

Surge for narrow-spectrum antibiotics in times of the MDR crisis: Systematic literature review to establish the role of amoxicillin in tonsillopharyngitis

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ABSTRACT

Background: Group A Streptococcus (GAS) is the predominant pathogen accountable for tonsillitis, making it the most prevalent and frequently encountered bacterial cause of upper respiratory infections. Although amoxicillin is a frequently prescribed antibiotic for the treatment of tonsillopharyngitis, alternate agents like macrolides are regularly recommended. The objective of this study was to evaluate and compare the effectiveness of amoxicillin, its side effects, and the associated risk ratio with alternative antibiotic treatments for respiratory tract infections and tonsillopharyngitis in both children and adults.

Material and Methods: An initial search was performed via five basic databases PubMed, Medline, Embase, clinicaltrial.gov and the Cochrane Central Register of Controlled Trials, to identify studies meeting the inclusion criteria spanning from July 2012 to June 2023. The primary search of studies resulted in 6260 from four databases during the study period.

Results: After the initial scan of titles and abstracts, 06 studies were included in the review, which reported clinical cure rates. Four out of six studies reported adverse events.

Conclusion: Our analysis infers that given their narrow spectrum of activity, low incidence of side effects, comparable efficacy and cost-effectiveness, penicillin or amoxicillin can be considered as preferable choice for the management of tonsillopharyngitis and broad-spectrum antibiotics offer no added advantage in disease management.

Keywords: Amoxicillin, Tonsillopharyngitis, Tonsillitis, Acute respiratory infection, Streptococcal infection, GAS, SLR, Systematic literature Review, Antibiotics

BACKGROUND

Tonsillopharyngitis is defined as an acute infection affecting the pharynx, palatine tonsils, or both. Being among the prevalent upper respiratory tract infections, it frequently leads individuals to seek medical care and receive antibiotic prescriptions. While a majority of cases of tonsillopharyngitis result from a viral etiology, which includes rhinovirus, respiratory syncytial virus, adenovirus, and coronavirus, bacterial infections are typically due to group A beta-hemolytic Streptococcus

(GABHS), also known as Streptococcus pyogenes. GABHS is recognized as the causative agent for acute pharyngitis in approximately 15-35% of children and 5-15% of adults.¹

Antibiotics are often indicated for the treatment of GABHS, for alleviating symptoms such as pain and fever), for shortening the duration of the illness, for preventing clinical relapse (i.e., recurrence of symptoms after initial resolution), and for preventing complications (suppurative complications, acute rheumatic fever, post-streptococcal glomerulonephritis).¹

As per the IDSA practice guidelines for the management of group A streptococcal pharyngitis, penicillin or amoxicillin are the antibiotics of choice.² Although beta lactams have been in continuous use, there have been no reports of penicillin resistance in GABHS, and the antibiotic remains susceptible and effective. On the other hand, increased rates of resistance are documented for both fluoroquinolones and macrolides, yet, physicians frequently choose these broad-spectrum antibiotics for the treatment of tonsillopharyngitis,

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despite their associated side effects. In fact, there has been a notable surge in the prescription of broad-spectrum antibiotics for the management of upper respiratory tract infections.^{3,4}

Narrow-spectrum antibiotics should be preferred over broad-spectrum antibiotics in the treatment of pharyngitis due to several reasons, supported by evidence. Firstly, narrow-spectrum antibiotics target specific bacteria, reducing the risk of disrupting the body's natural microflora and the development of antibiotic resistance.⁵ Secondly, they are effective against the most common causative agent of pharyngitis, GABHS, while minimizing the impact on other bacteria.⁶

The excessive use of broad-spectrum antibiotics constitutes another form of inappropriate prescribing and is associated with an increased risk of unnecessary bacterial resistance, drug-related adverse effects, and escalated costs. Antibiotic resistance further increases mortality, cost of care, and length of hospital stays.

Hence, this systematic review aimed to evaluate the available literature comparing the utilization of broad-spectrum antibiotics over amoxicillin in tonsillopharyngitis treatment. The findings from this review will contribute valuable data for evidence-based decision-making and, subsequently, play a pivotal role in policy development, education, and quality improvement initiatives. The assessment will aid in understanding the effectiveness, safety, and impact on patient outcomes, facilitating judicious antibiotic use and reducing the risk of resistance development. Based on this clinical scenario, the following research question was formulated: Do broad-spectrum antibiotics offer any added advantage over amoxicillin in the treatment of tonsillopharyngitis?

