


Amoxicillin versus Cotrimoxazole for Treating Non-severe Pneumonia in Children under 5 Years Old: A Systematic Review

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ABSTRACT

Introduction: Pneumonia is still one of the common causes of death in children under 5 years old in low-middle-income countries. The common cause of pneumonia is bacteria, requiring antibiotics as treatment. This systematic review evaluates the efficacy of amoxicillin and cotrimoxazole in treating pneumonia. **Methods:** This systematic review used PRISMA rules to analyze Pubmed and Europe PMC articles. The dose, duration, and therapeutic failure of amoxicillin and cotrimoxazole were assessed. **Results:** A total of 336 articles were selected for title and abstract screening. Four articles met the requirements, and two were selected for systematic review analysis. A total of 20,646 patients were analyzed, 11,633 (56.3%) received amoxicillin and 9,013 (43.7%) received cotrimoxazole. There was no significant difference in treatment failure between amoxicillin and cotrimoxazole. **Conclusion:** Amoxicillin has the same efficacy as cotrimoxazole for the management of non-severe pneumonia in children under 5 years old.

Keywords: Amoxicillin, children under 5 years old, cotrimoxazole, pneumonia, systematic review, treatment failure.

ABSTRAK

Pendahuluan: Pneumonia masih menjadi salah satu penyebab kematian tersering pada anak di bawah usia 5 tahun di negara berkembang. Etiologi utama pneumonia umumnya adalah bakteri, sehingga terapi utamanya memerlukan antibiotik. Tinjauan sitematik ini mengevaluasi efikasi *amoxicillin* dan *cotrimoxazole* untuk mengobati pneumonia. **Metode**: Tinjauan sistematis ini menggunakan kaidah PRISMA untuk menganalisis artikel-artikel yang berasal dari Pubmed dan Europe PMC. Dosis, durasi, dan kegagalan terapi *amoxicillin* dan *cotrimoxazole* dianalisis. **Hasil**: Total 336 artikel dipilih untuk menjalani skrining judul dan abstrak. Didapatkan 4 artikel yang memenuhi syarat dan 2 artikel dipilih untuk analisis tinjauan sistematis. Dari total 20.646 pasien, 11.633 (56,3%) menerima *amoxicillin* dan 9.013 (43,7%) pasien menerima *cotrimoxazole*. Tidak ada perbedaan bermakna dalam hal kegagalan terapi antara *amoxicillin* dan *cotrimoxazole*. **Simpulan**: *Amoxicillin* memiliki efikasi yang sama dengan *cotrimoxazole* untuk terapi pneumonia tidak berat pada anak di bawah usia 5 tahun. **Riana Suwarni, Anjar Nuryanto. *Amoxicillin* versus *Cotrimoxazole* untuk Terapi Pneumonia Tidak Berat pada Anak di Bawah Usia 5 Tahun: Tinjauan Sistematik.**

Kata Kunci: *Amoxicillin,* anak di bawah usia 5 tahun, *cotrimoxazole*, pneumonia, tinjauan sistematis, kegagalan terapi.

INTRODUCTION

Pneumonia is the most common cause of death in children under five years old in the world. In 2021, 725,557 deaths were due to pneumonia. This mortality rate ranked first, over stepping the mortality rate due to malaria and diarrhea. Although the under-five mortality rate due to pneumonia has decreased by 59% compared to 2000, the decline was slower than diarrhea which recorded a decline of 63%.[1] In Indonesia, pneumonia is the leading cause of death in children aged 12-59 months (12.5%) and in post-neonatal cases (15.3%).[2] The prevalence of pneumonia in children under five years old in Indonesia based on diagnoses from health workers in 2018 was 4.8%. Prevalence in West Kalimantan province is the same as national prevalence (4.8%).[3]

Pneumonia in children under 5 years old are caused by viruses, bacteria, or both; the common viruses include respiratory syncytial virus (RSV), coxsackievirus, enterovirus, coronavirus, adenovirus, parainfluenza virus, bocavirus, rhinovirus and human metapneumovirus; the most common is influenza virus and RSV. Various bacteria cause pneumonia in children, including Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Staphylococcus aureus, and Klebsiella pneumoniae. Among the most frequent are S. pneumoniae (49.5%), M. catarrhalis (42.7%), H. influenzae (27.5%), and S. aureus (7.3%).[4] Antimicrobial therapy for patients with non-severe pneumonia who do not require hospitalization includes amoxicillin, clarithromycin, and doxycycline.[5] The effective duration of treatment is 3-5 days.[6]

Indonesia is the largest archipelago in the world

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with a population density of approximately 141 per square km[7] and not every sub-district has hospital facilities. The limited availability of antibiotic syrup preparation in primary health care makes it difficult for general practitioners to treat pneumonia in children. General practitioners can only rely on antibiotics available in primary health care that consist of amoxicillin and cotrimoxazole. The efficacy of amoxicillin and cotrimoxazole for pneumonia treatment was reviewed.

