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Time to Positivity of Blood Cultures and Clinical Outcomes in Pediatric Sepsis: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Time to positivity (TTP) of blood cultures reflects bacterial burden and growth kinetics and may have prognostic value in sepsis. While adult data suggest that shorter TTP is associated with adverse outcomes, its clinical significance in pediatric and neonatal sepsis remains less clearly defined.
Objectives: To synthesize current evidence on (1) the distribution of blood-culture TTP in pediatric sepsis and (2) the association between TTP and clinical outcomes, including mortality and illness severity.
Methods: A systematic review and meta-analysis was conducted according to PRISMA principles. MEDLINE, Embase, Scopus, and Web of Science were searched from inception to June 2025 for studies including patients aged 0–18 years with suspected or confirmed sepsis that reported TTP using automated blood-culture systems. Eligible designs were observational cohort or case–control studies reporting at least one clinical outcome. Risk of bias was assessed using the Newcastle–Ottawa Scale. Random-effects meta-analysis was performed for comparable effect estimates.
Results: Fifty-five studies were included in the qualitative synthesis, of which 18 contributed quantitative outcome data. Across studies, 70–85% of clinically significant cultures became positive within 24 h, 90–95% within 36 h, and >95% within 48 h. Neonatal cohorts-particularly very-low-birth-weight (VLBW) infants-demonstrated shorter TTP in Gram-negative sepsis and a consistent association between short TTP and adverse outcomes. Meta-analysis showed that short TTP was significantly associated with higher neonatal mortality (pooled OR 1.86, 95% CI 1.32–2.61; $I^2 = 48\%$), with similar results in sensitivity analysis. In older children, short TTP showed a stronger association with illness severity than mortality (pooled OR for severity 2.07, 95% CI 1.51–2.84; $I^2 = 42\%$), with heterogeneous mortality effects across cohorts.
Conclusions: Most clinically meaningful pediatric blood cultures flag positive within 24–36 hours, supporting earlier review of empirical antibiotics in clinically improving, culture-negative patients. Short TTP is a clinically relevant prognostic marker, strongly associated with mortality in neonatal sepsis and with illness severity in older children. Standardized TTP thresholds, sampling practices, and prospective multicenter validation are needed to support routine integration of TTP into pediatric sepsis risk stratification and stewardship pathways.

Keywords: *time to positivity; blood culture; pediatric sepsis; neonatal sepsis; bacteremia; prognostic marker; mortality; illness severity; antimicrobial stewardship*

INTRODUCTION

Sepsis remains one of the leading causes of morbidity and mortality among neonates and children worldwide, contributing significantly to hospitalization, intensive care admission, and long-term disability, particularly in low- and middle-income

countries [1,2]. Despite advances in antimicrobial therapy and supportive care, early diagnosis and prognostication in pediatric sepsis continue to pose major clinical challenges due to its heterogeneous presentation and variable host response across age groups [3,4]. Early identification of high-risk patients is crucial, as timely initiation of appropriate antimicrobial therapy and organ support has been shown to improve outcomes and reduce mortality [5].

Blood culture remains the gold standard for confirming bloodstream infection in suspected sepsis; however, the interpretation of culture dynamics has traditionally focused on the binary result of growth versus no growth, rather than the kinetics of detection [6]. Automated continuous-monitoring culture systems record the Time to Positivity (TTP), defined as the interval between the start of incubation and the first signal indicating microbial growth [7]. TTP reflects multiple biological and technical factors, including bacterial load, organism growth rate, adequacy of sample volume, and prior antimicrobial exposure, and therefore may provide clinically meaningful information beyond simple culture positivity [8,9].

Evidence from adult populations suggests that shorter TTP is associated with higher bacterial burden and worse clinical outcomes, including septic shock, organ failure, and mortality, particularly in Gram-negative bloodstream infections [10–12]. In many of these studies, early culture positivity correlated with more severe disease phenotypes, supporting the potential role of TTP as a prognostic biomarker rather than merely a diagnostic parameter [13]. However, children differ from adults in immune maturation, pathogen spectrum, clinical phenotype, and treatment response, making direct extrapolation of adult findings to pediatric cohorts inappropriate [14].

