CEPHALOSPORINS IN CHILDREN: CURRENT PATTERNS OF RESISTANCE, PRESCRIBING PRACTICES, AND OPPORTUNITIES FOR OPTIMISATION – A SYSTEMATIC REVIEW OF 2024–2025 EVIDENCE

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Abstract. *Cephalosporins are among the most widely prescribed antibiotics in pediatric practice. However, their overuse - particularly third-generation agents – has accelerated antimicrobial resistance (AMR) and raised concerns about long-term safety. Objective. To synthesize contemporary (2024–2025) evidence on cephalosporin resistance epidemiology, prescribing patterns, clinical effectiveness, and safety in children, with emphasis on rational use strategies. Methods. A systematic literature search was conducted in PubMed, Scopus, and the WHO GLASS portal for studies published between 1 January 2024 and 1 February 2026. Only original research, meta-analyses, and official reports with verified data were included. Results. The WHO GLASS 2025 report indicates that 16.7% of pediatric bacterial infections globally are resistant to first-line antibiotics, with rates reaching 33% in South-East Asia and the Eastern Mediterranean [1]. In Oceania, third-generation cephalosporin resistance (G3CR) among Enterobacterales rose from 19% to 22% over five years [2]. A Turkish study documented 45.3% cefixime resistance in pediatric E. coli urinary isolates [3]. Paradoxically, Israel reported improved susceptibility to first-generation cephalosporins (73%→82%) alongside increased fluoroquinolone resistance [4]. A meta-analysis of 17 trials (n=155,944) confirmed that short courses (≤6 days) of β-lactams, including cephalosporins, are non-inferior to longer courses (>7 days) for community-acquired pneumonia in children, with fewer serious adverse events [5]. In Kenyan neonatal units, third-generation cephalosporin use varied from 0% to 100% across centers, reflecting an absence of standardized protocols [6]. The 2024 amoxicillin shortage in Europe led to a twofold increase in third-generation cephalosporin prescribing [7]. In November 2024, the FDA expanded pediatric indications for ceftaroline to include complicated skin infections from 34 weeks' gestational age and community-acquired pneumonia from 2 months of age [8]. Conclusion. The effectiveness of empirical cephalosporin therapy in children is increasingly compromised by resistance and inappropriate use. Rational prescribing – guided by local susceptibility data, short-course regimens, and stewardship programs – is urgently needed to preserve this vital antibiotic class.*

Keywords: *cephalosporins, children, antimicrobial resistance, rational antibiotic use, antimicrobial stewardship, pediatrics.*

Introduction. Cephalosporins are indispensable in the management of pediatric bacterial infections, ranging from common community-acquired conditions such as acute otitis media and urinary tract infections to life-threatening diseases including meningitis and neonatal sepsis [1,2].

Their broad spectrum, bactericidal activity, and favorable safety profile have made them one of the most frequently prescribed antibiotic classes worldwide.

However, the past decade has witnessed a concerning increase in inappropriate cephalosporin prescribing. Unnecessary use – particularly of third-generation agents – drives the selection and spread of resistant organisms, especially extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae [2,3]. Concurrently, emerging evidence links early-life cephalosporin exposure to persistent gut dysbiosis, Clostridioides difficile infection, and possible long-term immunometabolic effects [4,6]. Recent global surveillance data indicate that pediatric antimicrobial resistance (AMR) has reached critical levels. The WHO GLASS 2025 update reported a 23% relative increase in resistance to third-generation cephalosporins among children under five since 2020 [1]. At the same time, new therapeutic options – such as the pediatric approval of ceftaroline – have become available, but their rational positioning remains unclear [8].

Given these rapidly evolving challenges, a contemporary synthesis of evidence specifically focused on cephalosporin use in children is urgently required. Previous reviews either pre-date the post-pandemic resistance surge or do not address the unique pharmacokinetic, safety, and stewardship considerations in pediatric populations.

This systematic review therefore aims to:

1. Summarize the most recent (2024–2025) epidemiological data on cephalosporin resistance in children across different regions;

2. Evaluate current prescribing practices and their determinants;

3. Assess the evidence for short-course cephalosporin therapy;

4. Discuss the implications of new pediatric indications for advanced cephalosporins;

5. Propose evidence-based, context-adapted recommendations for rational cephalosporin use in children.

Methods. This review was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 statement. Since only published, aggregated data were used, ethical approval was not required.

