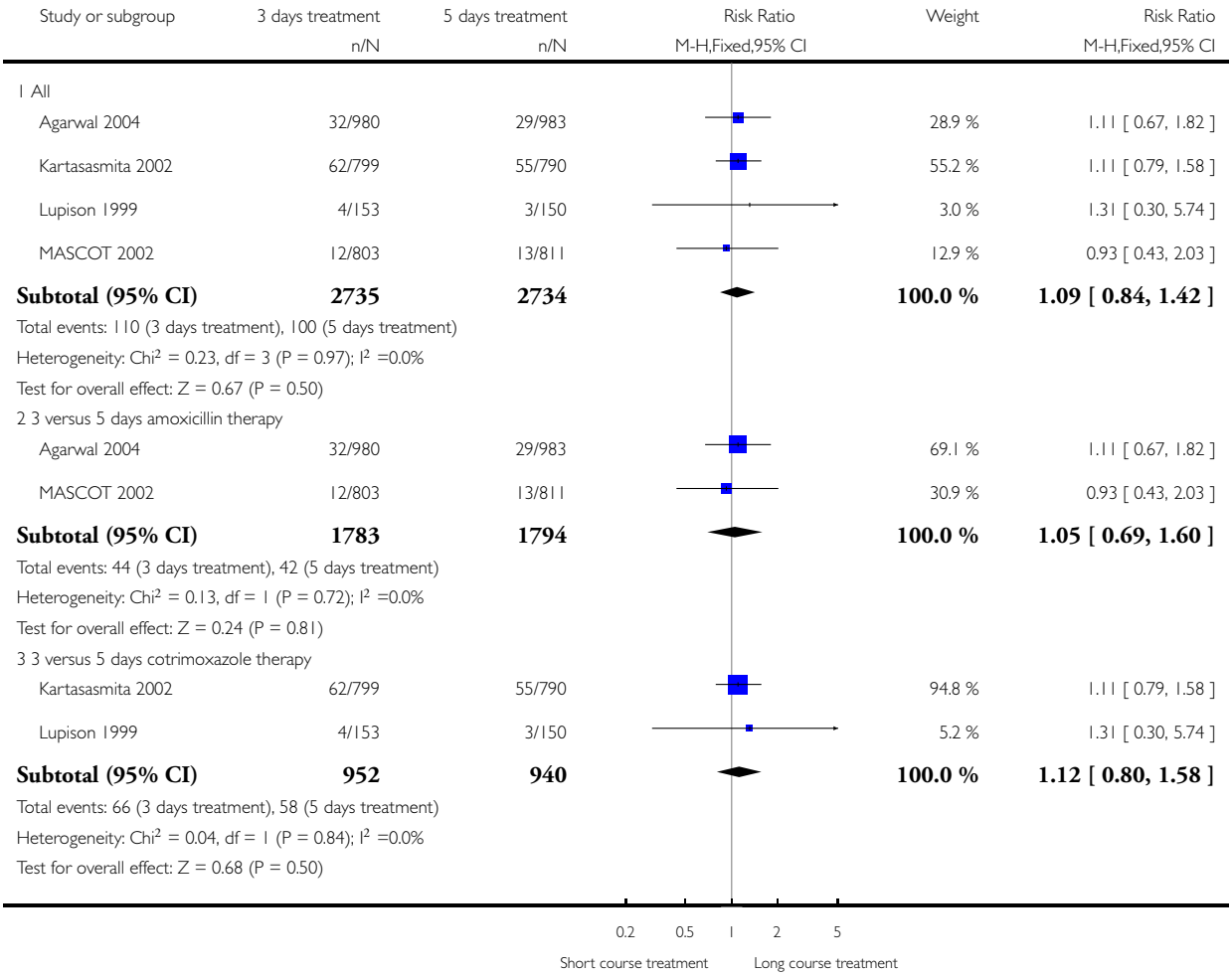
Analysis 1.3. Comparison 1 3 days versus 5 days treatment with the same antibiotic, Outcome 3 Relapse rate.

