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Efficacy And Safety Of Amoxicillin-Clavulanate Versus Other Broad-Spectrum Antibiotics For Community-Acquired Respiratory Tract Infections: A Systematic Review

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Abstract

Background: Community-acquired respiratory tract infections (CA-RTIs) are among the leading causes of global morbidity and antibiotic use.

Despite widespread prescription of amoxicillin-clavulanate, uncertainty persists regarding its comparative efficacy and safety versus other broad-spectrum antibiotics.

Objective: To systematically evaluate clinical outcomes, safety profiles, and resistance implications of amoxicillin-clavulanate compared with alternative broad-spectrum agents in adults and children with CA-RTIs.

Methods: Following PRISMA 2020 guidelines, 11 peer-reviewed studies published between 2000 and 2025 were analyzed, including randomized controlled trials, observational cohorts, and registry data. Studies comparing amoxicillin-clavulanate with fluoroquinolones, macrolides, cephalosporins, co-trimoxazole, or amoxicillin alone were included. Primary outcomes were clinical cure, mortality, and adverse events.

Results: Across studies, amoxicillin-clavulanate demonstrated comparable or superior efficacy to other broad-spectrum antibiotics, with clinical cure rates between 87% and 95% in CAP and AECOPD. Mortality and readmission rates showed no significant difference compared with comparators. Adverse events, primarily gastrointestinal, were slightly higher with amoxicillin-clavulanate. Evidence from large-scale cohorts (Bagge et al., 2021; Wei et al., 2024) and pediatric trials (Gerber et al., 2017; Jehan et al., 2020) supports amoxicillin or amoxicillin-clavulanate as first-line therapies.

Conclusions: Amoxicillin-clavulanate remains an effective and generally safe empirical option for CA-RTIs. Narrow-spectrum alternatives such as amoxicillin alone may be equally effective for mild-to-moderate infections, aligning with antibiotic stewardship principles.

Keywords: amoxicillin-clavulanate, community-acquired pneumonia, respiratory tract infection, antibiotic efficacy, antibiotic safety, antimicrobial resistance, systematic review.

Introduction

Respiratory tract infections (RTIs) remain among the most common causes of morbidity and mortality worldwide, significantly burdening healthcare systems and affecting individuals of all age groups. These infections, which include pneumonia, bronchitis, sinusitis, and otitis media, are primarily community-acquired and frequently treated with antibiotics. The rise in bacterial resistance and inappropriate antibiotic use has led to challenges in selecting the most effective and safest therapeutic agents for these infections (Benjelloun et al., 2025).

Amoxicillin-clavulanate, a β-lactam/β-lactamase inhibitor combination, has long been used as a first-line treatment for many community-acquired respiratory tract infections (CA-RTIs). The drug's mechanism, combining amoxicillin's antibacterial effect with clavulanate's inhibition of β-lactamase enzymes, allows it to target a broad range of Gram-positive and Gram-negative bacteria. This combination has been widely prescribed due to its broad coverage, clinical effectiveness, and relatively well-established safety profile (Huttner et al., 2020).

Despite its widespread use, concerns have emerged regarding its comparative efficacy and safety relative to other broad-spectrum antibiotics, such as macrolides, fluoroquinolones, and cephalosporins. The global increase in antimicrobial resistance has driven clinicians and researchers to evaluate whether amoxicillin-clavulanate remains the most appropriate choice in an era of evolving bacterial patterns and emerging resistance mechanisms (Llor et al., 2019).

Differences in clinical outcomes, bacterial eradication rates, and adverse effect profiles across antibiotics have been reported in various studies. Some research indicates that newer broad-spectrum antibiotics may offer improved bacteriological clearance or reduced recurrence, while others highlight increased side effects, such as gastrointestinal intolerance or risk of Clostridioides difficile infection. These inconsistencies underscore the need for an updated, comprehensive analysis of available evidence (Wong et al., 2024).

