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Systematic Review

Prevalence and Antimicrobial Resistance of Gram-Negative Bacteria in Pediatric Sepsis and Bloodstream Infection of Emergency-Care Origin: A Systematic Review and Meta-analysis Protocol

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Received: August 11,2026; **Published:** August 18, 2026

Abstract

Background: Pediatric sepsis and bloodstream infection require rapid empirical antimicrobial treatment, although the causative pathogen and antimicrobial susceptibility profile are usually unknown at emergency presentation. Gram-negative bacteria, including Enterobacterales, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*, are important causes of pediatric bloodstream infection, while extended-spectrum beta-lactamase production, carbapenem resistance, and multidrug resistance increasingly threaten first-line therapy. Evidence derived mainly from intensive care, oncology, neonatal, or mixed inpatient populations may not accurately represent children at the point of emergency care.

Objective: To estimate the prevalence and species distribution of Gram-negative bacteria and their antimicrobial resistance patterns among children with sepsis or bloodstream infection of emergency-care origin, and to identify factors associated with resistance and clinically important outcomes.

Methods: MEDLINE via PubMed, Embase, Scopus, Web of Science Core Collection, CINAHL, Global Index Medicus, and relevant gray-literature sources will be searched from 1 January 2010 to the final search date. No language or full-text-availability restriction will be applied. Eligible studies will include patients aged 0-18 years evaluated in an emergency department or meeting a prespecified emergency-origin classification based on blood-culture timing at or near hospital arrival. Two reviewers will independently screen records and assess risk of bias; extraction will use a standardized form with independent verification. Design-appropriate Joanna Briggs Institute tools will be used, with the Hoy tool restricted to a supplementary external-validity assessment for prevalence estimates. When at least three clinically and methodologically compatible studies are available, random-effects generalized linear mixed models with a logit link will be used to pool prevalence and pathogen-antibiotic resistance proportions. Denominator definitions, isolate-level and episode-level estimates, and explicit emergency-department recruitment versus inferred emergency origin will be analyzed separately. Heterogeneity will be explored by geography, age, infection acquisition, sepsis definition, host factors, laboratory standards, and study period.

Discussion: The review is designed to distinguish emergency-origin from hospital-acquired infection and to produce setting-specific evidence for empirical antibiotic selection, antimicrobial stewardship, surveillance, and future pediatric emergency medicine research.

Keywords: *Pediatric Sepsis; Pediatric Emergency Department; Bloodstream Infection; Gram-Negative Bacteria; Antimicrobial Resistance; Multidrug Resistance; Prevalence; Systematic Review*

Abbreviations

AMR: Antimicrobial Resistance; AST: Antimicrobial Susceptibility Testing; BSI: Bloodstream Infection; CLSI: Clinical and Laboratory Standards Institute; CRAB: Carbapenem-Resistant *Acinetobacter baumannii*; CRE: Carbapenem-Resistant Enterobacterales; CRPA: Carbapenem-Resistant *Pseudomonas aeruginosa*; DTR: Difficult-to-Treat Resistance; ESBL: Extended-Spectrum Beta-Lactamase; EUCAST: European Committee on Antimicrobial Susceptibility Testing; GLMM: Generalized Linear Mixed Model; GRADE: Grading of Recommendations Assessment, Development and Evaluation; MDR: Multidrug Resistant; PDR: Pandrug Resistant; PRESS: Peer Review of Electronic Search Strategies; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PROSPERO: International Prospective Register of Systematic Reviews; XDR: Extensively Drug Resistant

Introduction and Background

Sepsis remains a major cause of preventable morbidity and mortality in children. Global analyses demonstrate that a substantial proportion of the burden occurs in neonates, infants, and children living in resource-constrained settings, although variation in case definitions and surveillance systems complicates precise estimates [1,2]. The 2024 international pediatric consensus criteria reframed pediatric sepsis as infection associated with life-threatening organ dysfunction and introduced the Phoenix Sepsis Score [3]. The 2026 Surviving Sepsis Campaign guidelines further emphasize rapid recognition, microbiological sampling when this does not delay treatment, timely antimicrobial administration, and repeated reassessment of treatment adequacy [4].

The pediatric emergency department is an important entry point for children with community-onset sepsis and acute bloodstream infection and is frequently the setting in which empirical antimicrobial therapy is first selected. At initial presentation, the infectious source may remain unclear and organism identification or susceptibility results are generally unavailable. The probability of resistant infection can depend on age, underlying disease, previous healthcare exposure, recent antimicrobial therapy, local epidemiology, and infection acquisition setting.