Review: Short-course versus long-course antibiotic therapy for non-severe community-acquired pneumonia in children aged 2 months to 59 months

Comparison: 1 3 days versus 5 days treatment with the same antibiotic

Outcome: 3 Relapse rate



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APPENDICES

Appendix 1. Previous search

We searched The Cochrane Central Register of Controlled Trials (CENTRAL) and the Database of Abstracts of Reviews of Effects (DARE) (*The Cochrane Library* 2007, Issue 3); MEDLINE (OVID) (January 1966 to September 2007); EMBASE (Embase.com) (1974 to September 2007); and LILACS (1982 to September 2007).

The following search terms were combined with the highly sensitive search strategy devised by Dickersin et al (Dickersin 1994) and run in MEDLINE and CENTRAL. The terms were adapted to search EMBASE and LILACS.

MEDLINE (OVID)

1 exp Pneumonia/
2 exp Community-Acquired Infections/
3 and/1-2
4 (pneumonia or CAP).mp.
5 lower respiratory tract infection$.mp.
6 lower respiratory infection$.mp.
7 LRTI.mp.
8 or/3-7
9 exp Anti-Bacterial Agents/
10 antibiotic$.mp.
11 exp Anti-Infective Agents/
12 exp Amoxicillin/
13 exp Penicillins/
14 exp Ampicillin/
15 exp Trimethoprim-Sulfamethoxazole Combination/
16 exp Macrolides/
17 exp Erythromycin/
18 exp Azithromycin/
19 exp Clarithromycin/
20 (penicillin$ or amoxicillin or ampicillin or cotrimoxazole or macrolide$ or erythromycin or azithromycin or clarithromycin).mp.
21 or/9-20
22 exp Child/
23 (child or children).mp.
24 exp Infant/
25 (infant or infants).mp.
26 (pediatric or pediatric).mp.
27 or/22-26
28 8 and 21 and 27

We limited searches to human studies and there were no language or publication restrictions. We also searched the related conference proceedings for relevant abstracts. We contacted organisations and researchers in the field and pharmaceutical companies for information on unpublished and ongoing trials. We also checked the reference lists of all trials identified by the above methods.

Appendix 2. Embase.com search strategy

19. #15 AND #18
18. #16 OR #17
17. 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 assign*:ab,ti OR allocat*:ab,ti OR volunteer*:ab,ti OR ((singl* OR doubl*) NEAR/2 (blind* OR mask*)):ab,ti
16. 'randomized controlled trial'/exp OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR 'crossover procedure'/exp
15. #5 AND #11 AND #14
14. #12 OR #13

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13. infant*:ab,ti OR infancy:ab,ti OR baby*:ab,ti OR babies:ab,ti OR child*:ab,ti OR schoolchild*:ab,ti OR (school NEAR/2 (age* OR nursery OR primary OR elementary)):ab,ti OR preschool*:ab,ti OR kid:ab,ti OR kids:ab,ti OR toddler*:ab,ti OR boy*:ab,ti OR girl*:ab,ti OR pediatric*:ab,ti OR pediatric*:ab,ti
12. 'child'/exp OR 'pediatrics'/exp OR 'nursery school'/exp OR 'kindergarten'/exp OR 'primary school'/exp
11. #6 OR #7 OR #8 OR #9 OR #10
10. penicillin*:ab,ti OR amoxicillin*:ab,ti OR ampicillin*:ab,ti OR cotrimoxazole*:ab,ti OR macrolide*:ab,ti OR erythromycin*:ab,ti OR azithromycin*:ab,ti OR clarithromycin*:ab,ti OR 'trimethoprim-sulfamethoxazole':ab,ti
9. 'cotrimoxazole'/exp
8. 'antiinfective agent'/de
7. antibiotic*:ab,ti
6. 'antibiotic agent'/exp
5. #1 OR #2 OR #3 OR #4
4. 'lower respiratory tract infection':ab,ti OR 'lower respiratory tract infections':ab,ti OR 'lower respiratory infection':ab,ti OR 'lower respiratory infections':ab,ti OR lrti:ab,ti
3. 'lower respiratory tract infection'/de
2. pneumon*:ab,ti OR cap:ab,ti
1. 'pneumonia'/exp