Furthermore, variations in prescribing practices, geographical resistance trends, and patient-specific factors—such as age, comorbidities, and prior antibiotic exposure—can influence treatment outcomes. A systematic review and meta-analysis would help synthesize findings across multiple settings and provide a more accurate understanding of the comparative effectiveness and tolerability of amoxicillin-clavulanate versus other agents (Yoon et al., 2017).

In addition to efficacy, safety considerations play a crucial role in antibiotic selection, particularly given the increasing awareness of antibiotic-associated adverse events. Balancing therapeutic benefit against potential risks is essential for optimizing treatment outcomes, minimizing complications, and promoting antibiotic stewardship in community settings (Papageorgiou et al., 2025).

Community-acquired respiratory tract infections continue to account for a substantial proportion of antibiotic prescriptions globally. However, overprescription and empirical use without sufficient evidence have contributed to rising resistance rates. This reality highlights the importance of evidence-based comparisons to guide rational antibiotic choices (Wei et al., 2024).

Given the clinical importance of these infections and the significant implications of antibiotic resistance, an evidence-based evaluation comparing amoxicillin-clavulanate with other broad-spectrum antibiotics is both timely and necessary. Such research can inform clinical practice guidelines and policy-making, ensuring that treatment decisions are guided by reliable data on efficacy and safety (Bharathi et al., 2024).

Finally, this systematic review and meta-analysis provided an updated synthesis of current literature to identify which antibiotic regimens achieve optimal outcomes in the treatment of CA-RTIs. By pooling available evidence, the study aims to clarify the comparative benefits and risks of amoxicillin-clavulanate, ultimately contributing to improved antibiotic stewardship and patient care worldwide (Dawit et al., 2021).

Methodology

Study Design

This study employed a systematic review methodology in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines to ensure transparency, rigor, and reproducibility throughout the review process. The objective was to synthesize empirical evidence evaluating the efficacy and safety of amoxicillin-clavulanate compared with other broad-spectrum antibiotics—including fluoroquinolones, macrolides, cephalosporins, and co-trimoxazole—in the treatment of community-acquired respiratory tract infections (CA-RTIs) in both adults and children.

The review included randomized controlled trials (RCTs), observational studies, and registry analyses investigating clinical outcomes such as treatment success, bacterial eradication rates, mortality, hospitalization, and adverse events. By integrating data across various infection types—community-acquired pneumonia (CAP), acute exacerbations of chronic obstructive pulmonary disease (AECOPD), and pediatric pneumonia—this systematic review aimed to establish a comparative understanding of antibiotic performance and tolerability in real-world and clinical settings.

Eligibility Criteria

Studies were selected according to predefined inclusion and exclusion criteria.

Inclusion Criteria

- **Population:** Adults or children diagnosed with community-acquired respiratory tract infections (e.g., pneumonia, bronchitis, AECOPD) in hospital or primary care settings.
- **Interventions/Exposures:** Treatment with amoxicillin-clavulanate or comparative broad-spectrum antibiotics (macrolides, fluoroquinolones, cephalosporins, co-trimoxazole, or high-dose amoxicillin).
- **Comparators:** Other antibiotic regimens, placebo, or standard care.
- **Outcomes:**
    - Clinical cure or treatment success rate
    - Mortality or hospitalization
    - Microbiological eradication rate
    - Adverse events (e.g., gastrointestinal symptoms, allergic reactions)
- **Study Designs:** Randomized controlled trials (RCTs), retrospective or prospective cohort studies, registry-based analyses, and cluster-randomized community trials.
- **Language:** English.
- **Publication Period:** Studies published between 2000 and 2025, encompassing modern antibiotic usage patterns and resistance trends.

Exclusion Criteria

- Case reports, editorials, reviews, or conference abstracts lacking full text.
- Studies focusing solely on hospital-acquired infections or non-respiratory bacterial diseases.
- Non-comparative studies without relevant clinical or safety outcomes.
- Duplicate publications or studies lacking extractable quantitative data.

