

Data analysis from the Sepsis Registry study on the association between antibiotic use duration and clinical outcomes in neonatal sepsis

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Research Article

Keywords: Neonatal sepsis, time-to-antibiotic, antibiotic timing, in-hospital mortality, multicenter cohort study

Posted Date: April 27th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-9153479/v1>

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Additional Declarations: No competing interests reported.

Abstract

Background

Timely initiation of antibiotic therapy is a cornerstone of sepsis management, yet evidence supporting strict time-based targets in neonatal sepsis remains limited and inconsistent. Whether incremental delays in time-to-antibiotic (TTA) administration are independently associated with adverse outcomes in neonates is uncertain.

Methods

We conducted a multicenter retrospective cohort study using a neonatal sepsis registry from five centers between January 2018 and December 2023. Hospitalized neonates with clinically diagnosed sepsis and documented TTA were included. TTA was analyzed as both a continuous variable and categorized into < 1 h, 1–2 h, 2–3 h, 3–6 h, and > 6 h, with an additional binary comparison of early (< 1 h) versus delayed ($\geq$ 1 h) administration. The primary outcome was in-hospital mortality. Secondary outcomes included hospital length of stay, duration of mechanical ventilation, secondary infection, and a composite adverse outcome. Multivariable logistic regression and Cox proportional hazards models were used to estimate adjusted associations, controlling for prespecified clinical covariates.

Results

Among 1,500 neonates with sepsis, median TTA was 0.76 hours, and 58.0% received antibiotics within 1 hour. Overall in-hospital mortality was 15.9%. Mortality increased modestly across TTA categories, from 15.3% (< 1 h) to 20.0% (> 6 h) (trend $P \approx 0.024$). In adjusted analyses, each 1-hour delay in antibiotic administration was associated with a higher, but not statistically significant, odds of mortality (adjusted OR 1.090; 95% CI 0.975–1.217). Kaplan–Meier analyses demonstrated significant survival differences across detailed TTA strata, whereas the binary comparison of < 1 h versus $\geq$ 1 h was not significant. Longer TTA was associated with a small increase in hospital length of stay, while other secondary outcomes showed no clear linear association. Subgroup and sensitivity analyses yielded directionally consistent results.

Conclusions

In this multicenter cohort of neonates with sepsis, longer delays in antibiotic administration were associated with modestly worse outcomes, with excess risk concentrated among more prolonged delays rather than marginal deviations beyond 1 hour. These findings support efforts to minimize extreme treatment delays while suggesting that rigid application of a universal 1-hour threshold may not fully capture risk heterogeneity in neonatal sepsis.

Introduction

Neonatal sepsis remains a leading cause of morbidity and mortality worldwide, particularly among preterm and low-birth weight infants, despite advances in perinatal care and antimicrobial therapy[1–3]. The burden is especially pronounced in low- and middle-income settings, but substantial mortality persists even in high-resource neonatal intensive care units (NICUs) [4–6]. Early recognition and timely initiation of appropriate antimicrobial therapy are therefore central components of neonatal sepsis management and are emphasized across international guidelines[7–9].

In adult and pediatric populations, a robust body of evidence supports the concept that delays in antibiotic administration are associated with increased mortality in sepsis and septic shock [10–12]. This evidence has driven the widespread adoption of time-based performance metrics, most notably the “1-hour bundle,” which prioritizes prompt antibiotic delivery following sepsis recognition [13–16]. However, extrapolation of these findings to neonates is not straightforward. Neonatal sepsis differs fundamentally in its pathophysiology, clinical presentation, pathogen spectrum, and host immune response, and neonates are uniquely vulnerable to both undertreatment and overtreatment with antibiotics [1, 17, 18].