Appendix 3. LILACS search strategy

"PNEUMONIA" or "aspiration PNEUMONIA" or "bronchiolitis obliterans organizing PNEUMONIA" or "cryptogenic organizing PNEUMONIA" or "eosinophilic PNEUMONIA" or "lobar PNEUMONIA" or "mycoplasma PNEUMONIA" or "pneumocystis PNEUMONIA" or "staphylococcal PNEUMONIA" or "ventilator-associated PNEUMONIA" or "atypical interstitial PNEUMONIA of cattle" or "enzootic PNEUMONIA of swine" or "mycoplasmal PNEUMONIA of swine" or "PNEUMONIA of swine, enzootic" or "PNEUMONIA of swine, mycoplasmal" or "PNEUMONIA, aspiration" or "PNEUMONIA, atypical interstitial, of cattle" or "PNEUMONIA, bacterial" or "PNEUMONIA, eosinophilic" or "PNEUMONIA, interstitial" or "PNEUMONIA, interstitial plasma cell" or "PNEUMONIA, lipid" or "PNEUMONIA, lobar" or "PNEUMONIA, mycoplasma" or "PNEUMONIA, pneumococcal" or "PNEUMONIA, pneumocystis" or "PNEUMONIA, primary atypical" or "PNEUMONIA, radiation" or "PNEUMONIA, staphylococcal" or "PNEUMONIA, ventilator-associated" or "PNEUMONIA, viral" or "chlamydia PNEUMONIAe" or "chlamydophila PNEUMONIAe" or "diplococcus PNEUMONIAe" or "klebsiella PNEUMONIAe" or "meningitis, streptococcus PNEUMONIAe" or "mycoplasma PNEUMONIAe" or "streptococcus PNEUMONIAe" or "streptococcus PNEUMONIAe infections" [Subject descriptor] and (((((((("ANTIBIOTICS" or "ANTIBIOTICS, penicillin") or "AMOXICILLIN") or "PENICILLIN g") or "AMPICILLIN") or "TRIMETHOPRIM-SULFAMETHOXAZOLE combination") or "MACROLIDES") or "ERYTHROMYCIN") or "AZITHROMYCIN") or "CLARITHROMYCIN" [Subject descriptor] and (("CHILD") or "INFANT") or "PEDIATRICs" [Subject descriptor]
pneumon$ [Words] and antibiotic$ or penicillin$ or amoxicillin$ or ampicillin$ or macrolide$ or erythromycin$ or azithromycin$ or clarithromycin$ or cotrimoxazole$ [Words] and child$ or infan$ or preschool$ or toddler$ or paediatr$ or pediatr$ [Words]

WHAT'S NEW

Last assessed as up-to-date: 1 September 2010.

Date	Event	Description
2 September 2010	New search has been performed	This is an update of our last version which was published in 2008. One new study was found and included in this review. Overall, the conclusions remain unchanged

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HISTORY

Protocol first published: Issue 2, 2006

Review first published: Issue 2, 2008

Date	Event	Description
19 December 2007	Amended	Converted to new review format.
5 September 2007	New search has been performed	Searches conducted.

CONTRIBUTIONS OF AUTHORS

The protocol was written by Dr Batool Azra Haider (BAH) under the guidance of Dr Zulfiqar A Bhutta (ZAB). Data extraction was done by BAH and Zohra S Lassi (ZSL). BAH and ZSL entered the data, created the comparisons, carried out the analysis and wrote the text of the review. ZAB provided support and guidance for the review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Aga Khan University, Pakistan.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Bacterial Agents [*administration & dosage]; Community-Acquired Infections [drug therapy]; Drug Administration Schedule; Pneumonia [*drug therapy]; Randomized Controlled Trials as Topic; Recurrence; Treatment Outcome

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MeSH check words

Child, Preschool; Humans; Infant

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