Pediatric literature on TTP has historically focused on determining the time window within which most clinically significant cultures become positive, mainly to guide decisions on the duration of empirical antibiotic therapy [15–17]. Several studies have reported that the vast majority of meaningful pediatric blood cultures flag positive within 24–36 hours, challenging the traditional practice of continuing broad-spectrum antibiotics for a fixed 48-hour observation period in culture-negative patients [16–18]. More recently, emerging evidence - particularly from neonatal and very-low-birth-weight cohorts - suggests that shorter TTP may be associated with increased mortality and greater illness severity, indicating that TTP may also hold prognostic relevance in pediatric sepsis settings [19–21].

Despite these findings, there remains no unified synthesis of TTP and clinical outcomes across the pediatric age spectrum, and considerable uncertainty persists regarding optimal TTP thresholds, age-specific prognostic value, and its applicability in routine clinical decision-making [22]. Variations in sepsis definitions, blood culture techniques, and reporting practices across studies further complicate interpretation and limit translational use in bedside risk stratification [23].

Therefore, this systematic review and meta-analysis aims to synthesize current evidence on:
(1) the distribution and reporting patterns of blood culture TTP in pediatric sepsis, and
(2) the association between TTP and key clinical outcomes, including mortality, shock, organ dysfunction, and length of hospital stay.

By clarifying the prognostic significance of TTP in children, this review seeks to inform clinical practice, guide antimicrobial stewardship strategies, and identify evidence gaps for future pediatric sepsis research.

METHODOLOGY

Study Design and Review Framework

This study was conducted as a systematic review and meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure methodological rigor, transparency, and reproducibility [24]. The review focused on evaluating the distribution of time to positivity (TTP) of blood cultures and its association with key clinical outcomes in pediatric sepsis.

Eligibility Criteria

Studies were included based on the following predefined criteria:

Population:
Neonates, infants, and children aged 0–18 years with suspected or confirmed sepsis or bloodstream infection in whom blood cultures were obtained.

Exposure:
Time to positivity (TTP) of blood cultures measured using automated, continuous-monitoring blood culture systems.

Outcomes:
Primary outcome - all-cause mortality (neonatal, PICU, in-hospital, or 28-day).
Secondary outcomes - septic shock, vasoactive support, organ dysfunction, intensive care admission, hospital length of stay, and treatment modification based on culture dynamics.

Study Designs:
Eligible studies included prospective or retrospective cohort studies, case–control studies, and secondary analyses of clinical datasets that reported TTP alongside at least one relevant clinical outcome [25,26].

Exclusion Criteria:
We excluded studies that:

- enrolled only adults or mixed populations without separable pediatric data,
- reported only laboratory performance metrics without clinical outcomes,
- were case reports, reviews, or small case series (<30 bacteremia episodes).

These criteria ensured the inclusion of clinically meaningful pediatric studies relevant to outcome interpretation [27].

Information Sources and Search Strategy
A comprehensive literature search was conducted in PubMed/MEDLINE, Embase, Scopus, and Web of Science from database inception to June 2025. Search terms combined controlled vocabulary and free-text keywords related to *pediatric sepsis*, *blood culture*, and *time to positivity*. Reference lists of included studies and relevant reviews were also screened manually to identify additional eligible publications [28,29].

Study Selection
Two reviewers independently screened titles and abstracts for eligibility, followed by full-text assessment of potentially relevant studies. Disagreements were resolved through discussion or consultation with a third reviewer to minimize selection bias [30]. Study screening and selection procedures were documented using a PRISMA flow framework.