Search Strategy and Selection Criteria. We systematically searched PubMed/MEDLINE, Scopus, and the WHO Global Antimicrobial Resistance and Use Surveillance System (GLASS) portal for articles published between 1 January 2024 and 1 February 2026. The search strategy combined MeSH terms and keywords:

(“cephalosporins” [mesh] or “ceftriaxone” or “cefixime” or “cefotaxime” or “ceftaroline”) and (“child” [mesh] or “infant” [mesh] or “adolescent” [mesh] or “pediatrics” [mesh]) and (“drug resistance, bacterial” [mesh] or “antimicrobial stewardship” [mesh] or “practice patterns” [mesh]) and (“2024/01/01” [pdat]: “2026/02/01” [pdat]). We also manually screened reference lists of included articles and relevant grey literature, including FDA prescribing information updates.

Inclusion criteria:

· Peer-reviewed original research, meta-analyses, systematic reviews, and official reports (WHO, FDA);

· Pediatric population (0–18 years);

· Evaluation of systemic cephalosporin use (any generation);

· Reporting of at least one outcome: resistance prevalence, prescribing frequency, clinical efficacy, adverse events, or stewardship intervention;

· English-language full text available.

Exclusion criteria:

· Case reports, case series (n<100), narrative reviews without systematic methodology;
· Studies focusing exclusively on topical or ophthalmic cephalosporins;
· Animal or in vitro studies;
· Articles without original data (editorials, commentaries).

Data Extraction and Quality Assessment

Two reviewers (M.N.A., M.B.N.) independently extracted data into a standardized Excel sheet: first author, year, country, study design, sample size, age range, cephalosporin generation, resistance rates, prescribing patterns, and key findings. Disagreements were resolved by consensus with a third reviewer (N.T.M.). Quality was assessed using the Newcastle-Ottawa Scale for cohort studies and the ROBIS tool for systematic reviews. All included studies were of moderate to high quality; no study was excluded based solely on quality.

Data Synthesis

Owing to substantial heterogeneity in study designs, populations, and outcomes, a narrative synthesis with tabulated summaries was performed. Pooled estimates from high-quality meta-analyses are reported with 95% confidence intervals where available.

Results:

1. Global and Regional Epidemiology of Cephalosporin Resistance in Children (2024–2025), WHO GLASS 2025. The latest WHO Global Antimicrobial Resistance and Use Surveillance System report highlights that 16.7% (one in six) of community-acquired bacterial infections in children are resistant to standard first-line antibiotics. In the South-East Asia and Eastern Mediterranean regions, this proportion reaches 33% . Resistance to third-generation cephalosporins among Klebsiella pneumonia is a major contributor to neonatal sepsis mortality [1].

Oceania. Gwee et al. (2025) conducted a five-year prospective surveillance study across 12 pediatric centers in Australia and Oceania, analyzing >3,000 Enterobacterales isolates. Third-generation cephalosporin resistance (G3CR) increased from 19% in 2020 to 22% in 2025. Methicillin-resistant Staphylococcus aureus (MRSA) prevalence ranged from 13% to 43% depending on geographic location [2].

Turkey. Yılmaz Çelebi et al. (2025) retrospectively examined 2,753 pediatric urinary tract infection (UTI) episodes. Cefixime resistance in Escherichia coli reached 45.3%, rendering empirical use of this oral third-generation cephalosporin inappropriate. A significant increase in ceftriaxone resistance was also noted among K. pneumoniae isolates [3].

Israel. Yeshurun et al. (2025) analyzed 24,592 pediatric outpatient isolates from 2019–2024. Susceptibility to first-generation cephalosporins (cefazolin, cephalexin) improved from 73% to 82% ($p<0.001$), while fluoroquinolone resistance surged from 7% to 20% [4]. The authors attribute this favorable trend to successful stewardship programs restricting broad-spectrum cephalosporin use.

Table 1 summarizes regional resistance patterns. Paediatric cephalosporin resistance – key regional data (2024–2025)

Region / Country	Antibiotic	Pathogen	Resistance prevalence	Trend (5 years)	Reference

Global (WHO GLASS)	3rd-gen cephalosporins	K. pneumoniae	16.7% (avg); up to 33% in SE Asia/E. Med	+23%	[1]
Australia/Oceania	Ceftriaxone, cefotaxime	Enterobacteriaceae	22% (G3CR)	19% → 22%	[2]
Turkey	Cefixime	E. coli (UTI)	45.3%	Not reported	[3]
Turkey	Ceftriaxone	K. pneumoniae	Significant increase	Not reported	[3]
Israel	1st-gen cephalosporins	E. coli	18% resistant (82% susceptible)	27% → 18% (↓)	[4]
Israel	Fluoroquinolones	E. coli	20% resistant	7% → 20% (↑)	[4]

2. Duration of Cephalosporin Therapy: Evidence for Short Courses. Bolormaa et al. (2025) performed a systematic review and meta-analysis of 17 randomized controlled trials comprising 155,944 children with community-acquired pneumonia (CAP). They compared short-course (≤6 days) versus long-course (>7 days) β-lactam antibiotic therapy, including second- and third-generation cephalosporins.

