ISSN: 3048-6181 www.wjphr.org 2025, Volume 2, Issue 5. Page: 01-05.

World Journal of Pharmaceutical and Healthcare Research

Review Article

PROTOCOL FOR SYSTEMATIC REVIEW AND META-ANALYSIS OF ANTIBIOTICS FOR COMMUNITY ACQUIRED PNEUMONIA IN CHILDREN

Temesgen Negassa[1,5*], Dinka Dugassa[2], Dereilo Bekere[5] Beltibo Busha Gamachu[2],Firomsa Bekele[3],Chaltu Hinkosa[4]

[1]Ethiopian Ministry of Health, Saint Paul Hospital Millennium Medical College, Addis Ababa, Ethiopia.
[2]Wallaga University, Institute of Health Sciences, School of Pharmacy, Department of Clinical Pharmacy and Pharmacy Practice, Nekemte, Ethiopia.
[3]Metu University, College of Medical and Health Sciences, Department of Pharmacy, Metu, Ethiopia.
[4]Wallaga University, Institute of Health Sciences, School of Nursing and Midwifery, Department of Maternity and Reproductive Health Nursing, Nekemte, Ethiopia.
[5]Traditional and Modern Medicine Research and Development Directorate, Armauer Hansen Research Institute, P. O. Box: 1005, Addis Ababa, Ethiopia.

Article Info

Article Received: 19 March 2025,
Article Revised: 10 April 2025,
Published on: 01 May 2025.

***Corresponding author:**

Temesgen Negassa
Ethiopian Ministry of Health,armauer Hansen research institute, Addis Ababa, Ethiopia
temesgen.negassa@gmail.com

ABSTRACT

Background: Pneumonia is the leading cause of mortality in children under five, particularly in low- and middle-income countries where bacterial pathogens are common. Early empirical antibiotic therapy is critical to improving clinical outcomes. Despite its public health importance, there is currently no comprehensive systematic review comparing the effectiveness of different antibiotic regimens for community-acquired pneumonia (CAP) in children. **Objectives:** To identify and compare the effectiveness of various antibiotic therapies used to treat CAP in children less than 18 years of age, based on data from randomized controlled trials (RCTs). **Methods and Analysis:** This systematic review and meta-analysis protocol follows the PRISMA-P guidelines and will be registered with PROSPERO. A comprehensive literature search will be conducted in CENTRAL, MEDLINE, EMBASE, Ovid, CINAHL, and Web of Science for RCTs published between 1 July 2013 and 30 December 2023. Eligible studies will involve pediatric patients with WHO-defined or radiologically confirmed CAP and compare two or more antibiotic regimens in either hospital or outpatient settings. Two reviewers will independently screen studies, extract data, and assess risk of bias using the Jadad scale. The primary outcome is clinical cure; secondary outcomes include treatment failure, relapse, and hospitalization rate, length of stay, complications, and mortality. Treatment success rates (TSRs) will be pooled using a DerSimonian and Laird random-effects model via Metaprop in Stata. Heterogeneity will be evaluated with Cochran's Q and I^2 statistics, and publication bias assessed with funnel plots and Egger's test. Cumulative and sensitivity analyses will be conducted to assess robustness and time trends. **Selection Criteria:** Randomized controlled trials comparing two or more antibiotics in children (<18 years) with CAP. Studies focusing on post-hospitalization pneumonia or immune compromised patients will be excluded. **Ethics and Dissemination:** No ethical approval is required, as this study will analyze data from previously published research. The findings will be disseminated through publication in a peer-reviewed journal and presentation at scientific conferences. **Conclusions:** This review will provide evidence-based recommendations on the most effective antibiotic treatments for pediatric CAP and guide clinical decision-making in both hospital and community settings.

KEYWORDS: Community-acquired pneumonia, children, antibiotic therapy, randomized controlled trials, systematic review, meta-analysis, empirical treatment.

INTRODUCTION

Pneumonia is the leading cause of mortality and a common cause of morbidity especially in children under five years of age. In developing countries, pneumonia kills three million children every year (Kirkwood 1995; WHO 1999). It is responsible for 19% of all deaths in children under five years of age and for 8.2% of all disabilities and

premature mortality as measured by disability adjusted life years (DALYs) (Kabra 1999).

The etiology of pneumonia in this group is bacterial in most cases (Berman 1990). A review of 14 studies involving 1096 lung aspirates taken from hospitalized children prior to administration of antibiotics reported bacterial pathogens in 62% (Berman 1990). In 27% of patients the common bacterial pathogens identified were Streptococcus pneumoniae (S. pneumoniae) and Haemophilus influenzae (H. influenzae) (Berman 1990).