MATERIAL AND METHODS

In accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, we conducted a search in the PubMed, Medline, Embase, Clinicaltrial.gov and Cochrane databases for English-language articles published from July 2012 to June 2023.⁷ This involved curated Boolean search strings and a thorough review of the bibliography of studies identified through the database searches. These databases were selected due to their accessibility at no cost.

The following keywords were utilized: "Tonsillopharyngitis," "Tonsillitis," "Acute respiratory

infection," "Upper respiratory tract infections," "Streptococcal infections," and "Pharyngitis." Experimental studies consisting of randomized control trials; quasi-experimental studies consisting of non-randomized control studies, before-and-after studies, interrupted time series studies; and observational studies consisting of the cohort studies, and case-control studies were included. Review articles, guidelines, and commentaries were excluded from the review. Duplicate studies were also removed. Subsequently, two independent reviewers conducted iterative rounds of blinded title and abstract screening, followed by a thorough review of full-length articles. Any discrepancies were resolved through discussion. All the chosen studies were entered into Excel.

The initial search yielded a total of 6260 studies from five databases over the study period. The review included clinical trials, randomized controlled trials, case-control studies, comparative studies (comparison with other antibiotics) and interventional studies in English. Studies without full-text articles were not included in this review.

Our inclusion criteria involved quantitative studies conducted worldwide that compared oral amoxicillin with other antibiotics for treating tonsillopharyngitis in adults or children across various settings. The inclusion criteria were not restricted by dosage or duration of treatment.

Only studies involving participants meeting the criteria for the diagnosis of tonsillopharyngitis were considered. The primary outcome of interest centered on the resolution of symptoms following the prescription of amoxicillin compared to other antibiotics. Secondary outcomes of tonsillopharyngitis following treatment with amoxicillin, in comparison to other antibiotics, included considerations of dose, duration of treatment, and adverse events.

RESULTS

The preliminary investigation produced 6260 findings from five databases within the designated study period (Figure-I). After eliminating 2647 duplicated studies and excluding 281 with incomplete data, an additional 3326 were dismissed, encompassing conference papers, other intervention measures, systematic reviews, or editorials. Subsequent to the initial scrutiny of titles and abstracts, the review incorporated 6 studies. The qualitative synthesis of the review included 6 studies, whereas the meta-analysis reviewed 5 out of 6 studies.

Two independent authors evaluated the quality of the chosen studies across various domains, including the generation of allocation sequence, concealment of allocation, blinding of participants and personnel, blinding of outcome assessor, incomplete outcome data, and selective reporting. The assessment utilized the 'Risk of bias' tool outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011).⁸ The overall risk of bias was categorized as low, high, or unclear. Discrepancies between the authors regarding the quality assessment were resolved through consensus.

The risk ratio (RR) for clinical cure rates in patients treated with amoxicillin compared to other antibiotics was calculated. The results from the included studies were categorized based on the antibiotic treatment strategy. A random-effects model was employed to compute pooled results with a 95% confidence interval (CI). The heterogeneity of the studies was assessed using Cochran's Q test and Higgins I² statistic. The pooling of overall effect estimates was conducted using Review Manager web (RevMan web, The Cochrane Collaboration, Denmark).

All these studies were released within the past 11 years, with the earliest study dating back to 2000 and the most recent one published in 2022.⁹⁻¹⁴ The included studies examined a total of 274194 participants. Three retrospective studies compared penicillin/amoxicillin to broad-spectrum antibiotics including amoxicillin-clavulanate, cephalosporins, and macrolides for the treatment of acute respiratory tract infections along with treatment outcomes and adverse events. (Gerber 2017, Peng Li 2019, Mattan 2022).^{12,13,14}

One study compared the clinical efficacy of amoxicillin-clavulanate with amoxicillin for the treatment of pharyngolaryngitis or tonsillitis and the other study compared the performance of amoxicillin and intramuscular benzathine penicillin in relieving manifestations of streptococcal pharyngitis. (Kuroki 2013, Gerber 2017).^{10,12}