Existing evidence on the relationship between time-to-antibiotic (TTA) administration and outcomes in neonatal sepsis is limited and inconsistent. Several single-center studies and secondary analyses suggest potential harm associated with prolonged delays, particularly in critically ill or extremely preterm infants [19–21]. In contrast, other investigations have reported weak or non-significant associations once illness severity and perinatal factors are accounted for, raising questions about whether a universal 1-hour threshold is appropriate for all neonatal populations[3, 14, 22]. Importantly, most prior studies have been constrained by small sample sizes, heterogeneous definitions of exposure, limited adjustment for confounding, or binary categorizations of TTA that may obscure non-linear risk patterns.

Moreover, neonatal sepsis encompasses both early-onset sepsis (EOS), typically related to perinatal transmission, and late-onset sepsis (LOS), often associated with nosocomial or community-acquired pathogens. These entities differ in timing, microbiology, and clinical trajectory, yet are frequently pooled in analyses without formal interaction testing [3, 21]. Multicenter data capturing contemporary practice patterns, center-level variation, and detailed timing of antibiotic initiation remain scarce.

To address these gaps, we conducted a large multicenter retrospective cohort study using a standardized neonatal sepsis registry from five centers over a six-year period. Our objectives were to (1) characterize the distribution of TTA in routine clinical practice, (2) examine the association between incremental delays in antibiotic administration and in-hospital mortality using both continuous and categorical exposure definitions, and (3) explore potential effect modification across clinically relevant subgroups, including EOS versus LOS, gestational age, and illness severity. We further evaluated secondary outcomes related to healthcare utilization and complications to provide a comprehensive assessment of the clinical impact of antibiotic timing in neonatal sepsis.

Methods

Study design and data source

This was a multicenter retrospective cohort study using the Sepsis Registry from five centers between January 2018 and December 2023, including hospitalized neonates with clinically diagnosed sepsis.

Data extraction captured demographics, clinical variables, treatments, and outcomes from the registry; analysis followed a prespecified statistical plan.

Population and eligibility

We included 1,500 neonates with sepsis who received intravenous antibiotics and had documented time-to-antibiotic (TTA).

Key exclusions in the registry preprocessing were missing TTA, missing survival outcome, or duplicate encounters. Early-onset sepsis (EOS) and late-onset sepsis (LOS) were both retained (EOS 56.8%, LOS 43.2%).

Exposure definition

The main exposure was TTA, defined as hours from admission/diagnosis to first intravenous antibiotic dose, treated as a continuous variable and categorized as < 1 h, 1–2 h, 2–3 h, 3–6 h, and > 6 h.

A binary comparison of early (< 1 h) versus delayed ($\geq$ 1 h) administration was also examined.

Outcomes

Primary outcome: in-hospital mortality.

Secondary outcomes: hospital length of stay (LOS), mechanical ventilation duration, secondary infection, and a composite adverse outcome (per study plan).

Covariates

Prespecified covariates: gestational age, birth weight, 5-minute Apgar score, illness severity score, sepsis type (EOS/LOS), respiratory distress syndrome (RDS), necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), blood culture positivity, and major pathogen category.

Statistical analysis

Baseline characteristics were summarized overall and by early vs delayed groups; group differences used appropriate univariable tests (Table 1, Fig. 1).

Mortality was described across TTA strata with trend testing (Table 2, Fig. 2A) and binary early vs delayed comparison (Fig. 2C).

Multivariable logistic regression estimated the adjusted odds ratio (OR) for mortality per 1-hour delay, adjusting for the prespecified covariates (Table 3, Fig. 2B/Fig. 4 “Overall”).

Cox proportional hazards models estimated hazard ratios (HR) for time-to-event mortality; Kaplan–Meier curves with log-rank tests compared survival across TTA strata and by < 1 h vs ≥ 1 h (Fig. 3).

Subgroup analyses were predefined (EOS/LOS, gestational age strata, severity strata) with interaction assessment; center-level comparisons were descriptive (Fig. 4, Fig. 6).

Sensitivity analyses: culture-positive only, excluding extremely preterm, EOS-only, and period-specific analyses (2018–2020 vs 2021–2023) (Supplementary Table).