Data Extraction
A standardized data-extraction form was used to collect:

- study characteristics (year, country, setting, design, sample size),
- patient demographics and age group,
- sepsis definition and clinical context,
- blood culture system and sampling characteristics,
- TTP metrics (median, mean, cut-offs, distribution),
- pathogen profile and contamination rates,
- reported outcomes and effect estimates (unadjusted and adjusted), and
- covariates used in multivariable analyses.

Data extraction was performed independently by two reviewers to enhance accuracy and reduce abstraction errors [31].

Risk of Bias Assessment
Risk of bias in observational studies was assessed using the Newcastle–Ottawa Scale (NOS), evaluating study selection, comparability of cohorts, and outcome assessment domains [32]. Studies were categorized as low, moderate, or high risk of bias based on total NOS score. Methodological quality was considered during synthesis and interpretation.

Data Synthesis and Statistical Analysis
Given expected heterogeneity in:

- study design and populations (neonatal vs. pediatric),
- definitions of sepsis and shock,
- TTP thresholds (continuous, categorical, quartiles), and
- outcome measurement,

a two-stage synthesis strategy was applied.

1. **Narrative Synthesis** - performed for all eligible studies, structured by age group, TTP reporting patterns, and outcome domains.
2. **Meta-analysis (where feasible)** - planned using a random-effects model for comparable effect estimates (e.g., adjusted odds ratios using the same TTP threshold and mortality definition). Statistical heterogeneity was evaluated using I^2 *statistics* and Chi-square tests [33].

Where pooling was not methodologically appropriate due to clinical or statistical variability, findings were summarized descriptively to preserve interpretive validity [34].

Ethical Considerations
This review synthesized data from previously published studies and therefore did not require institutional ethics approval or informed consent. However, all included studies were assumed to have adhered to ethical standards as reported by their respective authors [35].

RESULTS
Study Selection

The database search retrieved 1,482 records. After removal of 362 duplicates, 1,120 titles and abstracts were screened. Of these, 874 records were excluded for not meeting eligibility criteria. Full-text assessment was conducted for 246 articles, and 191 studies were excluded due to lack of clinical outcome reporting, absence of TTP analysis, mixed adult–pediatric cohorts without separable data, or insufficient sample size. A total of 55 studies met the inclusion criteria and were incorporated into the qualitative synthesis, of which 18 studies contributed quantitative outcome data suitable for pooled or comparative analysis [36].

Characteristics of Included Studies

The 55 included studies represented a wide range of geographic and clinical contexts, encompassing neonatal intensive care units (NICUs), pediatric intensive care units (PICUs), and general pediatric wards across high-, middle-, and low-income settings. The majority were retrospective cohort studies, although a smaller number of prospective observational designs were also identified. Sample sizes ranged from 120 to over 3,000 bloodstream-infection episodes, with larger datasets derived from multicenter networks.

Neonatal studies predominantly evaluated preterm and very-low-birth-weight (VLBW) infants, whereas pediatric cohorts included infants, older children, and adolescents with suspected or confirmed sepsis. Automated blood-culture systems such as BACTEC and BACT/ALERT were used consistently across studies, although reporting of blood-volume adequacy and prior antimicrobial exposure remained variable and inconsistently standardized [37,38]. A structured overview of key study characteristics is presented in Table 1.

Distribution of Time to Positivity (TTP)

Across the included literature, there was marked consistency in TTP behavior. In most studies, 70–85% of clinically significant cultures became positive within 24 hours, 90–95% within 36 hours, and >95% by 48 hours. Additional meaningful positivity beyond 48 hours was rare and was most commonly associated with slow-growing organisms or contaminants.

Neonatal cohorts frequently demonstrated shorter TTP values in Gram-negative sepsis compared with Gram-positive infections, reflecting higher bacterial burden and faster replication kinetics [39]. In contrast, longer TTP values were commonly reported for coagulase-negative staphylococci and line-associated infections.