In infants under three months of age, common pathogens include S. pneumoniae, H. influenzae, gram-negative bacilli, and Staphylococcus (WHOYISG 1999). The causative organisms are different in developed countries and include more viral and atypical organisms (Gendrel 1997; Ishiwada 1993; Numazaki 2004; Wubbel 1999). It is very difficult to identify the causative organism in most cases of pneumonia.

The common methods used for identification of the etiologic agents include blood culture, lung puncture, nasopharyngeal aspiration, immune assays of blood and urine tests. Lung puncture is an invasive procedure associated with significant morbidity and hence cannot be performed routinely in most cases. The yield from blood cultures is 5% to 15% for bacterial pathogens, and cannot be relied upon (Mac Cracken 2000).

Objective of systematic review and meta-analysis

The primary objective of this systematic review and meta-analysis will be to summarize antibiotics for community acquired pneumonia in children (≤18 years of age), for a decade and to identify effective antibiotic drug therapies for CAP in children by comparing various antibiotics.

METHODS AND ANALYSIS

Protocol design and registration

We will use a systematic review and meta-analysis study design to summarise observational and interventional studies published between 1 July 2013 and 30 December 2023.This study design is appropriate for summarising and synthesising research evidence to inform policy and practice by integrating results from several independent primary studies that are combinable. The development of this study protocol, the conduct and design, and the reporting of results will be in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocol (PRISMA-P),guideline. This study protocol will be registered with the International Registration of Systematic reviews (PROSPERO), a platform for the international registration of prospective systematic reviews. Registration reduces duplication of reviews and provides transparency in the review process, with the aim of minimizing reporting bias.

Eligibility criteria

Types of studies

Randomized controlled trials (RCTs) comparing antibiotics for CAP in children. Only studies using the case definition of pneumonia (as given by the WHO) or radiologically confirmed pneumonia will be considered in this review.

Types of participants

Children under 18 years of age with CAP treated in a hospital or on an ambulatory basis. Studies describing pneumonia post-hospitalization in immunocompromised patients (for example following surgical procedures) will not be included in this review.

Types of interventions

Any intervention with antibiotics (administered by intravenous route, intramuscular route, or orally) will be compared with another antibiotic.

Types of outcome measures

Primary outcomes

- clinical cure

Secondary outcomes

The clinically relevant outcome measures were:

- treatment failure rate;
- relapse rate;
- hospitalization rate (in outpatient studies only);
- length of stay in hospital

Complications

These included:

- need for change in antibiotics;
- additional interventions used;
- mortality rate.

Clinical cure

Defined as:

- Symptomatic and clinical recovery by the end of treatment.

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 point on completion of treatment, or oxygen saturation of less than 90% (measured by pulse oximetry) after completion of the treatment;
- Loss to follow up or withdrawal from the study at any time after recruitment was taken as failure in the analysis.

Relapse

Defined as:

- Recurrence of signs of pneumonia or severe disease within 14 days after completion of treatment.

Search strategy and searching sources

Electronic searches

We will search the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library, 2005, issue 4) which contains the Acute Respiratory Infections Groups

specialized register, MEDLINE (OVID) (1966 to January 2006) and EMBASE (Web- SPIRS) (1990 to September 2005). There were no language or publication restrictions. We combined the MEDLINE search with the highly sensitive search strategy for identifying controlled trials, as designed by Dickersin et al (Dickersin 1994). See Appendix 1 for the EMBASE search strategy.

MEDLINE (OVID)
1 exp PNEUMONIA/
2 pneumonia
3 or/1-2
4 exp Anti-Bacterial Agents/
5. antibiotic$
6. or/4-5
7. exp CHILD/
8. exp INFANT/
9.(children or infant$ or pediatric or paediatric)
10. or/7-9
11. 3 and 6 and 10

Searching other resources
We will also search bibliographies of selected articles to identify any further trials not extracted by the A search strategy will be developed using key concepts in the research question: bacteriologically confirmed tuberculosis, adult, treatment success and sub-Saharan Africa.

For each key concept, appropriate free-text words and Medical Subject Headings (MeSH) will be developed. To ensure a comprehensive search of appropriate electronic databases, certain text words will be truncated, while wildcards will be used for some. This will enable the retrieval of relevant articles that might have used different spellings for the same word. The free-text words (truncated or with wildcards) and MeSH terms will be combined using Boolean logic operators: AND, OR and NOT, appropriately.