Secondary outcomes were compared across TTA categories with trend tests (Fig. 5). Two-sided $P < 0.05$ indicated statistical significance. Analyses were performed per the prespecified plan; no multiplicity adjustments were applied.

Results

Study population and baseline characteristics

We analyzed 1,500 neonates (5 centers). Median gestational age was 35.0 weeks (IQR 32.3–37.6), median birth weight 3,486 g; 55.1% were male. EOS accounted for 56.8%, and blood cultures were positive in 64.1% (Table 1, Fig. 1A–F).

Median TTA was 0.76 hours; 58.0% received antibiotics within 1 hour and 91.2% within 3 hours (Fig. 1C). Early (< 1 h) and delayed (≥ 1 h) groups had similar gestational age and birth weight; the early group showed slightly higher severity scores (median 39.7 vs 38.0, $P = 0.040$).

Primary outcome: mortality

Overall in-hospital mortality was 15.9% (Fig. 1F). Mortality by TTA showed a modest upward trend: < 1 h 15.3%, 1–2 h 16.2%, 2–3 h 18.9%, 3–6 h 16.2%, > 6 h 20.0% (Table 2, Fig. 2A; trend $P \approx 0.024$). Early vs delayed mortality was 15.3% vs 16.8% (Fig. 2C).

Adjusted logistic regression: OR 1.090 per 1-hour delay (95% CI 0.975–1.217, $P = 0.129$; Table 3; Fig. 2B/Fig. 4 “Overall”). Cox model was directionally consistent (HR 1.085; 95% CI 0.986–1.194).

Survival analysis

Kaplan–Meier curves across TTA strata differed significantly (log-rank $P < 0.001$), with 2–3 h and > 6 h groups showing the lowest survival (Fig. 3A).

The binary comparison (< 1 h vs ≥ 1 h) was not significant (log-rank $\text{Chi}^2 = 0.72$, $P = 0.3948$; Fig. 3B), suggesting excess risk is concentrated in the more extreme delays.

Subgroups and centers

Prespecified subgroups (EOS/LOS, gestational age strata, severity strata) showed ORs crossing 1 with no significant interactions (Fig. 4; Table 4). High-severity infants trended toward higher risk (OR 1.26; 95% CI 0.98–1.62).

Center-level TTA medians ranged ~ 0.6 – 1.0 h with mean differences < 0.5 h; mortality ranged roughly 13–18% without a clear center effect (Fig. 6).

Secondary outcomes

Hospital length of stay increased slightly with delay; regression from the analytic code estimated ~ 0.38 additional days per 1-hour delay (Fig. 5A). Mechanical ventilation duration showed minimal differences across TTA strata (mostly within ~ 2 days; Fig. 5B).

Secondary infection peaked in the 2–3 h group ($\sim 14\%$) but the trend test was nonsignificant ($P \approx 0.39$; Fig. 5C). Composite adverse outcome rates were 34–39% across strata with no significant linear trend ($P \approx 0.50$; Fig. 5D).

Temporal trends and sensitivity analyses

After 2020, TTA decreased and remained near or below the 1-hour target (mean ~ 0.9 h from 2021 onward; Fig. 7A), whereas mortality fluctuated between ~ 10 – 20% without a monotonic trend (Fig. 7B).

Sensitivity analyses (culture-positive only, excluding extremely preterm, EOS-only, and period-specific 2018–2020 vs 2021–2023) were consistent with the primary analysis: OR range 1.072–1.135, none statistically significant (Supplementary Table).

Discussion

In this multicenter cohort of 1,500 neonates with clinically diagnosed sepsis, we observed a modest but consistent directional association between longer time-to-antibiotic administration and worse outcomes, particularly mortality and hospital length of stay. While unadjusted analyses demonstrated an increasing mortality trend across TTA strata, multivariable models adjusting for gestational age, illness severity, comorbidities, and microbiological factors did not show a statistically significant increase in mortality per 1-hour delay. These findings suggest that, in contemporary neonatal practice, modest delays beyond the first hour may confer incremental risk, but that excess mortality is concentrated among infants experiencing more pronounced delays rather than those marginally exceeding the 1-hour benchmark.