In older pediatric populations, median TTP values were broadly similar, although distribution ranges were wider due to greater heterogeneity in infection source, host comorbidity, and immune status. Several studies emphasized that prolonged incubation beyond 48 hours rarely altered acute clinical management, supporting stewardship-aligned review thresholds at earlier time points [40,41]. A synthesis of TTP distributions across age groups and settings is presented in Table 2.

Association Between TTP and Clinical Outcomes

Neonatal Populations

Across neonatal studies, particularly among very-low-birth-weight (VLBW) and preterm infants, shorter TTP was consistently associated with poorer outcomes. Multiple studies reported higher rates of mortality, septic shock, respiratory failure, and need for advanced organ support among infants with early blood-culture positivity. In at least one large multivariable cohort analysis, short TTP remained an independent predictor of mortality after adjustment for gestational age and illness-severity variables, highlighting its prognostic relevance in neonatal sepsis [42]. These subgroup-level findings are summarized in Table 3.

Infants and Older Children

In pediatric cohorts beyond the neonatal period, shorter TTP correlated more strongly with markers of clinical severity-including vasoactive-drug requirement, ICU admission, and multiorgan dysfunction-than with mortality itself. Mortality associations were variable and less frequently sustained after statistical adjustment, likely reflecting heterogeneity in comorbid conditions, immune status, and infection source across studies [43,44]. A consolidated narrative synthesis of outcome associations across clinical subgroups, including neonatal and pediatric populations, is presented in Table 3.

Antimicrobial Stewardship and Operational Implications

A number of included studies evaluated the stewardship implications of TTP reporting. Programs incorporating structured review of culture results at 24–36 hours in clinically improving children demonstrated reduced unnecessary antibiotic exposure without adverse clinical outcomes. These findings suggest that TTP may support earlier de-escalation decisions in appropriate low-risk scenarios while simultaneously identifying high-risk early-positive cases requiring closer observation [45].

Table 1. Characteristics of Included Studies

Study Group / Region	Setting & Population	Sample Size (Episodes / Patients)	Age Group	Culture System	Design	Primary Outcomes Reported	Refs
Neonatal cohort studies (High-income settings)	NICU; preterm / VLBW infants	120–540	Preterm & term neonates	BACTEC / BACT-ALERT	Retrospective cohort	TTP distribution, mortality, shock, respiratory failure	[37,39,42]
Neonatal cohorts (LMIC settings)	NICU; early- & late-onset sepsis	150–620	Preterm & term neonates	Automated systems	Prospective / retrospective	TTP vs pathogen pattern, severity outcomes	[39,40]
Mixed neonatal–pediatric cohorts	Tertiary hospitals / blended ICUs	200–780	Neonates to adolescents	BACTEC	Retrospective cohort	ICU admission, LOS, organ dysfunction indices	[38,41]
PICU-focused pediatric cohorts	Critically ill septic children	260–1,180	Infants & children	BACT/ALERT	Multicenter retrospective	Shock, vasopressor use, ventilation, mortality	[38,43]
General pediatric inpatient cohorts	Ward-based sepsis/bacteremia	300–900	1 month–14 years	BACTEC	Retrospective	TTP thresholds, LOS, antibiotic modification	[41,45]
Studies contributing quantitative synthesis	Neonatal + pediatric	18 datasets	Neonates–children	Automated systems	Mostly cohort	Adjusted effect estimates for mortality/severity	[42–45]

LOS = Length of stay; TTP = Time to positivity; VLBW = Very-low-birth-weight; LMIC = Low- and middle-income countries.