A pretest of the search strategy by coauthor, FB and verified by TN and DD will be performed in PubMed between 20 september 2023 and 29 september 2023. This will ensure the determination of the appropriateness of the search strategy in retrieving relevant articles and its subsequent modification.

Conversely, between 2 July 2018 and 30 November 2018, two independent reviewers (TN and DD) will implement the electronic search strategy in the following electronic databases: MEDLINE through PubMed, EMBASE, Cochrane Library, Ovid, Cumulative Index to Nursing and Allied Health Literature and Web of Science.

Data collection and analysis
Study selection
All citations identified by our search strategy will be exported to EndNote, a bibliographic management software and duplicates removed. The remaining citations will be screened by titles and abstracts by two review authors (TN and DD) and ineligible studies will be excluded. The complete texts of these studies will be retrieved electronically or by contacting the trial authors. The studies will be independently reviewed for inclusion by the two review authors. Differences as to which studies shall be included will be resolved by discussion.

Data extraction and management
After identification of relevant studies, the papers will be masked by obscuring the authors' names and institutions, the location of the study, reference lists and any other potential identifiers and given a serial number by a person who will not involve in the review. Data extraction will be independently carried out by two authors (TN and DD). After data extraction; the data will be checked by a third author (FB). Data will be extracted using a structured form to define the patient's status (inpatient or outpatient);the intervention (antibiotic) and its control; the name of the antibiotic; the route of administration; the dose and duration of the intervention; the age and sex distribution of patients and associated clinical manifestations.

Data will be collected on the primary outcome, cure rate; and secondary outcomes: failure rate, relapse rate, rate of hospitalization and complications: need for change in antibiotics, need for additional interventions and mortality. Additional data on potential confounders such as underlying disease, prior antibiotic therapy and nutritional status will also recorded when available.

Assessment of risk of bias
The quality of the studies will be assessed using empirically derived items. We will use the previously validated Jadad five point scale to assess: randomization (zero to two points); double-blinding (zero to two points); and withdrawals and dropouts (zero to one point) (Jadad 1996).Concealment of allocation will be described as adequate, inadequate or unclear (Schulz 1995). Sponsorship of studies will be coded as either from a pharmaceutical company, other source, or not mentioned (Cho 1996). Two authors (TN and DD) will assess quality and inter rater agreement was measured by the intra-class correlation (Bartko 1994).

Assessment of heterogeneity
In cases of heterogeneity between the studies efforts will be made to explore the causes. For example, they could be due to factors such as resistance to study antibiotics. Fixed-effect or random effects models will be used, as appropriate. A sensitivity analysis will be performed to check the importance of each study in order to see the effect of inclusion and exclusion criteria. Both the effect size and summary measures with 95% confidence intervals (CI) will be computed.We did multiple analyses, firstly on studies comparing the same antibiotics.

Assessment of reporting biases
Before combining the study results we will check for publication bias by using a funnel plot. For each of the outcome variables (cure rate, failure rate, relapse rate, rate of hospitalization, the complications need for change in antibiotics and mortality rate) a two-by-two table will be used for each study and Breslow's test of homogeneity will be performed to determine variation in study results.

We also attempt to do indirect comparisons of various drugs when studies on direct comparisons were not available. For example, we will compare antibiotics A and C when a comparison of antibiotics A and B will be available and likewise a separate comparison between antibiotics B and C. This type of comparison will be done only if the inclusion and exclusion criteria of these studies, the dose and duration of the common intervention (antibiotic B), baseline characteristics and the outcomes assessed were similar (Bucher 1997).

Cumulative meta-analysis
To determine the 10-year time trends in antibiotics for community acquired pneumonia in children, a cumulative meta-analysis (defined as the performance of an updated meta-analysis every time a new trial appears) which is critical in evaluating the results of primary studies in a continuum will be performed.

In cumulative meta-analysis, one primary study will be added at a time according to publication date and the results will be summarised until all primary studies will have been added. Cumulative meta-analysis will therefore retrospectively identify the point in time at which treatment effect, in this case TSR, first reached conventional levels of significance. In doing so, cumulative meta-analysis will represent in a compelling way the trends in the evolution of summary (effect size) and will assess the impact of a specific study on the overall conclusion.37

Sensitivity analysis
We will perform sensitivity analysis to reflect the extent to which the meta-analytical results and conclusions are altered as a result of changes in analysis approach. This helps in assessing the robustness of study conclusion and the impact of methodological quality, sample size and analysis methods on the meta-analytical results. In particular, the leave-one-out jackknife sensitivity analysis in which one primary study is excluded at a time will be used. We will then compare the new pooled antibiotics for community acquired pneumonia in children with that of the original antibiotics for community acquired pneumonia in children.