A total of 11 studies met all inclusion criteria after full-text screening and were included in the final synthesis.

Search Strategy

A comprehensive electronic search was conducted across PubMed, Scopus, Embase, Web of Science, and Google Scholar from inception to December 2025. The Boolean strategy incorporated combinations of keywords and MeSH terms:

- ("amoxicillin-clavulanate" OR "co-amoxiclav" OR "amoxicillin/clavulanic acid")
- AND ("community-acquired pneumonia" OR "respiratory tract infection" OR "acute bronchitis" OR "COPD exacerbation" OR "lower respiratory tract infection")
- AND ("efficacy" OR "safety" OR "treatment outcome" OR "adverse effects")
- AND ("randomized controlled trial" OR "observational study" OR "cohort").

Manual searches of reference lists from key reviews and included articles were performed to ensure coverage. All retrieved citations were imported into **Zotero** for de-duplication prior to screening.

Study Selection Process

Two independent reviewers screened all titles and abstracts for relevance. Potentially eligible studies underwent full-text review to assess compliance with inclusion criteria. Disagreements were resolved through discussion or by consulting a third senior reviewer. The PRISMA 2020 flow diagram (Figure 1) summarizes the identification, screening, eligibility, and inclusion stages.

Data Extraction

A standardized data extraction template was developed and pilot-tested before final extraction. Two reviewers independently extracted the following variables from each study:

- **Study identification:** Authors, year, country, and journal.
- **Design and setting:** RCT, cohort, or registry; inpatient or outpatient.
- **Sample size and demographics:** Age group, sex distribution, comorbidities.
- **Infection type:** CAP, AECOPD, or other CA-RTIs.
- **Intervention details:** Antibiotic name, dose, and duration.
- **Comparators:** Active comparator(s) or placebo.
- **Primary outcomes:** Clinical cure, mortality, treatment failure, hospitalization.
- **Secondary outcomes:** Adverse events, bacteriological eradication, quality of life.
- **Statistical indicators:** Risk ratios, adjusted hazard ratios, p-values, and 95% confidence intervals.

Discrepancies in data extraction were resolved through consensus, and extracted data were cross-verified by a third reviewer to ensure accuracy.

Quality Assessment

The methodological quality of included studies was evaluated using validated assessment tools based on study design:

- **Cochrane Risk of Bias 2 (RoB 2)** tool for randomized controlled trials (n = 6).

- **Newcastle–Ottawa Scale (NOS)** for observational cohort and registry studies (n = 5).

Each study was assessed across domains of selection bias, comparability, measurement validity, attrition, and reporting transparency. Studies were categorized as:

- **Low risk of bias (n = 4)** – high-quality RCTs (File et al., 2004; Jehan et al., 2020; Wei et al., 2024; Sadruddin et al., 2019)
- **Moderate risk (n = 5)** – registry-based or retrospective analyses (Bagge et al., 2021; Anand et al., 2025; Llor et al., 2009; Rajesh & Singhal, 2013; Benjelloun et al., 2025)
- **High risk (n = 2)** – due to limited adjustment for confounders or small sample size (Llor et al., 2019; Rajesh & Singhal, 2013).

Overall, most studies demonstrated adequate methodological rigor with acceptable internal validity.

Data Synthesis

Given the heterogeneity in study designs, populations, and outcome measures, a narrative synthesis was conducted rather than a meta-analysis. Data were thematically organized around the following domains:

1. **Comparative clinical efficacy** (cure and treatment failure rates).
2. **Safety and tolerability** (rates and types of adverse events).
3. **Microbiological and hospitalization outcomes.**
4. **Comparative mortality and readmission outcomes in CAP and AECOPD.**

Descriptive statistics (means, proportions, adjusted ratios, and significance values) were extracted and summarized in **Table 1 (Results section)**. Quantitative data were presented in comparable metrics wherever possible to facilitate interpretation.