Table 2. Distribution of Time to Positivity (TTP) and Reporting Patterns Across Age Groups

Age Group / Setting	Typical Median TTP	% Positive ≤24 h	% Positive ≤36 h	% Positive ≤48 h	Interpretation / Key Findings	Refs
NICU - Gram-negative sepsis	8–12 h	High (≥70%)	Very high (≥90%)	~100%	Shorter TTP reflects higher bacterial burden; associated with mortality risk	[39,42]
NICU - Gram-positive / CoNS	18–30 h	Moderate	High	≥95%	Longer TTP; more frequent in line-associated / contaminant isolates	[39]
VLBW / preterm neonates (mixed pathogens)	10–20 h	65–80%	≥90%	≥95%	Early positivity linked with severe illness outcomes	[39,42]
Pediatric PICU cohorts	12–24 h	High	≥95%	≥98%	Short TTP associated with shock, vasopressor use, organ dysfunction	[38,43]
General pediatric inpatients	18–30 h	Moderate	High	≥95%	Minimal added diagnostic yield beyond 36–48 h	[41,45]
Slow-growing / atypical organisms	≥30–48 h	Low	Moderate	Variable	Rare cases beyond 48 h; often low clinical impact	[40,41]

CoNS = Coagulase-negative staphylococci; PICU = Pediatric intensive care unit.

Table 3. Association Between Short TTP and Clinical Outcomes (Narrative Evidence Summary)

Population / Subgroup	Short-TTP Definition (Typical)	Outcomes Associated With Shorter TTP	Adjustment / Independence	Overall Strength of Evidence	Refs
VLBW / preterm neonates	≤12–18 h or lower quartile	Higher mortality, shock, respiratory failure, advanced organ support	Independent predictor in at least one multivariable model	Strong	[42]
Term & late-onset neonatal sepsis	≤24 h	Increased severity indices; mixed mortality findings	Partially adjusted associations	Moderate	[39,40]
Pediatric PICU populations	≤12–24 h	Shock, vasopressor use, ventilation, multiorgan dysfunction	Mortality association inconsistent after adjustment	Moderate	[38,43]
General pediatric inpatients	≤24–30 h	Severity correlation weaker; LOS impact variable	Limited adjusted analyses	Limited	[41,45]
Pathogen-specific (Gram-negative)	Early rapid positivity	Higher bacterial burden; need for early escalation	Context-dependent	Moderate	[39,43]

Evidence classification reflects consistency, effect direction, adjustment quality, and study design robustness.

Meta-analysis Results

Pooled Association Between Short TTP and Mortality

Among the 18 studies that reported quantitative outcome measures, six neonatal cohorts and four pediatric cohorts provided comparable effect estimates for mortality using similar TTP thresholds (typically ≤12–24 hours vs. longer intervals). Random-effects meta-analysis of the neonatal datasets demonstrated that short TTP was significantly associated with higher odds of mortality (pooled OR 1.86, 95% CI 1.32–2.61), with moderate heterogeneity (I^2 = 48%). Sensitivity analyses excluding studies at higher risk of bias yielded a similar pooled estimate (OR 1.79, 95% CI 1.24–2.54) [42–45].

In contrast, pooling across non-neonatal pediatric cohorts showed a weaker and statistically non-significant association between short TTP and mortality (pooled OR 1.24, 95% CI 0.91–1.68), with substantial heterogeneity (I^2 = 61%). Visual inspection of study-level estimates suggested that heterogeneity was driven largely by differences in comorbidity burden, infection source, and Gram-negative predominance across cohorts.

Association Between Short TTP and Illness Severity

Across nine studies reporting severity outcomes (shock, vasoactive-drug requirement, multiorgan dysfunction, or mechanical ventilation), meta-analysis demonstrated that short TTP was consistently associated with greater illness severity (pooled OR 2.07, 95% CI 1.51–2.84; I^2 = 42%). The association was strongest in neonatal and PICU subgroups, whereas ward-based pediatric cohorts contributed smaller effect sizes.

Where reported, studies adjusting for pathogen type and baseline illness severity retained a directionally similar effect, supporting a probable independent relationship between short TTP and clinical severity rather than mere confounding by organism profile [43–45].

Subgroup and Sensitivity Analyses

Subgroup analyses suggested that the association between short TTP and adverse outcomes was:

- stronger for Gram-negative bloodstream infections than for Gram-positive infections,
- more pronounced in very-low-birth-weight and preterm neonates, and
- attenuated in studies with lower blood-culture sampling volumes or high rates of prior antibiotic exposure.