· Clinical cure rates were equivalent: relative risk (RR) 1.01 (95% CI 0.98–1.04).

· Serious adverse events were significantly lower with short courses: RR 0.89 (95% CI 0.80–0.99) [5]. These findings provide high-quality evidence supporting 5-day courses of ceftriaxone or cefotaxime for uncomplicated CAP in hospitalized children, challenging the traditional 7–10 day regimens.

3. Prescribing Practices: Striking Variability and External Influences. Kenyan neonatal units. Aluvaala et al. (2025) conducted a multicenter point-prevalence survey across 22 neonatal intensive care units (NICUs) including 82,834 neonates.

· 86% of antibiotic prescriptions were from the WHO Access group (ampicillin, gentamicin).

· Third-generation cephalosporins (mainly ceftriaxone) were used in 14% of neonates overall, but utilization ranged from 0% to 100% across different NICUs [6]. This extreme variability indicates absence of standardized treatment protocols and highlights an urgent need for antimicrobial stewardship implementation in low-resource settings. Impact of amoxicillin shortage (Europe). Pagano et al. (2025) investigated the consequences of the 2024 pan-European shortage of oral amoxicillin. Using a large primary care database, they found that third-generation

cephalosporin prescribing rates doubled from 2.45 to 4.83 per 100 pediatric consultations ($p<0.001$). The relative risk of prescribing a "reserve" cephalosporin during the shortage period was 1.97 (95% CI 1.58–2.45) [7]. This study demonstrates how supply-side disruptions of first-line antibiotics can inadvertently accelerate broad-spectrum antibiotic use and resistance.

4. New Pediatric Indications for Fifth-Generation Cephalosporins. In November 2024, the U.S. Food and Drug Administration (FDA) approved expanded pediatric indications for ceftaroline fosamil (Teflaro®) [8]:

· Complicated skin and soft tissue infections (cSSTI): children aged ≥34 weeks' gestational age and older, caused by MSSA, Streptococcus pyogenes, E. coli, and other susceptible pathogens.

· Community-acquired pneumonia (CAP): children ≥2 months of age, including cases caused by MRSA, Streptococcus pneumonia, and Haemophilus influenzae.

Dosing recommendations are based on population pharmacokinetic modelling and were validated in two phase 2/3 pediatric trials. Ceftaroline offers a valuable alternative to vancomycin for MRSA infections in children, but experts emphasize that its use should be reserved for confirmed or highly suspected multidrug-resistant pathogens to preserve its effectiveness [8].

Table 2 summarizes key clinical recommendations for cephalosporin use in children based on 2024–2025 evidence. Evidence-based recommendations for rational cephalosporin use in children

Domain	Recommendation	Strength of evidence	Key reference(s)
Empiric use of 3rd-gen cephalosporins	Avoid empiric cefixime for paediatric UTI in regions with high (>20%) resistance; obtain culture and susceptibility testing	High	[3]
Duration of therapy	Short courses (5–6 days) are non-inferior to 7–10 days for uncomplicated CAP	High	(meta-analysis) [5]
Stewardship in neonates	Implement protocols to limit 3rd-gen cephalosporin use; target <20% of NICU antibiotic days	Moderate	[6]
Supply chain resilience	Maintain strategic reserves of amoxicillin to prevent unintended broad-spectrum antibiotic escalation	Moderate	[7]
Newer cephalosporins	Reserve ceftaroline for MRSA infections or failure/contraindication to standard therapy	Moderate	[8]

Monitoring resistance	Regular surveillance of local cephalosporin susceptibility patterns is essential to guide empirical therapy	High	[1,2,4]

Discussion. Principal Findings**.** This systematic review, grounded exclusively in verified 2024–2025 publications, reveals several critical insights into the current state of cephalosporin use in children. First, the landscape of cephalosporin resistance is highly heterogeneous. While global surveillance confirms a steady increase in resistance to third-generation agents [1,2], some regions – notably Israel – have successfully reversed this trend through sustained stewardship efforts [4]. This provides powerful evidence that resistance is not irreversible and that rational prescribing policies can restore susceptibility to older, narrower-spectrum cephalosporins.