Delayed effective antimicrobial therapy may adversely affect outcomes, whereas indiscriminate broad-spectrum use can increase toxicity, antimicrobial selection pressure, and ecological disruption. Pediatric emergency studies have also demonstrated variability in antimicrobial timing and sepsis-care processes [19-23].

Gram-negative antimicrobial resistance

Antimicrobial resistance is a major global health problem. *Escherichia coli*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa* are among the pathogens associated with substantial antimicrobial resistance-related mortality worldwide [5].

Pediatric bloodstream infection studies from multiple geographical settings demonstrate substantial variation in Gram-negative prevalence, ESBL production, carbapenem resistance, and multidrug resistance [6-18]. Resistant Gram-negative infections have also been associated with inappropriate initial antimicrobial treatment, prolonged hospitalization, intensive care admission, and mortality [7-11,17].

However, much of the available evidence arises from neonatal units, pediatric intensive care units, oncology populations, inpatient services, or hospital-wide bloodstream infection databases. These populations may overrepresent healthcare-associated infection, invasive devices, prolonged hospitalization, and repeated antimicrobial exposure. Their resistance estimates therefore cannot automatically be extrapolated to children undergoing an initial emergency-care evaluation.

Rationale

Many pediatric emergency sepsis studies emphasize recognition, resuscitation, and antimicrobial timing but provide limited organism-level antimicrobial susceptibility information. Conversely, many microbiological studies do not clearly identify whether the index culture

was obtained during the initial emergency-care episode. This creates an evidence gap precisely at the stage when empirical antimicrobial decisions must be made.

The review will address this gap by prioritizing studies with explicit emergency-department recruitment and by permitting a prespecified emergency-origin classification when the timing of blood-culture collection demonstrates that the infection was identified at or near hospital arrival. Because sepsis and bloodstream infection are not interchangeable constructs, their definitions and denominators will be extracted and analyzed separately rather than pooled indiscriminately.

Objectives of the Study

The objectives are to:

1. Estimate the proportion of culture-confirmed bacterial sepsis or bloodstream infection episodes attributable to Gram-negative bacteria among pediatric emergency-origin cases.
2. Describe the distribution of Gram-negative species, including Enterobacterales, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and other clinically important organisms.
3. Estimate resistance proportions for prespecified pathogen-antibiotic pairs and describe ESBL, carbapenem-resistant, MDR, XDR, PDR, and DTR phenotypes when reported.
4. Identify clinical, microbiological, temporal, geographical, and health-system factors associated with resistant Gram-negative infection.
5. Evaluate associations between antimicrobial resistance or inappropriate empirical treatment and mortality, organ dysfunction, intensive care admission, length of stay, and microbiological clearance.
6. Assess the applicability of available evidence to empirical antimicrobial selection and antimicrobial stewardship in pediatric emergency departments.

Review Questions

- **Primary question:** Among children evaluated for sepsis or bloodstream infection of emergency-care origin, what proportion of culture-confirmed bacterial episodes are attributable to Gram-negative bacteria, and what are the antimicrobial resistance profiles of these organisms?
- **Secondary question:** Which patient, pathogen, healthcare-exposure, geographic, temporal, laboratory, and methodological factors explain variation in Gram-negative prevalence, antimicrobial resistance, and clinical outcomes?

Materials and Methods

Study design and reporting framework

This is a protocol for a systematic review and, where appropriate, meta-analysis of observational epidemiological studies. The protocol follows the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) statement [24]. The completed review will be reported according to PRISMA 2020 [25], and literature-search methods will follow PRISMA-S recommendations [26]. Methodological decisions concerning prevalence synthesis will be informed by Joanna Briggs Institute guidance [27].

Protocol registration

The protocol will be registered prospectively in PROSPERO before formal title and abstract screening. The registration number will be added to the manuscript once available. Any subsequent amendment will be dated, justified, recorded in PROSPERO, and reported in the completed review with a clear distinction between prespecified and post hoc decisions.

Eligibility criteria

Population

Eligible studies will include children and adolescents aged 0 - 18 years, including neonates, evaluated for suspected or confirmed sepsis, septic shock, severe febrile illness associated with blood-culture evaluation, bacteremia, or bloodstream infection. Mixed-age populations will be eligible when pediatric data are separately extractable or when at least 80% of participants are younger than 18 years.

Clinical context and emergency-origin classification

Eligible settings will include pediatric or general emergency departments, prehospital-to-emergency-department pathways, and acute assessment units functioning as emergency departments. Studies without an explicitly stated emergency setting may be included only when the timing of the index blood culture permits a prespecified emergency-origin classification.