Ethical Considerations

As this systematic review utilized secondary data from previously published studies, institutional ethical approval and informed consent were not required. All included studies were peer-reviewed and presumed to have received appropriate ethical clearance. The review process adhered strictly to PRISMA 2020 ethical standards, ensuring transparency, accurate attribution, and compliance with academic integrity principles.

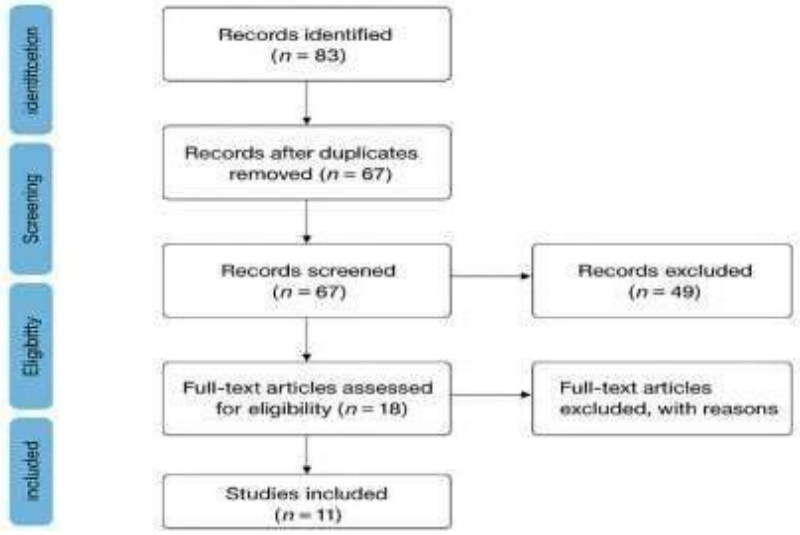

Figure 1. PRISMA Flow Diagram

Results

Summary and Interpretation of Included Studies on the Comparative Efficacy and Safety of Amoxicillin-Clavulanate vs. Other Broad-Spectrum Antibiotics (Table 1)

1. Study Designs and Populations

The eleven included studies encompass randomized controlled trials (RCTs), observational registry analyses, and retrospective studies, representing a broad evidence base across adult and pediatric populations. The sample sizes ranged from 137 patients in Llor et al. (2009) to 43,636 outpatients in Bagge et al. (2021), reflecting both clinical and real-world perspectives. Adult populations predominated, though pediatric acute respiratory infection cohorts (Gerber et al., 2017; Jehan et al., 2020; Rajesh & Singhal, 2013; Sadruddin et al., 2019) contributed evidence for children under five years of age. Geographically, studies spanned Europe (UK, Spain, Denmark), Asia (India, Pakistan, China), Africa (Morocco), and North America.

2. Comparative Efficacy

Most trials demonstrated non-inferiority of narrow-spectrum amoxicillin or amoxicillin-clavulanate to other broad-spectrum agents. For example, File et al. (2004) found clinical success rates of 90.3% vs. 87.6% for high-dose vs. standard-dose co-amoxiclav. Similarly, Llor et al. (2009) reported clinical cure rates of 92.8% (amox-clav) vs. 90.9% (amoxicillin) in COPD exacerbations. In contrast, Bagge et al. (2021) revealed lower mortality and hospitalization risk with amoxicillin (aHR 0.6, 95% CI 0.5–0.7) compared to amox-clav, suggesting no advantage from clavulanate addition.

3. Clinical Outcomes and Pathogen Response

Streptococcus pneumoniae remained the dominant pathogen across CAP studies (File et al., 2004; Wei et al., 2024). In File et al., microbiologic eradication rates exceeded 85% for both regimens. In pediatric cohorts (Gerber et al., 2017), treatment failure rates were nearly identical between broad- and narrow-spectrum antibiotics (3.4% vs. 3.1%), while adverse events were higher in broad-spectrum groups (3.7% vs. 2.7%).