METHODS

This systematic review uses the PRISMA method on Pubmed and Europe PMC on articles published between 2014 and 2024 with keywords: (Comparison OR Comparative OR Versus OR vs) AND (amoxicillin) AND (cotrimoxazole) AND (community pneumonia). Two reviewers screened the journal title and abstract. Full-text articles with randomized controlled trial study design will be included according to the eligibility criteria and then entered into the Microsoft Excel workbook. Details of pneumonia patients who received oral amoxicillin and oral cotrimoxazole were recorded. The dose and duration and the final outcome of therapy were also recorded. This systematic review is reported according to the PRISMA 2020 checklist.[8]

The inclusion criteria were children aged 0-59 months, suffering from non-severe pneumonia, not hospitalized, and receiving oral amoxicillin or oral cotrimoxazole therapy. The exclusion criteria are having comorbidities and non-English language articles.

RESULT

A total of 344 articles (14 from PUBMED, 330 from Europe PMC) were selected for title and abstract screening; 8 duplicate articles were removed. After titles and abstracts screening, 4 articles met the requirements and underwent full-text screening. The final results are 2 articles that met the eligibility criteria for final analysis.

The final analysis included a total of 20,646 patients from two studies between 2014-2024. All studies in this systematic review had an RCT design. All studies were done in Pakistan **(Table 1).**

Of the total 20,646 patients in the studies, 11,633 (56%) patients received oral amoxicillin and 9,013 (44%) received oral cotrimoxazole **(Table 1)**. The amoxicillin preparation used in both studies was 250 mg/5 mL amoxicillin syrup. In the first study, the dose of amoxicillin was differentiated based on age, while in the other study it was based on the patient's weight. The duration of amoxicillin therapy is 3 days.[8,9]

Both studies used sulfamethoxazole (SMZ) 200 mg and trimethoprim (TMP) 40 mg/5 mL syrup preparations. However, the dosage is different, one study was based on age and the other was based on weight. The efficacy and failure of therapy were assessed after 5 days.[8,9] Details of preparations, doses, and duration of therapy can be seen in **Table 2** and **Table 3**.

The effectiveness of amoxicillin and cotrimoxazole was compared through treatment failure rates. The lower the failure rate, the more effective the therapy. Treatment failure in the intervention group using amoxicillin was assessed on day 4 and on day 6, while in the cotrimoxazole group on day 6 **(Table 4).**

Ahmed, *et al*, divided the failure and success rates of amoxicillin cummulatively on day 4 and then day 6, while the cotrimoxazole group was assessed only on day 6. There was a difference in the rate of amoxicillin treatment failure on day 4 (72 patients) and 6 (62 patients) because on day 4, there were still patients who had not recovered. On day 6, the number of recovered patients increased by 10 patients, so the recovery rate increased and the treatment failure rate decreased from 72 patient (2.9%) to 62 patients (2.5%).