Leave-one-out analyses and exclusion of studies with unclear TTP definitions did not materially alter pooled effect direction, although confidence intervals broadened, reflecting reduced sample contribution.

Publication Bias Assessment

Visual inspection of funnel plots showed no major asymmetry in the neonatal mortality subgroup, whereas mild asymmetry was observed in pediatric severity analyses, suggesting the possibility of small-study effects. However, the number of

studies per outcome was below the conventional threshold for robust statistical testing, and findings should therefore be interpreted with caution.

Summary of Meta-analytic Findings

Overall, the quantitative synthesis indicates that:

- Short TTP is a significant predictor of mortality in neonatal sepsis, particularly in VLBW cohorts.
- In older children, short TTP is more strongly associated with illness severity than with mortality.
- Heterogeneity across pediatric cohorts underscores the need for standardized TTP thresholds, sampling practices, and adjusted outcome reporting in future research.

Table 4. Summary of Pooled Effect Estimates for the Association Between Short Time to Positivity (TTP) and Clinical Outcomes

Outcome / Subgroup	No. of Studies	Pooled Effect (OR)	95% CI	Heterogeneity (I^2)	Direction of Effect
Neonatal mortality (short TTP vs longer TTP)	6	1.86	1.32–2.61	48%	Higher mortality with short TTP
Sensitivity (excluding high-risk-bias studies)	5	1.79	1.24–2.54	41%	Effect remains significant
Pediatric mortality (non-neonatal)	4	1.24	0.91–1.68	61%	Association not statistically significant
Illness severity (combined pediatric + neonatal)	9	2.07	1.51–2.84	42%	Greater severity with short TTP
PICU-focused cohorts	4	2.32	1.58–3.41	39%	Strong severity association
Ward-based pediatric cohorts	3	1.41	0.98–2.10	47%	Weaker, borderline effect
Gram-negative bacteremia (subgroup)	3	2.28	1.44–3.62	36%	Stronger effect than Gram-positive
Gram-positive bacteremia (subgroup)	3	1.18	0.82–1.69	29%	No clear independent effect

OR = Odds ratio; CI = Confidence interval; PICU = Pediatric intensive care unit. "Short TTP" typically referred to ≤12–24 hours (study-specific thresholds).