The last study compared amoxicillin with a placebo in the management of tonsillopharyngitis. (Leelarasamee 2000).⁹

Two studies employed the drug-controlled, randomized, comparative study design to measure the efficiency of amoxicillin against other antibiotics.^{11,13} Peng Li *et al.* reported no statistical significance for the clinical and bacteriological eradication efficacy between

azithromycin, cefaclor and amoxicillin.¹³ Eslami *et al.* reported that once-daily therapy with amoxicillin is as effective as intramuscular benzathine penicillin G for the treatment of GABHS pharyngitis, but penicillin was significantly more effective in reducing exudate and concurrent signs vs. amoxicillin.¹¹ Mattan *et al.* reported that amoxicillin and penicillin-V treatments were associated with fewer additional primary physician visits compared to other antibiotic treatments.¹⁴ Kuroki *et al.* reported that clinical response rate of treatment with amoxicillin-clavulanate compared to amoxicillin was equivalent.¹⁰ Leelarasamee *et al.* reported that amoxicillin therapy conferred no benefit or harm when compared to a placebo.⁹

Since Leelarasamee *et al.* did not compare penicillin or amoxicillin to another antibiotic agent, it was not included in further analysis, as it did not fulfil our research questions. Out of the remaining 5 studies, only four studies reported adverse events due to the treatments given.

Figure-IV describes the individual assessment of each study included in the meta-analysis. All studies were classified with a low risk of bias.

The pooled analysis with the outcome of treatment success of tonsillopharyngitis was also performed for oral antibiotic therapy with amoxicillin and other antibiotics. Five studies (143954 patients) reported clinical cure rates.

Clinical Efficacy of Amoxicillin versus other Antibiotics: The results indicate no significant difference between amoxicillin and other antibiotics for treating tonsillopharyngitis (Figure-II, Amoxicillin vs. any antibiotics, RR: 1.59, 95% CI: 0.73–3.48, $p = 0.25$, $I^2 = 100\%$). The p -value of 0.25 indicates that there is no statistically significant difference in treatment success between the “any antibiotics” group and the amoxicillin group Figure-II.

Adverse Events of Amoxicillin versus other Antibiotics: Four out of five studies reported adverse events. The results indicate that amoxicillin was associated with a significantly lower risk of adverse events (pooled RR: 0.64, 95% CI: 0.42–0.98, $p = 0.04$, $I^2 = 82\%$).

In this systematic investigation, we examine the documented side effects of amoxicillin in comparison to other antibiotics. The review scrutinized each study, examining its findings on amoxicillin's side effects and comparing them with those of other antibiotics.

Euroki *et al.* provided useful insights on the side effect profile of amoxicillin and its comparison with other antibiotics. The main side effects related to amoxicillin were diarrhea (n=5) and upper airway inflammation (n=1), whereas diarrhea (n=22), urticaria (n=1), and eruptions (n=1) with associated with other antibiotics. Fever was the most often reported side effect related to amoxicillin administration, by Mattan *et al.*, with an incidence of n=117 compared to other antibiotics (Fever, n=141). Similarly, Peng Li *et al.* reported diarrhea (n=4), rash (n=2), and nausea (n=3) with amoxicillin as compared to other antibiotics (diarrhea, n=3), (rash, n=5), (nausea, n=3). Lastly, Gerber *et al.* reported overall 849 adverse events with amoxicillin compared to 189 events reported with other antibiotics, as shown in Table-I.

Individuals who received amoxicillin treatment had a 36% decreased risk of experiencing adverse events compared to those who received other antibiotics, according to the pooled risk ratio (RR) of 0.64. The p-value of 0.04 indicates that the difference in adverse events between the amoxicillin and other antibiotics groups is statistically significant (Figure-III).

Risk of Bias: Using the RoB-2 technique, we assessed the total risk of bias in six studies (Leelarasamee 2000, Haruo 2013, Eslami 2014, Jeffrey 2017, Peng Li 2019, and Mattan 2022).⁹⁻¹⁴ While Leelarasamee 2000 and Jeffrey 2017 indicated some concerns in D5 (bias in the selection of reported results), the rest of the research demonstrated a minimal risk of bias in the domains studied. These findings provide assurance about the dependability of the research outcomes in most studies examined in Figure-IV.