Our results align with and extend prior neonatal studies reporting attenuated or non-significant associations between antibiotic timing and mortality after adjustment for severity of illness[3, 23, 24]. In contrast to adult sepsis, where each hour of delay has been associated with a clear stepwise increase in mortality [1, 25, 26], neonatal outcomes appear more sensitive to baseline vulnerability and disease phenotype. The slightly higher severity scores observed in the early-treatment group in our cohort further underscore the complexity of confounding by indication: sicker infants may receive antibiotics earlier, potentially biasing unadjusted comparisons toward the null or even reversal of effect.

Importantly, survival analyses revealed significant differences across finer TTA categories, whereas the binary comparison of < 1 hour versus ≥ 1 hour did not. This pattern suggests a non-linear relationship in which extreme delays—particularly beyond 2–3 hours or more than 6 hours—are associated with poorer survival, while smaller deviations around the 1-hour threshold may be clinically less consequential. Such findings challenge the rigid application of adult-derived performance metrics to neonatal care and support a more nuanced interpretation of timing targets [27, 28].

Subgroup analyses did not identify statistically significant effect modification by EOS versus LOS, gestational age strata, or illness severity, although point estimates suggested higher risk among infants with greater baseline severity. The lack of significant interactions may reflect limited power within subgroups or genuine homogeneity of effect across these dimensions. Nevertheless, the directionally consistent findings across sensitivity analyses—including culture-positive cases and exclusion of extremely preterm infants—enhance the robustness of our conclusions.

With respect to secondary outcomes, longer TTA was associated with a small but measurable increase in hospital length of stay, translating to approximately 0.4 additional days per hour of delay. This finding is clinically relevant at a population level and suggests that delayed therapy may prolong recovery even when mortality differences are modest. In contrast, mechanical ventilation duration, secondary infection rates, and composite adverse outcomes did not demonstrate clear linear associations with TTA, indicating that antibiotic timing alone is unlikely to be the dominant driver of these complex outcomes.

Temporal analyses showed progressive improvement in antibiotic timeliness after 2020, with mean TTA consistently near or below 1 hour in later years. Notably, this improvement was not accompanied by a parallel monotonic decline in mortality, further reinforcing the notion that outcomes in neonatal sepsis are multifactorial and influenced by advances in supportive care, infection prevention, and case mix [29–31]. These observations caution against overinterpreting antibiotic timing as a singular quality metric without consideration of broader clinical context.

Several limitations merit consideration. First, the retrospective observational design precludes causal inference, and residual confounding—particularly related to unmeasured aspects of clinical decision-making—cannot be excluded. Second, TTA was derived from registry timestamps and may be subject to measurement error, although standardized data collection across centers mitigates this concern. Third, while the multicenter nature enhances generalizability, participating centers were all tertiary units, and

findings may not extend to lower-resource settings. Finally, we did not adjust for multiple comparisons, and secondary and subgroup analyses should be interpreted as exploratory.

Despite these limitations, our study has notable strengths, including its large sample size, inclusion of both EOS and LOS, granular modeling of TTA as a continuous and categorical exposure, and comprehensive sensitivity analyses. Collectively, the findings suggest that while prompt antibiotic administration remains a cornerstone of neonatal sepsis management, strict adherence to a universal 1-hour threshold may oversimplify a more complex risk landscape. Efforts to minimize extreme delays appear particularly important, whereas marginal delays beyond 1 hour may have limited independent impact after accounting for illness severity.

Future research should prioritize prospective studies and pragmatic trials to better delineate optimal timing strategies tailored to neonatal risk profiles. Integration of antibiotic timing with severity-adjusted decision support tools may offer a more balanced approach, aligning the urgency of treatment with the imperative to avoid unnecessary antibiotic exposure. In the interim, our findings support continued emphasis on timely therapy while encouraging flexibility and clinical judgment in the application of time-based benchmarks for neonatal sepsis.