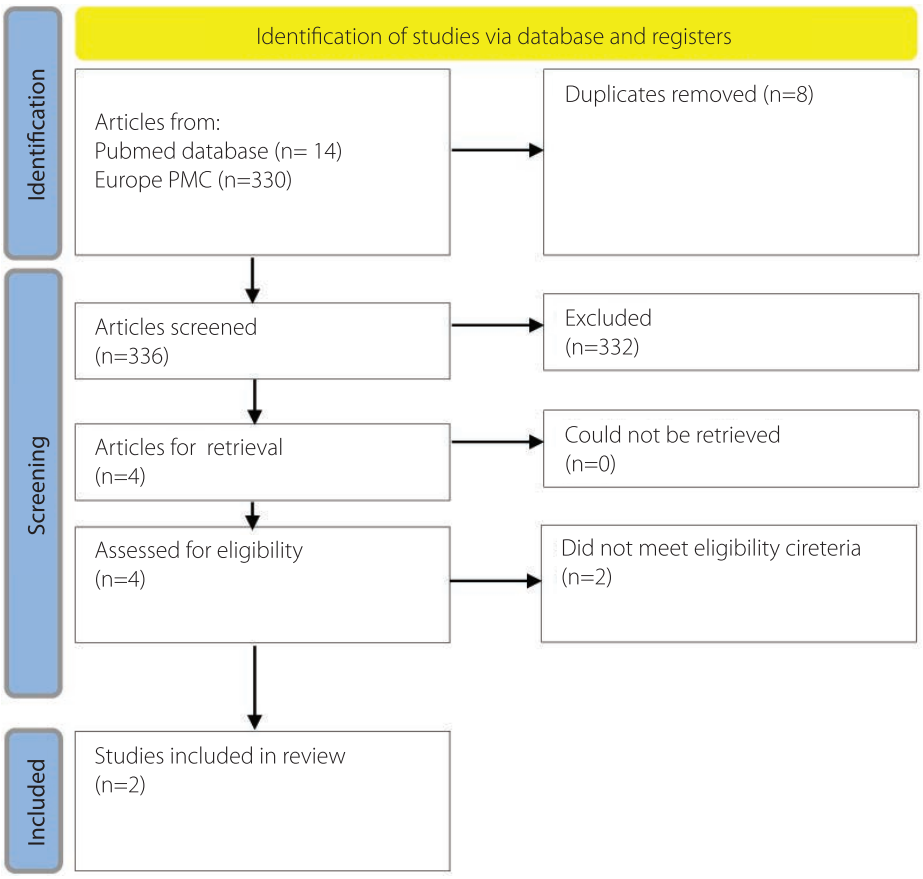

Figure. Prisma chart of screening and inclusion process of amoxicillin versus cotrimoxazole for pneumonia related articles.

Table 1. Study design, location, and total samples.

N	Author/Year	Study Design	Country	Total Patients
1.	Ahmed. *et al*. 2022.	Cluster randomized trial	Pakistan	4,984
2.	Sadruddin. *et al*. 2019.	Cluster randomized trial	Pakistan	15,662


In cotrimoxazole group, researchers only focused on measuring the cure and failure rates on day 6, that were 102 patients out of 2504 samples (4.1%), so no data on cure and failure rates on day 4 in the cotrimoxazole group. There was no significant difference between 4 days of amoxicillin versus 6 days of cotrimoxazole, nor 6 days of amoxicillin versus 6 days of cotrimoxazole.

DISCUSSION

Pneumonia in children aged 0-59 months has the initial symptom of fast breathing. The definition of fast breathing in children aged 2-11 months is respiratory rate ≥50 times/minute and in children aged 1-5 years is respiratory rate ≥40 times/minute.[10] Diagnosis of non-severe pneumonia can be made if one or two of the symptoms of fast breathing and lower chest retraction are found in physical examination.[10] The etiology of pneumonia can be a bacterial or viral infection or both. Antibiotics must be given to treat patients with pneumonia without identifying the causative pathogens because the most common causative pathogens of pneumonia are bacteria.[11]

There is no significant difference between the efficacy of amoxicillin on day 4 and cotrimoxazole on day 6 in treating pneumonia (97.1% vs 95.9% and 96.3% vs 90.9%), so both antibiotics can be an option for treating pneumonia.[9,12] Amoxicillin on day 4 showed lower treatment failure than cotrimoxazole on day 6 (2.9% vs 4.1% with a risk difference of -0.94 (-2.8, 0.96)).[12] This is in line with Salim, *et al*, finding that amoxicillin treatment failure on day 4 was lower than cotrimoxazole on day 6 (3.6% vs 9.1%).[9] Amoxicillin on day 6 also showed lower treatment failure than cotrimoxazole on day 6 (2.5% vs 4.2% with a risk difference of -1.51 (-3.21, 0.18)).[12] Criteria for amoxicillin treatment failure in those research are mostly due to persistent respiratory rate exceeding 50 times/minute (70.8%), while cotrimoxazole treatment failure is due to persistent lower chest indrawing (50%).[12] Other studies mostly used treatment failure criteria if respiratory rates exceeds 50 breaths/minute in both the amoxicillin and cotrimoxazole groups.[9] The cause of treatment failure is not known, but it can be because of non-bacterial pathogens etiology.[13]

Research in Mali aims to find the causative pathogen in children under 5 years old with pneumonia. The sample consisted of two groups, namely a pneumonia group and a control non-pneumonia group. Both groups were hospitalized patients and nasal samples were taken within the first 48 hours and were examined using the Real-Time Polymerase Chain Reaction (RT-PCR) method which can detect 19 viruses and 5 bacteria. The most common bacteria were *Streptococcus pneumoniae* (72%), *Staphylococcus aureus* (19.5%) and *Haemophilus influenza* (6.8%), while the most common viruses found were RSV (25.4%), *Rhinovirus* (22.9%), *Bocavirus* (11.0%), *Human metapneumovirus* (10.2%), and *Influenza A* (9.3%). Uniquely, this causative pathogen was also found in the non-pneumonia group but with fewer results. When compared with the non-pneumonia group, the most common bacterial found was *Streptococcus pneumoniae* (OR: 3.4), while the

Table 2. Samples treated with oral amoxicillin and oral cotrimoxazole.