Table-I: Displays the characteristics of the studies included.

Author (Year)	Population	Total Participants	Age of Participants, Range (Year)	Study design	Dosages/ Duration of Treatment of Studies	Adverse events of studies
Mattan (2022)	Children and adults suffering from tonsillitis or pharyngitis	242366	3 to >46	Retrospective study	SYR. Amoxicillin 250mg/5ml, TAB. Amoxicillin 500mg	Amoxicillin: Fever (n=117) Comparative drug: Fever (n=141)
Peng Li (2019)	Children with tonsillitis	256	2 to 12	A drug-controlled, randomized, comparative trial study	Group 1: amoxicillin 30 mg/kg/ day/3 for 10 days Group 2: azithromycin 10 mg/kg/day/1 for 3 days Group 3: cefaclor 20 mg/kg/day/3 for 5 days	Amoxicillin: Diarrhea (n=4), Rash (n=2), Nausea (n=3) Comparative drug: Diarrhea (n=3), Rash (n=5), Nausea (n=3)
Gerber (2017)	Children With Acute Respiratory Tract Infections	30159	6 months to 12 years	A retrospective cohort study assessing clinical outcomes and a prospective cohort study assessing patient-centered outcomes		Amoxicillin: Adverse events (849) Comparative drug: Adverse events (189)
Eslami (2014)	Children with pharyngitis	99	6 to 15	Prospective randomized controlled clinical trial	Group 1: Amoxicillin 750 mg orally once daily Group 2: a single shot of BPG 600.000 IU and 1.200.000 IU for children weighed less than 27 kg	
Kuroki (2013)	Children with pharyngolaryngitis or tonsillitis	97	< 15	A drug-controlled, open-label, multicenter study	Group 1: Amoxicillin 30 mg/kg/day/3 for 10 days Group 2: Combination of CVA 6.4 mg/kg/day	Amoxicillin: Diarrhea (n=5), Upper airway inflammation (1), Comparative drug:

Leelarasa mee (2000)	Children and adults nonexudative pharyngotonsillitis.	1217	>5	Randomized, double-blinded, placebo controlled trial.	and AMPC 90 mg/kg/day in two divided doses for 3 days Group 1: Amoxicillin: 1 capsule (250 or 500 mg] 3 or 4 times daily) or syrup was given for 7 days at a dose of 50 mg/kg per day in three or four divided doses. Group 2: placebo	Diarrhea (n=22), Urticaria (n=1), Eruption (n=1) Amoxicillin: Nausea (n=4) Vomiting (n=4) Epigastric distress (n=4) Diarrhea (n=1) Rash (n=5) Placebo: Nausea (n=3) Vomiting (n=3) Epigastric distress (n=3) Diarrhea (n=1) Rash (n=3)
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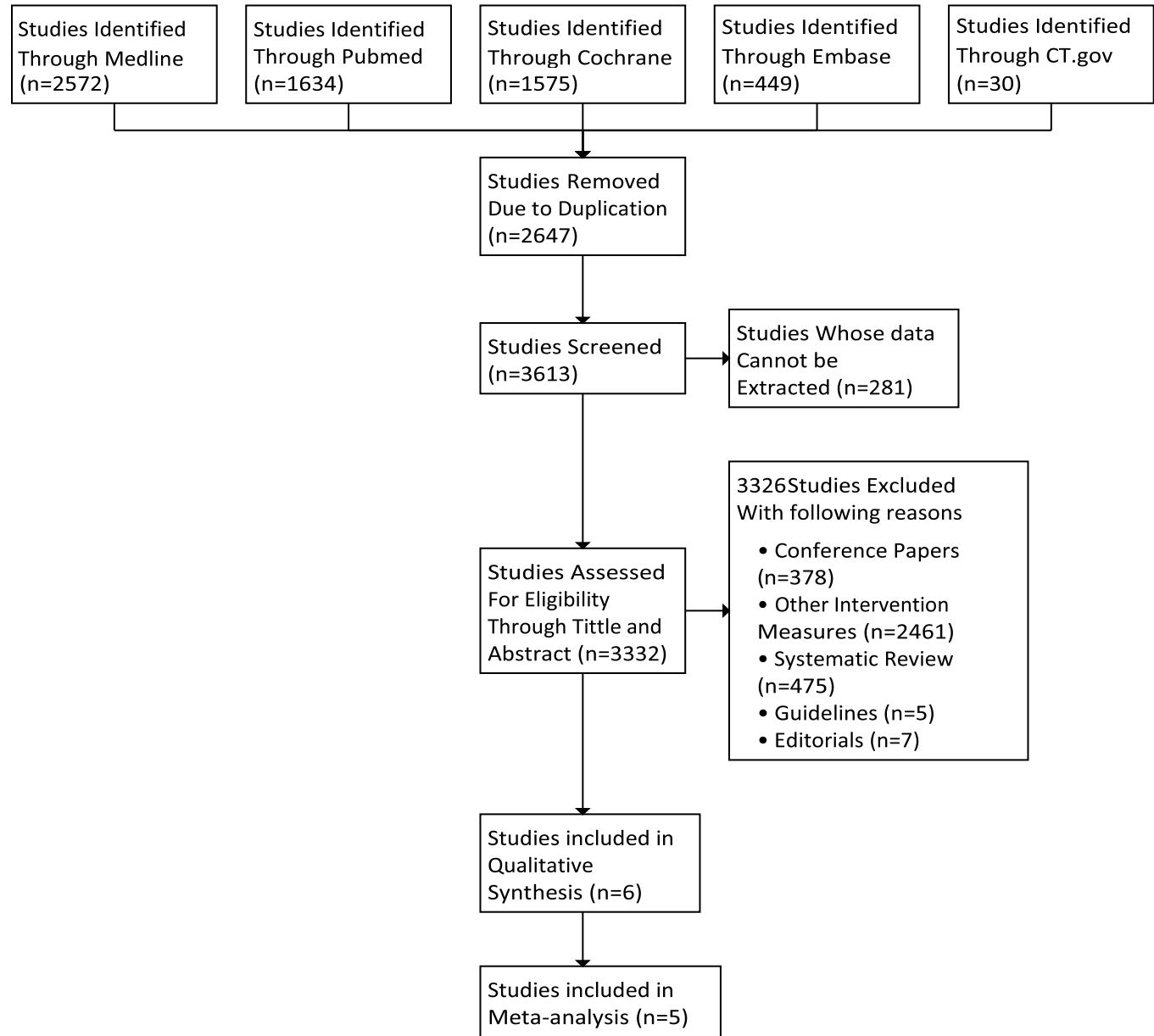


Figure-I: Flow chart illustrating the selection process of studies.