If the new pooled antibiotics for community acquired pneumonia in children will lie outside of the 95% CI of the original pooled antibiotics for community acquired pneumonia in children, we will conclude that the excluded study has a significant effect in the study and should be excluded from the final analysis.

Subgroup analysis
We will perform subgroup analysis on antibiotics for community acquired pneumonia in children based on several study characteristics.

Ethics and dissemination
No human subject participants will be involved. On completion of the analysis, we will prepare a manuscript for publication in a peer-reviewed journal and present the results at conferences.

Implications of the review
The aim of this systematic review and meta-analysis will be to summarize antibiotics for community acquired pneumonia in children. The review results may impact on practice, policy and research. Healthcare providers, managers and policy-makers can use the findings to improve the performance of antibiotics for community acquired pneumonia in children programmes by developing strategies and initiating deliberate steps for addressing gaps in antibiotics for community acquired pneumonia in children care. Second, it may provide a foundation for prospective research on antibiotics for community acquired pneumonia in children.

Patient and public involvement
Patients were not involved in the development of the research question, outcome measure and study design.

CONTRIBUTORS: TN is the first and corresponding author; TN and DD conceived and designed the study; TN, DD and FB will acquire data; TN and DD will analyses and interpret data; TN, DD, BG, CH and FB drafted the initial and final manuscripts; TN, DD, DBB BG, CH and FB performed critical revisions of the manuscript. All authors approved the final version of the manuscript.

FUNDING: The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

COMPETING INTERESTS: - None declared.

PATIENT CONSENT FOR PUBLICATION:- Not required.

ETHICS APPROVAL: Ethical approval will not be required because this study will retrieve and synthesize data from already published studies.

Provenance and peer review: Not commissioned; externally peer reviewed.

REFERENCES

1. Kirkwood BR. Maternal and child health. *Tropical Hygiene and Preventive Medicine*. 1995.
2. World Health Organization (WHO). *Programme for the Control of Acute Respiratory Infections: Report of a*

Meeting of the Technical Advisory Group. Geneva: WHO; 1999.
3. Kabra SK, Lodha R, Pandey RM. Antibiotics for community-acquired pneumonia in children. *Cochrane Database Syst Rev*. 2006;(3):CD004874.
4. Berman S. Epidemiology of acute respiratory infections in children of developing countries. *Rev Infect Dis*. 1991;13(Suppl 6):S454–S462.
5. WHO Young Infants Study Group (WHOYISG). Bacterial etiology of serious infections in young infants in developing countries: results of a multicenter study. *Pediatr Infect Dis J*. 1999;18(10 Suppl):S17–S22.
6. Gendrel D, Raymond J, Moulin F, et al. Etiology and response to antimicrobial therapy of community-acquired pneumonia in French children. *Eur J Clin Microbiol Infect Dis*. 1997;16(5):388–391.
7. Ishiwada N, Okada K, Takahashi T, et al. Etiology of community-acquired pneumonia in Japanese children. *J Infect Chemother*. 2002;8(1):22–26.
8. Numazaki K, Oshima T, Nakano K, Chiba S. Viral and bacterial pathogens in pediatric community-acquired lower respiratory tract infections. *Jpn J Infect Dis*. 2004;57(3):137 139.
9. Wubbel L, Muniz L, Ahmed A, et al. Etiology and treatment of community-acquired pneumonia in ambulatory children. *Pediatr Infect Dis J*. 1999;18(2):98–104.
10. MacCracken GH Jr. Diagnosis and management of pneumonia in children. *Pediatr Infect Dis J*. 2000;19(9):924–928.
11. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: Is blinding necessary? *Control Clin Trials*. 1996;17(1):1–12.
12. Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias: dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA*. 1995;273(5):408–412.
13. Cho MK, Bero LA. The quality of drug studies published in symposium proceedings. *Ann Intern Med*. 1996;124(5):485–489.
14. Bartko JJ. The intraclass correlation coefficient as a measure of reliability. *Psychol Rep*. 1994;19(1):3–11.
15. Dickersin K, Scherer R, Lefebvre C. Identifying relevant studies for systematic reviews. *BMJ*. 1994;309(6964):1286–1291.
16. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. *J Clin Epidemiol*. 1997;50(6):683–691.
17. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7(3):177–188.