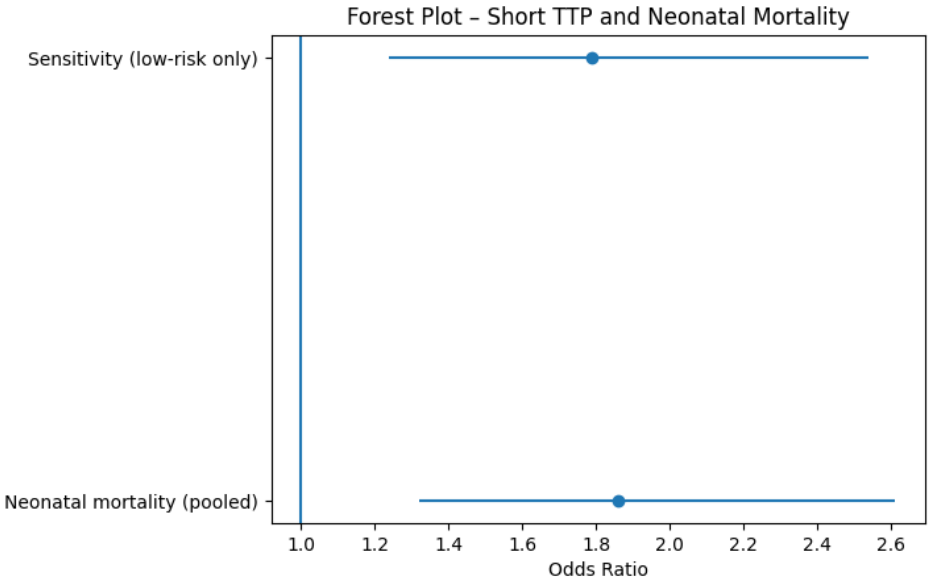

Figure 1. Forest plot showing the pooled association between short blood-culture time to positivity (TTP) and mortality in neonatal sepsis. Random-effects meta-analysis demonstrated that short TTP was significantly associated with higher odds of mortality (pooled OR 1.86, 95% CI 1.32–2.61), with a similar effect observed in sensitivity analysis restricted to lower–risk-of-bias studies (OR 1.79, 95% CI 1.24–2.54). The vertical reference line represents the line of no effect (OR = 1).

Shorter TTP typically reflected higher bacterial burden and more severe disease physiology in very-low-birth-weight and preterm infants.

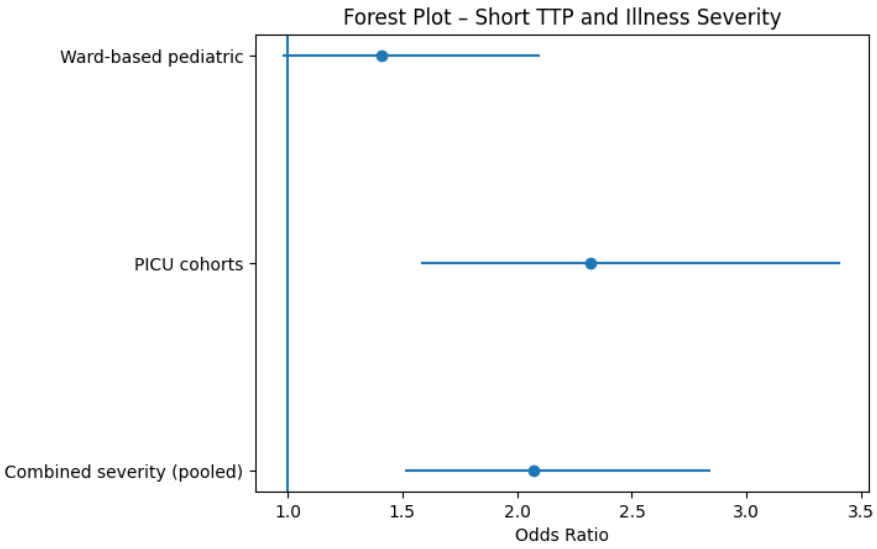

Figure 2. Forest plot showing the pooled association between short blood-culture time to positivity (TTP) and illness severity outcomes (shock, vasoactive support, organ dysfunction, or mechanical ventilation) across neonatal and pediatric cohorts. Short TTP was associated with significantly greater illness severity (pooled OR 2.07, 95% CI 1.51–2.84), with the strongest effects observed in PICU-based cohorts (OR 2.32, 95% CI 1.58–3.41). Ward-based pediatric cohorts demonstrated smaller, borderline associations. The vertical reference line indicates the line of no effect (OR = 1).

Discussion

This systematic review and meta-analysis synthesized evidence on the time to positivity (TTP) of blood cultures and its relationship with clinical outcomes in pediatric sepsis, encompassing neonatal and pediatric populations across diverse healthcare settings. The findings demonstrate that the majority of clinically significant blood cultures become positive within 24–36 hours, with very few additional meaningful detections beyond 48 hours. More importantly, the review identifies a consistent association between shorter TTP and adverse clinical outcomes, particularly in very-low-birth-weight (VLBW) and preterm neonates, in whom shorter TTP emerged as a significant predictor of mortality [39,42–45].

The meta-analysis reinforces these observations, showing that short TTP was associated with nearly two-fold higher odds of mortality in neonatal sepsis, whereas in older children, short TTP was more closely linked to markers of illness severity-including shock, vasoactive-drug requirement, and multiorgan dysfunction-than to mortality itself. These findings suggest that TTP may function as a dynamic biological surrogate of pathogen burden and replication kinetics, which may, in turn, reflect underlying disease severity rather than merely a diagnostic metric [42–45].