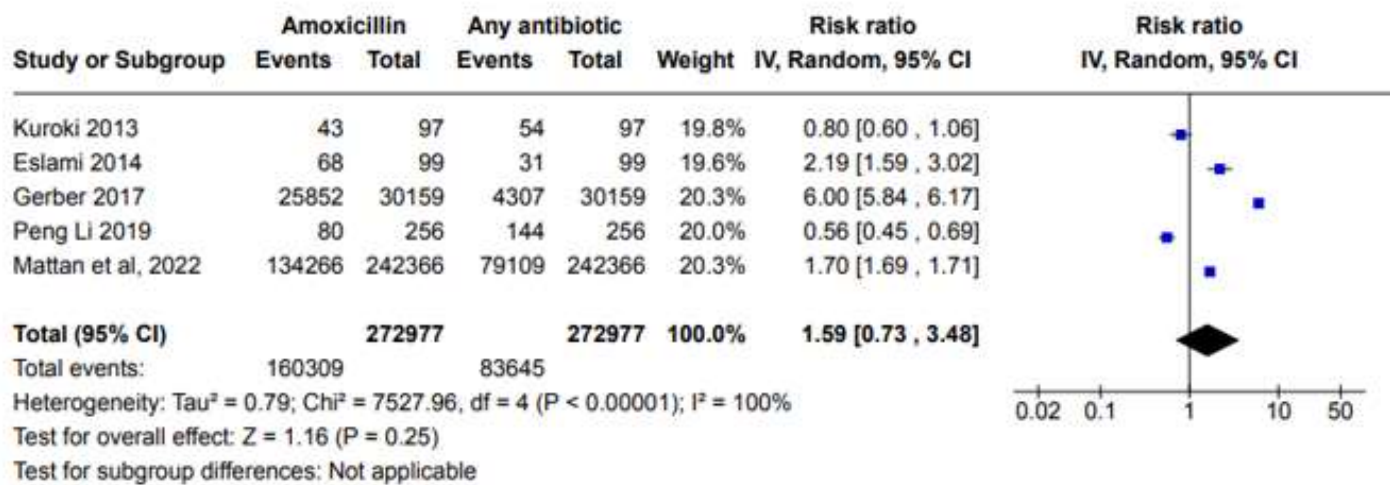


Figure-II: Forest plot of the risk ratio of Amoxicillin vs. another antibiotic regimen

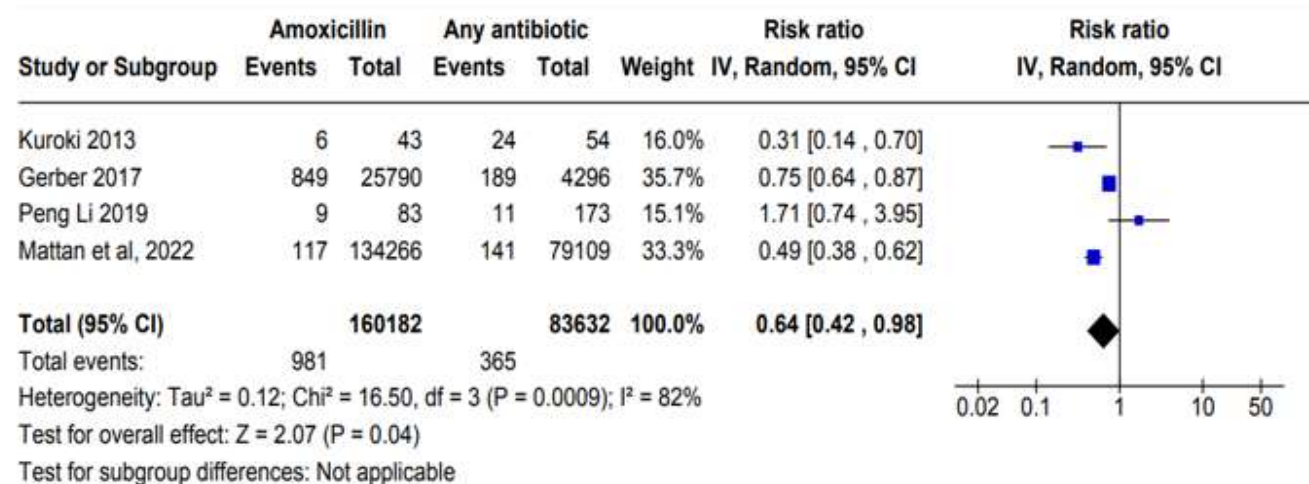


Figure-III: Forest plot of the risk ratio for adverse events due to treatment of URTIs with Amoxicillin vs. another antibiotic regimen