N	Author/Year	Intervention (Oral Amoxicillin)	Control (Oral Cotrimoxazole)	Total Number
1.	Ahmed, *et al*. 2022.	2,480 (50%)	2,504 (50%)	4,984
2.	Sadruddin, *et al*. 2019.	9,153 (58%)	6,509 (42%)	15,662
Total		11,633 (56%)	9,013 (44%)	20,646

Table 3. Details of dose and duration of oral amoxicillin and oral cotrimoxazole treatment.

N	Author/Year	Doses and Preparation		Duration	
		Amoxicillin	Cotrimoxazole	Amoxicillin	Cotrimoxazole
1.	Ahmed. *et al.* 2022.	Preparation: ■ Amoxicillin syrup 250 mg/5 mL Dose : ■ 2-11 months: 62.5 mg twice daily ■ 12-59 months: 187.5 mg twice daily	Preparation: ■ SMZ 200 mg + TMP 40 mg/5 mL Dose: ■ 2-6 months: SMZ 100 mg + TMP 20 mg twice daily ■ 6-59 month: SMZ 200 mg + TMP 40 mg twice daily	3 days	5 days
2.	Sadruddin. *et al*. 2019.	Preparation: ■ Amoxicillin syrup 250 mg/5 mL Dose: ■ 50 mg/kg/day twice daily	Preparation: ■ 1Z 200 mg + TMP 40 mg/5 mL Dose: ■ SMZ 40 mg/kg/day and TMP 8 mg/kg/day twice daily	3 days	5 days

Abbreviations: N: Number, SMZ: Sulfamethoxazole, TMP: Trimethoprim.

Table 4. Details of treatment failure.

N	Author/Year	N	Treatment Failure		Risk Difference (95% CI)
			Amoxicillin	Cotrimoxazole	
1.	Ahmed, *et al*. 2022.	4,984	Day 4: 72/2480 (2,9%)	Day 6: 102/2504 (4,1%)	-0.94 (-2.84, 0.96)
		4,984	Day 6: 62/2480 (2,5%)	Day 6: 102/2504 (4,1%)	-1.51 (-3.21, 0.18)
2.	Sadruddin, *et al*. 2019.	15,662	Day 4: 326/9153 (3.6%)	Day 6: 592/6509 (9.1%)	-5.5% (-7.3, -3.7)

Abbreviations: Sn: Serial number, N: Number.

most common viruses found were *Human metapneumovirus* (OR: 17.2), *Influenza A* (OR: 10.7), and RSV (OR: 7.4).[14]

Respiratory tract diseases are the most common cause of death in children, one of which is pneumonia.[15] Giving appropriate initial antibiotics in pneumonia has been shown to reduce mortality.[16] Amoxicillin or cotrimoxazole can be the first choice because they are widely available in primary health care, and have the same effectiveness against pneumonia. Although amoxicillin is more expensive than cotrimoxazole, amoxicillin provides a faster recovery effect and has lower resistance.[12] Amoxicillin can be given for short durations of 3 and 5 days and has the same effectiveness as long-term administration (10 days); short-term therapy can reduce side effects of amoxicillin such as gastroenteritis and skin rashes, and also reduces medication non-adherence.[17]

Amoxicillin and cotrimoxazole are safe antibiotics and rarely cause side effects. This is in accordance with a prospective study by Efendy, *et al*, on 50 patients who received amoxicillin therapy and 4 people who received cotrimoxazole; no side effects in both groups after 72 hours of monitoring.[18] Availability, same effectiveness, and minimal side effects make these two antibiotics can be the main choice for pneumonia treatment, but amoxicillin has a shorter duration of therapy.

This review has several limitations. There was no evidence that the samples had been microbiologically diagnosed, so non-bacterial pneumonia could not be ruled out. Doses of amoxicillin and cotrimoxazole were also different in the two studies. The researches only came from one country, so the results are difficult to be applied throughout the world, but it can be a reference for low middle income countries.

CONCLUSION

Amoxicillin or cotrimoxazole can be used for the initial management of non-severe pneumonia in children under 5 years old in lower-middle-income countries. Amoxicillin has the same efficacy as cotrimoxazole with a shorter treatment duration.