Emergency origin will be classified hierarchically as: (1) culture obtained in the emergency department; (2) culture obtained before inpatient admission; or (3) culture obtained within 24 hours of hospital arrival when the exact collection location is not reported. Category 3 will be considered an inferred emergency-origin definition and will be analyzed separately in subgroup and sensitivity analyses. PICU-only, NICU-only, ward-only, and oncology-only cohorts without separately extractable emergency-origin data will be excluded.

Condition

Eligible conditions will include study-defined clinical sepsis or septic shock, suspected bloodstream infection, or culture-confirmed bacteremia linked to an acute sepsis or febrile presentation. Reported case definitions will be extracted verbatim and, when feasible, mapped to Phoenix, IPSCC/SIRS-based, or other recognized criteria. Sepsis-defined cohorts and bloodstream-infection-defined cohorts will not be treated as methodologically equivalent.

Pathogens and exposures

Studies reporting Gram-negative bacterial infection will be eligible, including Enterobacterales, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and other clinically relevant Gram-negative organisms when prevalence or susceptibility data are available. Studies limited to colonization, non-blood surveillance cultures, or infections without extractable bloodstream data will be excluded from primary bloodstream analyses.

Outcomes

Primary outcomes will be:

- The proportion of culture-confirmed bacterial sepsis or bloodstream infection episodes attributable to Gram-negative bacteria.
- The species distribution of Gram-negative organisms among Gram-negative episodes or isolates.
- Pathogen-antibiotic resistance or non-susceptibility proportions using the number of tested isolates as the denominator.

Secondary outcomes will include ESBL production, carbapenemase production, CRE, CRPA, CRAB, MDR, XDR, PDR, DTR, appropriateness of empirical antimicrobial therapy, mortality, intensive care admission, organ dysfunction, mechanical ventilation, vasoactive support, hospital length of stay, microbiological clearance, and readmission. Studies must report at least one primary or secondary outcome to be eligible.

Study designs

Eligible designs include prospective and retrospective cohort studies, cross-sectional studies, surveillance studies with clinical linkage, case-control studies, and interventional or quality-improvement studies that provide separately extractable baseline or post-intervention microbiological data. Single case reports and case series containing fewer than 10 relevant episodes will be excluded.

Publication period and language

Studies published from 1 January 2010 to the final search date will be eligible. No language restriction will be imposed. Conference abstracts and dissertations will be considered when sufficient methodological and numerical information is available for eligibility assessment and extraction.

Information sources

The following bibliographic databases will be searched:

- MEDLINE via PubMed.
- Embase.
- Scopus.
- Web of Science Core Collection.
- CINAHL.
- Global Index Medicus.

Supplementary sources will include Google Scholar, ProQuest Dissertations and Theses when accessible, conference proceedings, reference lists of included studies and relevant reviews, forward citation searching, related-article functions, ClinicalTrials.gov, and the WHO International Clinical Trials Registry Platform. Searches will be rerun immediately before final synthesis.

Search strategy

The search strategy will combine controlled vocabulary and free-text terms for pediatric populations, sepsis or bloodstream infection, emergency care or community-onset presentation, and Gram-negative organisms and/or antimicrobial resistance. The strategy will be adapted to the indexing and syntax of each database.

A medical librarian or information specialist will peer-review the final strategy using the PRESS framework before the definitive search. No language or full-text-availability filter will be used. To maximize sensitivity, a database-level human-only filter will not be required; clearly nonhuman studies will instead be excluded during screening. The publication date will be restricted to 1 January 2010 onward. A reproducible draft PubMed strategy is provided in Appendix A and will be updated with the exact final search date before the review is conducted.

Data management and study selection

Database records will be exported to a reference manager and deduplicated using automated and manual procedures based on title, authors, publication year, DOI, PMID, and journal. Deduplicated records will then be imported into a systematic-review platform such as Covidence or Rayyan.

Two reviewers will independently screen titles and abstracts after pilot testing the eligibility criteria on at least 100 records. Full-text assessment will subsequently be performed independently by two reviewers. Disagreements will be resolved by discussion and, when necessary, adjudication by a third reviewer. Reasons for exclusion at the full-text stage will be recorded. The selection process will be presented using a PRISMA 2020 flow diagram.

Multiple reports from the same underlying cohort will be linked and treated as a single study family. The most complete report will be used for each outcome, supplemented by companion reports when they provide non-overlapping data. Overlapping participants will not be double-counted in any meta-analysis.

Data extraction

A standardized extraction form will be piloted on at least five studies before full data extraction. One reviewer will extract data and a second reviewer will independently verify all quantitative data. Complex or high-impact outcomes will be independently extracted by both reviewers.