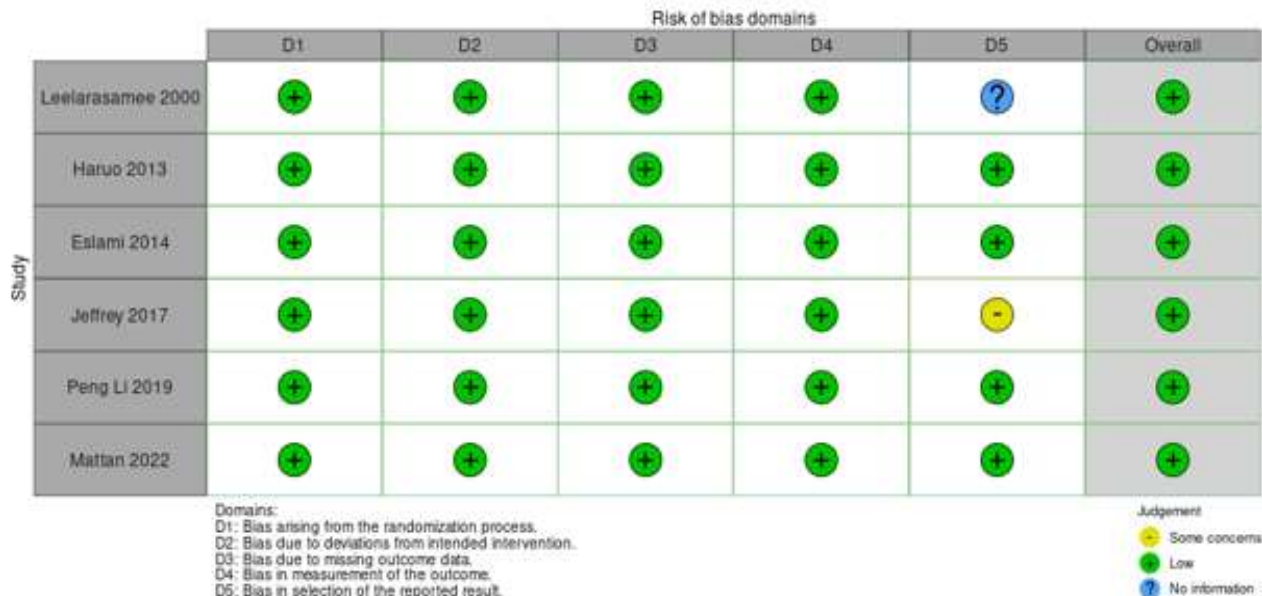


Figure-IV: Critical appraisal according to the RoB-2 tool for assessing Risk of bias in randomized trials and observational studies.

DISCUSSION

In this study, we conducted a systematic review and meta-analysis to analyze if broad-spectrum antibiotics offer any added advantage over narrow spectrum antibiotics like penicillin or amoxicillin in the treatment of tonsillopharyngitis. Our findings suggest broad-spectrum antibiotics are not superior to narrow-spectrum antibiotics and show no significant difference in efficacy or treatment success rate. Amoxicillin was associated with a significantly lower risk of adverse events compared to broad-spectrum antibiotics.

Despite covering an 11-year timeframe in our literature review, we encountered a scarcity of comparative effectiveness studies assessing narrow- and broad-spectrum antibiotic therapy for the prevalent bacterial URTIs, especially tonsillopharyngitis.

We identified three recent Cochrane reviews that aligned with our study objectives.¹⁵⁻¹⁷ Spinks *et al.* assessed the effects of antibiotics for reducing symptoms of sore throat for child and adult patients. They reported, though antibiotics may decrease the incidence of sore throat and lower the chances of certain complications associated with sore throat. However, since the impact on symptoms might be marginal, clinicians need to individually assess whether prescribing antibiotics is clinically justified, taking into account the likely bacterial origin of the sore throat. They stated that it was crucial to recognize the delicate balance between modest symptom relief and the potential risks of antimicrobial resistance.¹⁵

Another review reported by van Driel ML *et al.* assessed the comparative efficacy of different antibiotics along with the incidence of adverse effects and the risk-benefit of antibiotic treatment for streptococcal pharyngitis. They stated that though antibiotic affects were similar, and all antibiotics caused side effects, but there was no strong evidence to show meaningful differences between antibiotics. Studies did not report on long-term complications; therefore, it was unclear if any class of antibiotics was better in preventing serious but rare complications.¹⁶

The third review reported by Altamimi *et al.* investigated the evidence regarding the efficacy of two to six days of newer oral antibiotics (short duration) compared to 10 days of oral penicillin (standard duration) in treating children with acute GABHS pharyngitis. They stated that short duration of newer

oral antibiotics had comparable efficacy compared to the standard duration 10-day course of oral penicillin.¹⁷ We did not identify any systematic reviews pertinent to our research objectives. The only other systematic review uncovered in our search focused on antibiotics for recurrent acute pharyngo-tonsillitis and was therefore excluded from our assessment.¹⁸

We acknowledge that GABHS pharyngitis necessitates the administration of an effective antibiotic, at an appropriate dosage, for an adequate duration to eradicate the pathogen from the pharynx, typically recommended for a 10-day period.² Due to their limited spectrum of activity, minimal occurrence of adverse effects, and cost-effectiveness, penicillin or amoxicillin is considered the preferred option for patients, hence, aligning with the outcomes observed in our study.