Conclusion

In a large multicenter cohort of neonates with sepsis, we found that delays in antibiotic initiation were associated with modest increases in mortality and hospital length of stay, although the independent effect of incremental delays was attenuated after adjustment for illness severity and perinatal factors. Survival differences were evident across detailed time-to-antibiotic categories, whereas a simple dichotomization at the 1-hour threshold did not distinguish outcomes. These results indicate that the clinical impact of antibiotic timing in neonatal sepsis is non-linear, with greater risk associated with more substantial delays. Strategies aimed at preventing extreme delays, rather than rigid enforcement of a universal timing cutoff, may better align quality metrics with the complex clinical realities of neonatal sepsis.

Declarations

Conflicts of Interest

The authors declared that they have no conflicts of interest regarding this work.

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Longyan First Affiliated Hospital of Fujian Medical University (approval number: [2024-ETH-017]) and the institutional review boards of all participating centers. Because this was a

retrospective analysis of anonymized data from a routinely collected registry, the requirement for written informed consent was waived by the approving committees.

Funding

Sponsored by Longyan City Science and Technology Plan Project (2024LYF17064)

Author Contribution

Weixiao Hu: Conceptualization, Methodology, Writing - Original Draft, Investigation, Data Curation, Formal Analysis. Zhenhai Qiu: Investigation, Resources, Validation. Dachun Wang: Visualization, Software, Formal Analysis. Li Zhang: Writing - Review & Editing, Investigation. Jie Tong: Writing - Review & Editing, Supervision, Funding Acquisition.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

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Tables

Tables are available in the Supplementary Files section.