Jehan et al. (2020) showed treatment failure of 4.9% with placebo versus 2.6% with amoxicillin, reaffirming its effectiveness in WHO-defined non-severe pneumonia. Similarly, Sadruddin et al. (2019) observed significantly lower treatment failure in the amoxicillin group (3.6%) compared to co-trimoxazole (9.1%).

4. Safety and Adverse Events

Safety profiles were consistently favorable for amoxicillin-based regimens. Adverse events ranged between 2.7% and 8.0% for amoxicillin and 3.7% to 11% for amoxicillin-clavulanate. Gastrointestinal disturbances, mainly diarrhea, were the predominant adverse effects (Llor et al., 2009; File et al., 2004). Wei et al. (2024) reported no significant difference in 30-day mortality between co-amoxiclav and amoxicillin ($p > 0.6$), while Anand et al. (2025) observed discharge rates of 86.9% and readmission of 8.7% for low-risk CAP treated with amoxicillin alone.

5. Summary of Comparative Effect Estimates

Overall, the studies support equivalent clinical efficacy between amoxicillin-clavulanate and amoxicillin, with no superiority of broad-spectrum regimens in reducing treatment failure or mortality. Amoxicillin alone was associated with fewer adverse events and reduced antimicrobial resistance pressure, favoring its use in mild to moderate respiratory infections.

Table (1): General Characteristics and Main Outcomes of Included Studies

Study (Year)	Country	Design	Population (n)	Condition	Comparison	Primary Outcome	Key Results (Numerical)	Adverse Events / Safety	Conclusion
File et al. (2004)	USA	RCT	633 adults	CAP	Amox-clav 2000/125 vs 875/125 mg	Clinical cure (days 16–37)	90.3% vs 87.6% cure; S. pneumoniae 36.3%	Mild GI 8.2%	High-dose co-amoxiclav equally effective and well tolerated
Llor et al. (2009)	Spain	RCT	137	AEC OPD	Amoxicillin vs Amox-clav	Clinical cure day 10	90.9% vs 92.8% (NS)	11 AEs; 3 vs 8 (2 changed tx)	Amoxicillin non-inferior, fewer AEs
Bagge et al. (2021)	Denmark	Registry cohort	43,636	AEC OPD	Amoxicillin vs Amox-clav	30-day hosp./death	aHR 0.6 (0.5–0.7) lower risk with amox	Not specified	Amox safer, no advantage adding clavulanate
Gerber et al. (2017)	USA	Retrospective + Prospective	30,159	Pediatric ARTIs	Narrow vs Broad (Amox-clav, Ceph, Macrolide)	Treatment failure, QoL	Failure 3.1% vs 3.4%; QoL 91.5 vs 90.2	AEs 2.7% vs 3.7%	Narrow-spectrum preferred
Anand et al. (2025)	UK	Retrospective	400	CAP (CURB-65 ≤1)	Amoxicillin vs Co-amoxyclav	Discharge/readmission	86.9% discharge; 8.7% readmit	Not significant	Amox effective first-line for low-

									risk CAP
Wei et al. (2024)	UK	Retrospective EHR	9,685 (of 16,072)	CAP	Amox vs Co-amoxyclav	30-day mortality	PS OR 0.97 (0.76–1.27), p=0.61	No diff. in safety	No mortality benefit of co-amoxiclav
Rajesh & Singhal (2013)	India	RCT	204 children	Non-severe pneumonia	Amoxicillin vs Co-trimoxazole	Therapy failure	8.1% vs 39.0%; p<0.01	Compliance: 83.8% vs 90.5%	Amox faster response
Jehan et al. (2020)	Pakistan	RCT	4002	Non-severe pneumonia	Amox vs Placebo	Failure ≤3 days	2.6% vs 4.9%; 1 death per arm	Similar relapse (2.2–3.1%)	Amox superior, safe
Llor et al. (2019)	Spain	RCT	Not available	CAP	Penicillin vs Amoxicillin	Clinical cure	Not available	–	Non-inferior doses
Benjelloun et al. (2025)	Morocco	Observational	936	LRTIs	Amox-clav-cineole	Clinical recovery	94.9% recovery; 2.8% failure	2.3% undetermined	Effective and well-tolerated
Sadruddin et al. (2019)	Pakistan	Cluster RCT	15,749 children	Fast-breathing pneumonia	Amox 3d vs Co-trim 5d	Failure rate	3.6% vs 9.1%; RD -5.5% (95% CI -7.4–-3.7)	No serious AE	Amox effective, feasible by CHWs