While numerous treatment guidelines advocate penicillin or amoxicillin as the primary choices for pharyngitis, physicians continue to dispense alternative agents, especially macrolides. This review was conducted to reinforce the existing literature's evidence in favor of narrow-spectrum agents and discourage physicians from prescribing azithromycin, which should be reserved for treating extensively-drug-resistant *Salmonella typhi*. Azithromycin remains the last remaining oral option for this difficult-to-treat infection. The lack of a significant difference in treatment success rates between amoxicillin and other antibiotics raises intriguing questions about the management of URTIs. When choosing an antibiotic, it is crucial to assess factors such as the spectrum of activity, possible side effects, and trends in antibiotic resistance. Our review's results align with previous researches, indicating no statistically significant difference in efficacy between amoxicillin and other antibiotics. Our findings report that broad-spectrum antibiotic treatment provided minimal additional benefit compared to amoxicillin and was more likely to be associated with antibiotic resistance.¹⁹

Our meta-analysis found a notable and clinically meaningful link between amoxicillin treatment and a lower incidence of side events when compared to other antibiotics. When compared to other antibiotics, amoxicillin had a 36% lower probability of being associated with side effects. When compared with other antibiotics, Peng Li 2019 found that amoxicillin had relatively low incidences of diarrhea (n=4), rash (n=2),

and nausea (n=3), whereas other antibiotics had slightly higher incidences of diarrhea (n=3), rash (n=5), and nausea (n=3). These data imply that amoxicillin may have a comparable safety profile regarding these adverse effects, making it a feasible option for patients needing antibiotic therapy. Finally, the findings of this study state that the most reported side effects of amoxicillin in comparison to other antibiotics, were diarrhea, fever, rash, and nausea. A study conducted by Koga *et al.* indicated a higher frequency of minor side effects in the azithromycin therapy group compared to the amoxicillin treatment group, correlating with our findings.²⁰

The safety profile of narrow-spectrum antibiotics versus broad-spectrum antibiotics is already well-known and adequately characterized. The decreased risk of adverse events reported with amoxicillin is significant clinically and has crucial implications for patient safety and treatment outcomes. Healthcare practitioners can potentially reduce the occurrence of adverse events by using amoxicillin, contributing to enhanced patient tolerability and adherence to treatment.

Variations in study designs, patient groups, dosage regimens, and adverse event reporting may have influenced the found heterogeneity among the included studies. Furthermore, the possibility of publication bias should be considered, as research with positive outcomes is more likely to be published, thus impacting the total findings. Considering the limited sample size in our review, attributed to the scarcity of applicable studies, it is recommended that future research endeavors focus on larger, high-quality study samples to improve the reliability and validity of systematic review findings.

Despite these limitations, our meta-analysis provides strong evidence supporting amoxicillin's improved safety profile in treating URTIs. These findings highlight the need for evidence-based prescribing strategies, in which healthcare practitioners should examine the advantages of amoxicillin over other antibiotics to reduce the risk of adverse events while effectively managing tonsillopharyngitis.

CONCLUSION

In conclusion, given its comparable efficacy to other antibiotics and reduced incidence of adverse effects, this research supports the use of amoxicillin as a preferred

antibiotic choice for the treatment of tonsillopharyngitis. The findings highlight the significance of evidence-based decision-making in antibiotic selection to enhance patient outcomes and battle the evolution of antibiotic resistance. Future research should focus on filling knowledge gaps, developing personalized treatment regimens, and analyzing the impact of antibiotic resistance on URTI therapy.

CONFLICT OF INTEREST

None

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AUTHOR CONTRIBUTION:

Summiya Nizamuddin: Study design and concept, literature review, manuscript review

Sana Anwar: Study design and concept, literature review, manuscript review

Usman Ashraf: Literature search, statistical analysis, data collection, data analysis, data interpretation questionnaire design, data collection

Kamran Khan: Manuscript writing

Abdul Aleem Siddiqui: Literature review, manuscript review

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