REFERENCES

1. UNICEF. A child dies of pneumonia every 43 seconds [Internet]. 2023 [cited 2024 Feb 20]. Available from: https://data.unicef.org/topic/child-health/pneumonia/.
2. Kemenkes RI. Laporan nasional Riskesdas 2018. Lembaga Penelitian dan Pengembangan Kesehatan (LPB): Indonesia; 2019.
3. Kemenkes RI. Profil kesehatan Indonesia 2022. Kemenkes RI: Jakarta; 2023.
4. Ciptaningtyas VR, De Mast Q, De Jonge MI. The burden and etiology of lower respiratory tract infections in children under five years of age in Indonesia. J Infect Dev Ctries 2021;15(5):603–14. DOI: 10.3855/jidc.14268.
5. Meyer Sauteur P. Childhood community-acquired pneumonia. European Journal of Pediatrics 2024;183:1129-36. DOI: 10.1007/s00431-023-05366-6.
6. Kuitunen I, Jaaskelainen J, Korppi M, Renko M. Antibiotic treatment duration for community-acquired pneumonia in outpatient children in high-income countries—A systematic review and meta-analysis. Clinical Infectious Diseases 2023;76(3):e1123-28. DOI: 10.1093/cid/ciac374.
7. Wahyudi N, Winardi W, Karyono Y, Nugroho A, Sofyan A, Budiati I, et al. Statistik Indonesia 2023. Badan Pusat Statistik: Jakarta; 2024.
8. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ. 2021;372(71):1–9. DOI: 10.1136/bmj.n71.
9. Sadruddin S, Khan IUH, Fox MP, Bari A, Khan A, Thea DM, et al. Comparison of 3 days amoxicillin versus 5 days cotrimoxazole for treatment of fast-breathing pneumonia by community health workers in children aged 2-59 months in Pakistan: A cluster-randomized trial. Clin Infect Dis. 2019;69(3):397–404. DOI: 10.1093/cid/ciy918.
10. Zar H, Moore DP, Andronikou S, Argent AC, Avenant T, Cohen C, et al. Diagnosis and management of community-acquired pneumonia in children: South African Thoracic Society guidelines. African Journal of Thoracic and Critical Care Medicine 2020;26(3):98–116. DOI: 10.7196/AJTCCM.2020.v26i3.104.
11. Smith DK, Kuckel DP, Recidoro AM. Community-acquired pneumonia in children: Rapid evidence review. Am Fam Physician 2021;104(6).
12. Ahmed S, Ariff S, Muhammed S, Rizvi A, Ahmed I, Soofi SB, et al. Community case management of fast-breathing pneumonia with 3 days oral amoxicillin vs 5 days cotrimoxazole in children 2-59 months of age in rural Pakistan: A cluster randomized trial. J Glob Health 2022;12:04097. DOI: 10.7189/jogh.12.04097.
13. Tramper-Stranders GA. Childhood community-acquired pneumonia: A review of etiology- and antimicrobial treatment studies. Paediatr Respir Rev. 2018;26:41–8. DOI: 10.1016/j.prrv.2017.06.013.
14. Benet T, Sylla M, Messaoudi M, Picot VS, Telles JN, Diakite AA, et al. Etiology and factors associated with pneumonia in children under 5 years of age in Mali: A prospective case-control study. PLoS One 2015;10(12):1–15. DOI: 10.1371/journal.pone.0145447.
15. Kamianowska M, Kamianowska A, Wasilewska A. Causes of death in neonates, infants, children, and adolescents at the University Children's Clinical Hospital of Białystok between 2018 and 2021. Medical Science Monitor 2023;29:1–9. DOI: 10.12659/MSM.939915.
16. Khan R, Bakry M, Islahudin F. Appropriate antibiotic administration in critically ill patients with pneumonia. Indian J Pharm Sci 2015;77(3):299–305. DOI: 10.4103/0250-474x.159623.
17. Li Q, Zhou Q, Florez ID, Mathew JL, Shang L, Zhang G, et al. Short-course vs long-course antibiotic therapy for children with nonsevere community-acquired pneumonia. JAMA Pediatr 2022;176(12):1199–207. DOI: 10.1001/jamapediatrics.2022.4123.
18. Efendy SA, Ismunandar A, Maulana LH. Monitoring efek samping amoxicillin dan cotrimoxazole pada pasien anak di Puskesmas Paguyangan tahun 2022. Pharmacy Peradaban Journal 2023;3(1):12–21.