Figures

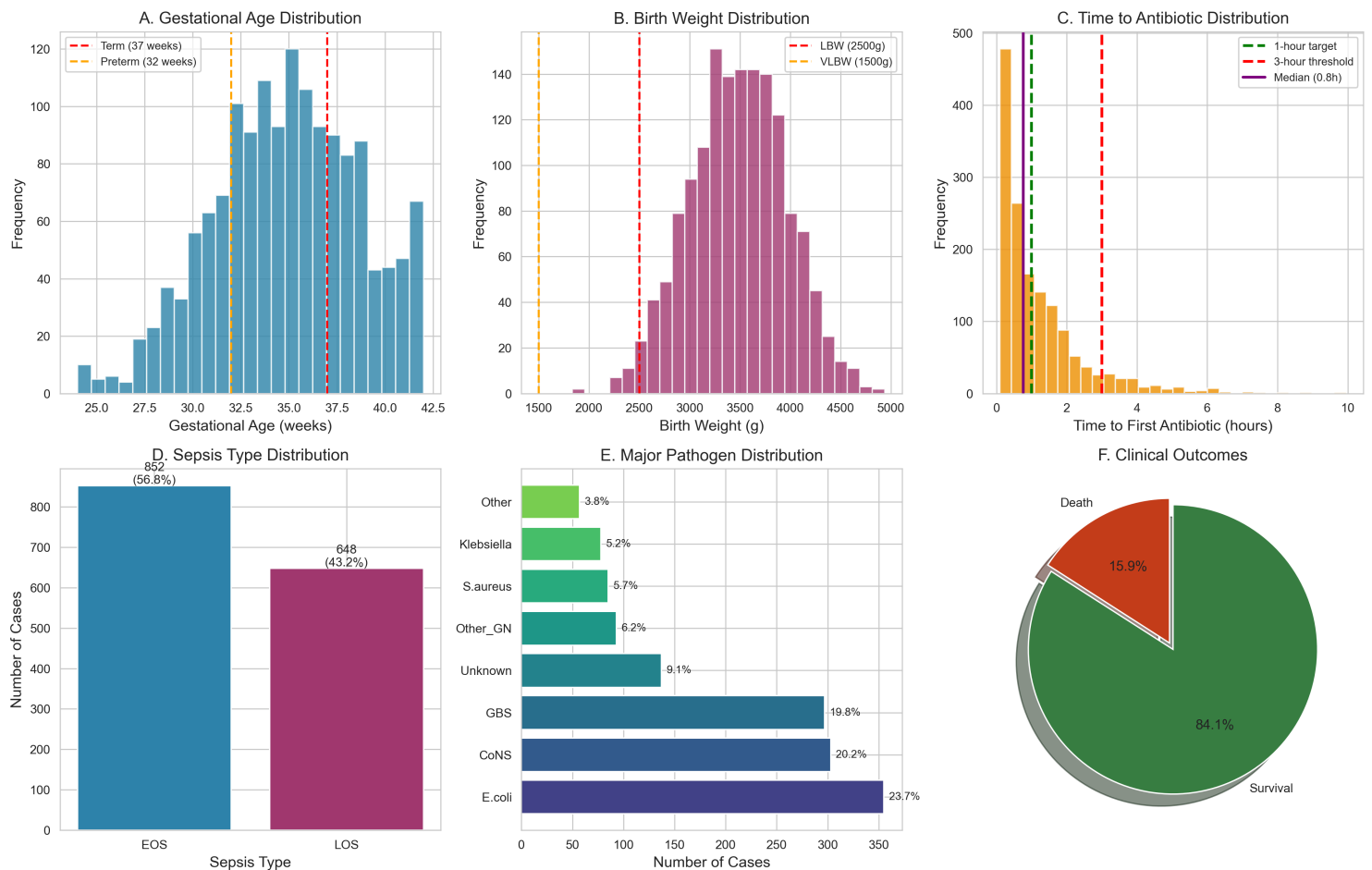


Figure 1

Study population characteristics and distribution of time-to-antibiotic administration (A–F: center distribution, gestational age, birth weight, time-to-antibiotic density, sepsis type, overall mortality)