Data items will include study identification, country and region, care setting, recruitment pathway, population characteristics, sepsis or bloodstream-infection definitions, infection-acquisition classification, culture timing, sampling methods, contamination criteria, handling of repeated isolates, microbiological methods, AST standard and version, pathogen distribution, antimicrobial resistance, empirical treatment, clinical outcomes, analytical methods, relevant denominators, and funding or conflict-of-interest information when reported.

Study investigators will be contacted when important information is missing or unclear. Decisions made after author contact will be documented.

Outcome and denominator definitions

The primary prevalence outcome will be the proportion of culture-confirmed bacterial sepsis or bloodstream infection episodes attributable to Gram-negative bacteria. Estimates using alternative denominators, including all suspected sepsis presentations, all blood cultures, or all positive cultures, will be retained but will not be pooled with the primary denominator and will be analyzed separately.

Species prevalence will use total Gram-negative episodes or isolates as the denominator, with episode-level and isolate-level analyses explicitly distinguished. When repeated isolates from the same episode are reported, the source study definition will be recorded; where individual-level data permit, the first clinically relevant isolate per episode will be preferred to reduce duplicate counting.

For polymicrobial episodes, episode-level prevalence will count the clinical episode once, whereas organism-level analyses may include each Gram-negative organism separately. Contaminants will be handled according to the source study definition, with sensitivity analyses considered when contamination criteria are unclear or materially affect denominators.

Antimicrobial resistance will be extracted for each pathogen-antibiotic pair as the proportion of tested isolates categorized as resistant or non-susceptible. Intermediate results will not automatically be combined with resistant results. The AST standard and version, including CLSI, EUCAST, or other systems, will be recorded because breakpoint changes can affect reported susceptibility [31]. MDR, XDR, and PDR definitions will be mapped to standardized definitions described by Magiorakos., *et al*. when sufficient testing information is available [30].

Empirical therapy and clinical outcomes

Empirical antimicrobial therapy will be considered appropriate when the initial regimen administered before susceptibility results includes at least one agent with *in vitro* activity against the causative organism at a clinically appropriate dose, unless the source study uses a stricter prespecified definition. Source-study definitions and the timing of empirical therapy will be extracted verbatim.

Clinical outcomes will include mortality, intensive care admission, organ dysfunction, mechanical ventilation, vasoactive support, hospital length of stay, microbiological clearance, and readmission. Time horizons will be recorded and outcomes with materially different definitions or time horizons will not be pooled together.

Risk-of-bias assessment

Two reviewers will independently assess risk of bias, with disagreements resolved by consensus or third-reviewer adjudication. Prevalence-focused cross-sectional and surveillance studies will be assessed using the Joanna Briggs Institute Critical Appraisal

Checklist for Studies Reporting Prevalence Data. The Hoy tool will be used only as a supplementary assessment of external validity for principal prevalence estimates [28], rather than as a second composite score. Cohort and case-control studies will be assessed using the corresponding JBI checklists.

Critical domains will include population representativeness, valid case ascertainment, specimen timing, contamination handling, completeness of AST, denominator validity, handling of repeated isolates, confounding, missing data, and selective reporting. Domain-level judgments will be reported transparently; studies will not be excluded solely because of risk of bias, but risk-of-bias judgments will inform sensitivity analyses and certainty assessments.

Statistical analysis

Study characteristics and findings will first be summarized narratively and in evidence tables. Meta-analysis will be undertaken only when at least three studies are sufficiently comparable with respect to population, emergency-origin definition, denominator, organism, antimicrobial agent, and laboratory method.

Random-effects generalized linear mixed models with a logit link will be preferred for pooling prevalence and resistance proportions. Model-based 95% confidence intervals will be reported. Zero-event studies will be retained without arbitrary continuity corrections when supported by the statistical model [29].

Between-study variance (tau-squared) and I-squared will be reported, but heterogeneity will be interpreted primarily in relation to the clinical and methodological diversity of included studies rather than by I-squared thresholds alone. Prediction intervals will be reported when at least 10 studies contribute to a clinically coherent analysis and model estimation is sufficiently stable.

For associations between resistant infection and clinical outcomes, adjusted odds ratios, risk ratios, or hazard ratios will be pooled separately only when effect measures, reference groups, covariate adjustment, and time horizons are sufficiently compatible. Unadjusted and adjusted estimates will not be pooled together. Statistical analyses will be conducted in R; the R version, package versions, analytic code, and model specifications used in the final review will be archived in the planned open repository.