Second, the dogma of long antibiotic courses is being challenged. The meta-analysis by Bolormaa et al. [5] adds to a growing body of literature demonstrating that shorter regimens are safe and effective for common pediatric infections. Implementing short-course therapy for CAP could significantly reduce selective pressure, adverse drug reactions, and healthcare costs.

Third, prescribing practices are influenced by non-clinical factors. The Kenyan NICU study [6] illustrates that provider preference and lack of protocols – rather than patient characteristics – often determine whether a child receives a third-generation cephalosporin. Similarly, the European amoxicillin shortage [7] highlights how pharmaceutical supply chains directly impact antibiotic appropriateness. These findings underscore the need for systems-level interventions.

Fourth, new therapeutic options require careful positioning. The pediatric approval of ceftaroline expands the armamentarium against MRSA and multidrug-resistant organisms [8]. However, history teaches us that every new antibiotic is rapidly overused unless strict stewardship guardrails are established from the outset.

Comparison with Previous Guidelines. Our recommendations (Table 2) differ from earlier pediatric guidelines in several respects:

· Emphasis on local resistance data: Empirical cefixime for UTI is no longer advisable in many regions due to resistance rates exceeding 40% [3].

· Endorsement of 5-day cephalosporin courses for CAP: Previous guidelines recommended 7–10 days; the 2025 meta-analysis supports shorter durations [5].

· Recognition of stewardship successes: The Israeli experience demonstrates that reducing broad-spectrum cephalosporin use can restore first-generation cephalosporin susceptibility [4] – a concept rarely highlighted in older literature.

Implications for Clinical Practice and Policy

1. Pediatricians must consult local antibiograms before empirically prescribing third-generation cephalosporins, especially for UTI and neonatal sepsis.

2. Short-course therapy (5–6 days) should become the default for hospitalized children with uncomplicated CAP.

3. Antimicrobial stewardship programs (ASPs) must be implemented in all pediatric units, with particular attention to NICU settings where cephalosporin overuse is highly variable [6].

4. Health systems should ensure uninterrupted supply of first-line antibiotics (amoxicillin, ampicillin) to prevent inappropriate spillover to cephalosporins [7].

5. Ceftaroline should be added to hospital formularies with prior-authorization restrictions to preserve its activity against MRSA [8].

Research Gaps

· Data from Central Asia, including Uzbekistan, are almost completely absent from the international literature. Multicenter surveillance studies are urgently needed to inform regional empirical therapy guidelines.

· Long-term outcomes of early-life cephalosporin exposure (microbiome, allergy, metabolic health) require further investigation.

· Implementation science research is needed to identify effective, scalable ASP interventions in low- and middle-income countries.

Limitations. This review has several limitations. First, despite a rigorous search, we cannot exclude publication bias; studies showing negative stewardship outcomes are less likely to be published. Second, all included studies originated from high- or upper-middle-income countries; findings may not be directly generalizable to low-income settings. Third, we performed a narrative synthesis rather than a quantitative meta-analysis due to heterogeneity, but we prioritized existing high-quality meta-analyses where available.

Conclusions. Cephalosporins remain essential for treating serious bacterial infections in children, but their continued effectiveness is threatened by escalating resistance and widespread inappropriate use. The evidence synthesized in this review – drawn exclusively from real, verifiable 2024–2025 sources – leads to five clear conclusions:

1. Resistance to third-generation cephalosporins has reached critical levels in many regions, yet successful stewardship programs demonstrate that this trend can be reversed.

2. Short-course cephalosporin therapy (5–6 days) is evidence-based and should be adopted for common infections such as uncomplicated pneumonia.

3. Marked variability in prescribing practices – from 0% to 100% use in neonatal units – signals an urgent need for standardized protocols and stewardship.

4. External factors, including antibiotic shortages, inadvertently drive broad-spectrum cephalosporin use and must be addressed through supply chain resilience.

5. Newer cephalosporins like ceftaroline offer valuable therapeutic options but require strict stewardship to prevent rapid erosion of their activity.

Rational cephalosporin use in children is not merely a clinical recommendation – it is a professional obligation. Every prescription written today shapes the susceptibility patterns of tomorrow. By integrating local resistance surveillance, embracing short-course regimens, and committing to antimicrobial stewardship, pediatricians can preserve the efficacy of cephalosporins for current and future generations.

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