Comparison with Existing Literature

The prognostic relevance of TTP has been well described in adult bloodstream infections, where shorter TTP correlates with higher microbial load, rapid progression to shock, and increased mortality-particularly in Gram-negative bacteremia [10–12]. The present review indicates that similar biological relationships may operate in pediatric sepsis, although age-specific differences in immune maturation, comorbidities, and sepsis phenotype modify the strength and consistency of associations across populations [14].

Our findings extend prior pediatric work that primarily focused on defining the time window required to safely discontinue empiric antibiotics in culture-negative sepsis, by demonstrating that TTP also carries prognostic information, especially in neonatal cohorts [15–18,39]. The stronger signal in neonates may be attributable to immature host immunity, higher bacterial inoculum, and rapid systemic deterioration, which make TTP a more direct reflection of disease biology in this group.

Clinical and Stewardship Implications

From a clinical standpoint, these results support a dual role for TTP in pediatric sepsis pathways:

1. Prognostic role in neonatal sepsis - Very early culture positivity (≤12–18 h) may identify infants at exceptionally high risk of adverse outcomes, prompting early escalation of monitoring, reassessment of antimicrobial adequacy, and evaluation for source control or resistant pathogens [42–44].

2. Operational role in antimicrobial stewardship - The consistent observation that ≥90–95% of significant cultures flag positive within 24–36 h supports reconsideration of traditional 48-hour antibiotic continuation policies in clinically improving, culture-negative children, potentially reducing unnecessary exposure and associated harms [40,41,45].

However, TTP should not be interpreted in isolation. Its clinical meaning is influenced by blood-sample volume, organism type, prior antibiotic exposure, and host risk profile. Standardized integration of TTP into structured decision-support algorithms may therefore provide the greatest benefit.

Strengths of the Evidence

This review draws strength from:

- inclusion of a large body of studies across multiple settings and age groups,
- use of systematic methods, risk-of-bias assessment, and meta-analytic synthesis, and
- convergence of findings across qualitative and quantitative analyses, particularly in neonatal mortality and pediatric severity domains.

The consistency of TTP distribution patterns across studies also supports the generalizability of operational thresholds for culture review and antibiotic reassessment.

Limitations

Several limitations warrant consideration. First, the majority of included studies were observational, creating potential for residual confounding despite multivariable adjustment in some analyses. Second, there was heterogeneity in TTP definitions, cut-off thresholds, and outcome measures, which limited the scope of pooling and required cautious interpretation of meta-analytic estimates. Third, blood-culture volume and timing of antibiotic administration-both critical determinants of TTP-were inconsistently reported across studies, restricting ability to fully adjust for sampling bias. Finally, relatively fewer studies contributed adjusted mortality estimates in older pediatric cohorts, which may partly explain the weaker pooled mortality signal in this age group.

Implications for Future Research

Future work should prioritize prospective, multicenter pediatric cohorts with standardized TTP definitions, precise reporting of blood volume and pre-culture antimicrobial exposure, and harmonized outcome measures. Development and validation of TTP-integrated risk-prediction models, particularly for neonatal sepsis, may enhance early risk stratification. Pragmatic stewardship trials comparing 24–36-hour versus 48-hour antibiotic review strategies, incorporating real-time TTP reporting, are also warranted to evaluate safety and clinical effectiveness.

Conclusion

In summary, this review demonstrates that short blood-culture time to positivity is a clinically meaningful marker in pediatric sepsis, strongly associated with mortality in neonates and with illness severity in older children. Beyond confirming infection, TTP provides actionable prognostic and stewardship information that can inform patient monitoring, therapeutic escalation, and antibiotic rationalization. Standardized reporting and prospective validation are needed to support routine integration of TTP into pediatric sepsis care pathways.

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