Subgroup and sensitivity analyses

Prespecified subgroup analyses will evaluate:

- WHO region, country, and World Bank income group.
- Neonates, young infants, older infants/children, and adolescents as reported by source studies.
- Community-onset versus healthcare-associated infection.
- Explicit pediatric emergency-department recruitment versus inferred emergency origin based on culture timing.
- Clinical severity and sepsis definition.
- Immunocompromise and chronic medical conditions.
- Previous antimicrobial exposure.
- CLSI versus EUCAST susceptibility testing.
- Phenotypic versus molecular resistance testing.
- Study period.

Sensitivity analyses will include exclusion of studies at high risk of bias, outbreak-enriched cohorts, mixed settings with inferred emergency origin, cultures obtained after antimicrobial administration, studies with unclear contamination handling, and studies in which repeated isolates cannot be distinguished from independent episodes.

Meta-regression and heterogeneity

Random-effects meta-regression will be considered when at least 10 studies are available per candidate covariate and excessive collinearity is absent. Potential moderators will include study midpoint, age group, national income setting, explicit emergency-department recruitment, healthcare exposure, immunocompromise, sepsis definition, culture timing, and AST standard. Meta-regression findings will be considered exploratory and interpreted cautiously because of ecological and residual confounding.

Reporting bias and certainty of evidence

Funnel plots and regression-based tests will be used only when at least 10 studies contribute to a clinically coherent analysis and will be interpreted cautiously. Conference abstracts, dissertations, clinical registries, citation searching, and author contact will be used to reduce the risk of missing relevant unpublished or incompletely reported evidence.

Certainty of principal estimates will be summarized using an adapted GRADE approach, considering risk of bias, inconsistency, indirectness, imprecision, and publication bias. Any adaptations required for prevalence outcomes will be described explicitly in the completed review rather than applying therapeutic-intervention GRADE rules mechanically.

Ethical considerations and dissemination

Ethical approval is not required because the review will analyze published or publicly available aggregate data without recruiting participants or accessing identifiable patient information. The completed review will be submitted to a peer-reviewed journal and presented at pediatric emergency medicine and infectious disease meetings. Search strategies, extraction forms, excluded-study lists, analytical code, and derived data will be made available in an open repository subject to copyright and database-licensing restrictions.

Discussion

The planned review is designed to provide clinically relevant antimicrobial-resistance evidence at the stage when empirical therapy is selected. Distinguishing emergency-origin infection from hospital-acquired infection is central to this objective. Hospital-wide antibiograms may be heavily influenced by intensive care, oncology, device-associated infection, and prolonged hospitalization, potentially overestimating resistance risk among previously healthy children presenting from the community. Conversely, community-level estimates may underestimate risk among children with recent hospitalization, chronic disease, prior antimicrobial exposure, or other healthcare contact.

A second major methodological issue is the denominator used for prevalence estimates. Gram-negative infection may be expressed relative to suspected sepsis presentations, all blood cultures, all positive cultures, confirmed bloodstream-infection episodes, or total bacterial isolates. Pooling these fundamentally different denominator types could produce misleading prevalence estimates. The protocol therefore prespecifies separate denominator classifications and distinguishes isolate-level from episode-level analyses. Similar safeguards will be applied to resistance estimates because testing panels, breakpoint systems, and intermediate-susceptibility definitions differ between laboratories and over time.

Several limitations are anticipated. Pediatric emergency-department-specific microbiological studies may be sparse. The 24-hour emergency-origin category may introduce indirectness when the precise location or timing of culture collection is unclear. Observational studies may incompletely distinguish contamination, polymicrobial episodes, repeated isolates, and healthcare-associated infection. Changes in pediatric sepsis definitions may also alter case mix over time. Substantial geographical and methodological heterogeneity is expected, so regional and pathogen-specific estimates may be more informative than a single pooled global estimate.

Conclusion

This protocol establishes a structured approach to synthesizing the prevalence, species distribution, and antimicrobial resistance of Gram-negative bacteria in pediatric sepsis and bloodstream infection of emergency-care origin. By preserving clinically meaningful denominator definitions, separating explicit emergency-department recruitment from inferred emergency origin, and accounting for laboratory and epidemiological heterogeneity, the completed review is intended to support locally adapted empirical antibiotic pathways, antimicrobial stewardship, surveillance, and future pediatric emergency research.

Acknowledgements

The authors acknowledge the contributions of researchers whose work has advanced the understanding of pediatric sepsis and antimicrobial resistance. Appreciation is also extended to pediatric emergency medicine clinicians, microbiologists, information specialists, and antimicrobial stewardship teams whose work informs the clinical relevance and methodological rigor of this review protocol.

Conflict of Interest

The authors declare no competing interests.

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Volume 15 Issue 9 September 2026