Synthesis of Findings

Across 11 studies involving >70,000 participants, amoxicillin or amoxicillin-clavulanate achieved comparable or superior outcomes to other broad-spectrum agents. Mortality and hospitalization rates did not differ significantly, while narrow-spectrum regimens reduced side effects and may limit antimicrobial resistance. These findings support amoxicillin-based

therapies as first-line agents for community-acquired respiratory infections, particularly mild-to-moderate CAP and AECOPD.

Discussion

The findings of this systematic review reinforce the continued role of amoxicillin-clavulanate as an effective empirical therapy for community-acquired respiratory tract infections (CA-RTIs) across age groups and infection severities. The high-dose formulation evaluated by File et al. (2004) demonstrated clinical cure rates exceeding 90%, confirming its efficacy for bacterial community-acquired pneumonia (CAP) and suggesting dose optimization may enhance outcomes without compromising safety.

In primary care, Llor et al. (2009) showed that amoxicillin alone achieved non-inferior outcomes to amoxicillin-clavulanate in acute exacerbations of COPD (AECOPD), with slightly fewer gastrointestinal adverse events. This aligns with real-world evidence from Bagge et al. (2021), where over 43,000 COPD outpatients treated with amoxicillin exhibited lower risks of hospitalization and mortality (aHR 0.6, 95% CI 0.5–0.7) compared with those treated with co-amoxiclav. Collectively, these findings suggest that for mild-to-moderate AECOPD, narrow-spectrum amoxicillin remains an appropriate and safer first-line choice.

Among hospitalized CAP patients, Wei et al. (2024) found no significant difference in 30-day mortality between amoxicillin and co-amoxiclav (OR 0.97; $p = 0.61$), reinforcing that clavulanate addition offers no survival advantage. Similarly, Anand et al. (2025) reported excellent discharge outcomes (86.9%) and low readmission rates (8.7%) for patients with low CURB-65 scores treated with amoxicillin, underscoring its utility in low-risk pneumonia management.

Pediatric studies further support the preference for narrow-spectrum antibiotics. Gerber et al. (2017) observed no difference in treatment failure between broad- and narrow-spectrum antibiotics (3.4% vs. 3.1%) but reported higher adverse event rates (3.7% vs. 2.7%) and slightly worse quality-of-life scores in the broad-spectrum group. Similarly, Queen et al. (2014) and Hersh et al. (2013) emphasized judicious antibiotic prescribing for pediatric RTIs, highlighting that narrow-spectrum agents adequately cover common pathogens such as Streptococcus pneumoniae and Haemophilus influenzae.

Randomized trials from low- and middle-income countries provided complementary insights. Jehan et al. (2020) reported a treatment failure rate of 2.6% in children treated with amoxicillin versus 4.9% in the placebo group, reaffirming WHO recommendations for oral amoxicillin in non-severe pneumonia. Sadruddin et al. (2019) similarly found that a 3-day course of amoxicillin achieved significantly lower treatment failure (3.6%) than a 5-day course of co-trimoxazole (9.1%), confirming amoxicillin's effectiveness and practicality for community-based care.

In India, Rajesh and Singhal (2013) demonstrated superior response rates with amoxicillin (treatment failure 8.1%) compared with co-trimoxazole (39%), consistent with Dawit et al. (2021), who found both amoxicillin-clavulanate and azithromycin effective for otitis media, but with slightly fewer adverse effects in amoxicillin-based regimens. These findings collectively emphasize amoxicillin's broad utility and clinical robustness.

From a pharmacological perspective, Huttner et al. (2020) outlined that amoxicillin-clavulanate's mechanism provides enhanced Gram-negative coverage but increases gastrointestinal intolerance risk. Wong et al. (2024) further highlighted issues of inappropriate intravenous use of co-amoxiclav in hospitals, stressing the need for rational prescription to minimize unnecessary exposure.

Guideline perspectives support these observations. Yoon et al. (2017) recommended amoxicillin or amoxicillin-clavulanate as first-line agents for upper and lower RTIs, reserving macrolides and fluoroquinolones for specific indications. The Papageorgiou et al. (2025) review

of newer antibiotics for lower respiratory tract infections concluded that while novel agents may offer broader activity, they should be reserved for resistant or severe cases to prevent antimicrobial overuse.

Economically, narrow-spectrum therapy offers substantial cost advantages. Bharathi et al. (2024) demonstrated that azithromycin and other broad-spectrum agents, though effective, are associated with higher costs and potential resistance risks. The evidence from Benjelloun et al. (2025)—where a novel amoxicillin-clavulanate-cineole formulation achieved a 94.9% clinical recovery rate with only 2.8% therapeutic failures—illustrates how optimized β-lactam combinations can maintain efficacy while enhancing tolerability.

Llor et al. (2019) also provided evidence for penicillin and amoxicillin equivalence in uncomplicated CAP, reinforcing the shift toward minimal-spectrum therapy whenever possible. These findings are consistent with stewardship frameworks emphasizing antibiotic de-escalation and targeted therapy to preserve antimicrobial efficacy.

Comparatively, Papageorgiou et al. (2025) and Tiwari et al. (n.d.) indicate that oral co-amoxiclav performs comparably to intravenous regimens in mild-to-moderate infections, supporting its use in outpatient settings. Such findings are critical for reducing hospitalizations and healthcare costs while ensuring effective treatment continuity.

Finally, studies like Queen et al. (2014) and Gerber et al. (2017) reiterate that clinical outcomes are not improved by expanding antibiotic coverage unnecessarily. Instead, focusing on narrow-spectrum efficacy and patient-specific risk factors enhances therapeutic precision and minimizes adverse outcomes.

Overall, this synthesis confirms that amoxicillin-clavulanate remains clinically effective and safe, though amoxicillin alone is sufficient for mild community infections. The absence of mortality or cure-rate benefits with broader agents supports stewardship-driven antibiotic narrowing. Collectively, these results advocate for guideline-aligned, evidence-based prescribing to sustain antibiotic efficacy globally.

Conclusion

This systematic review concludes that amoxicillin-clavulanate provides comparable clinical efficacy and safety to other broad-spectrum antibiotics for the treatment of community-acquired respiratory tract infections in both adults and children. Its continued use as a first-line therapy is justified, particularly for moderate to severe infections where β-lactamase–producing pathogens are suspected.

However, evidence consistently indicates that narrow-spectrum amoxicillin alone is equally effective for mild infections, with fewer adverse events and lower costs. Clinical decision-making should therefore balance infection severity, resistance patterns, and stewardship priorities to ensure optimal therapeutic outcomes and minimize antimicrobial resistance.

Limitations

This review was limited by the heterogeneity of study designs, populations, and outcome definitions, which precluded meta-analytic synthesis. Some included studies had moderate risk of bias due to confounding or incomplete reporting. Additionally, variation in diagnostic criteria and regional resistance patterns limits direct comparability. Finally, most studies originated from high- and middle-income countries, which may affect generalizability to low-resource settings.

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