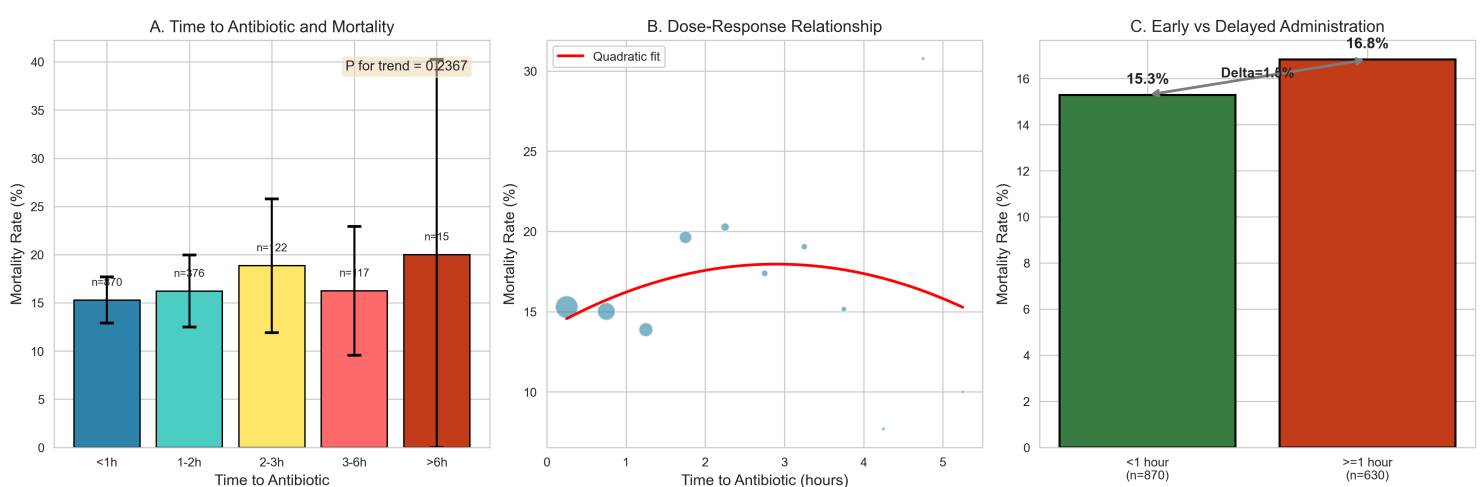


Figure 2

Association between time-to-antibiotic administration and in-hospital mortality (A) Mortality by TTA categories; (B) adjusted odds ratio per 1-hour delay; (C) early (<1 h) versus delayed (≥1 h) comparison

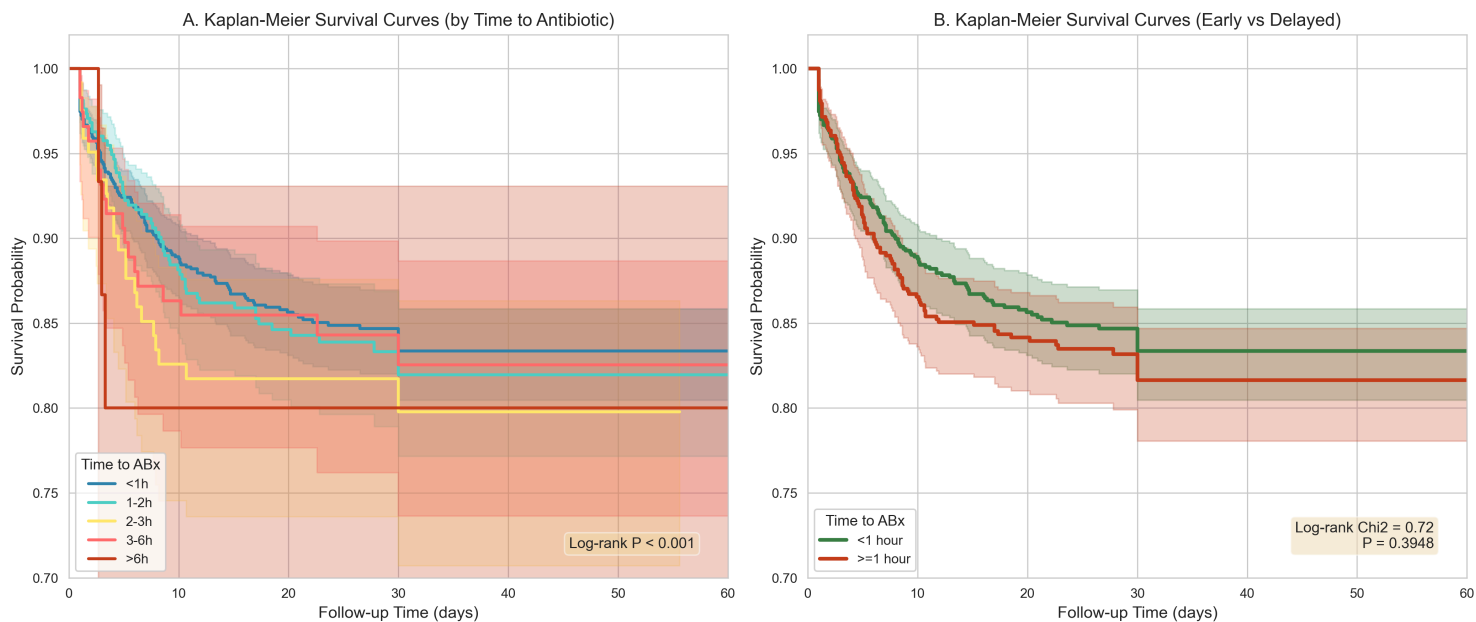


Figure 3

Kaplan–Meier survival curves stratified by time-to-antibiotic administration (A) Multiple TTA categories; (B) early (<1 h) versus delayed (≥ 1 h) administration

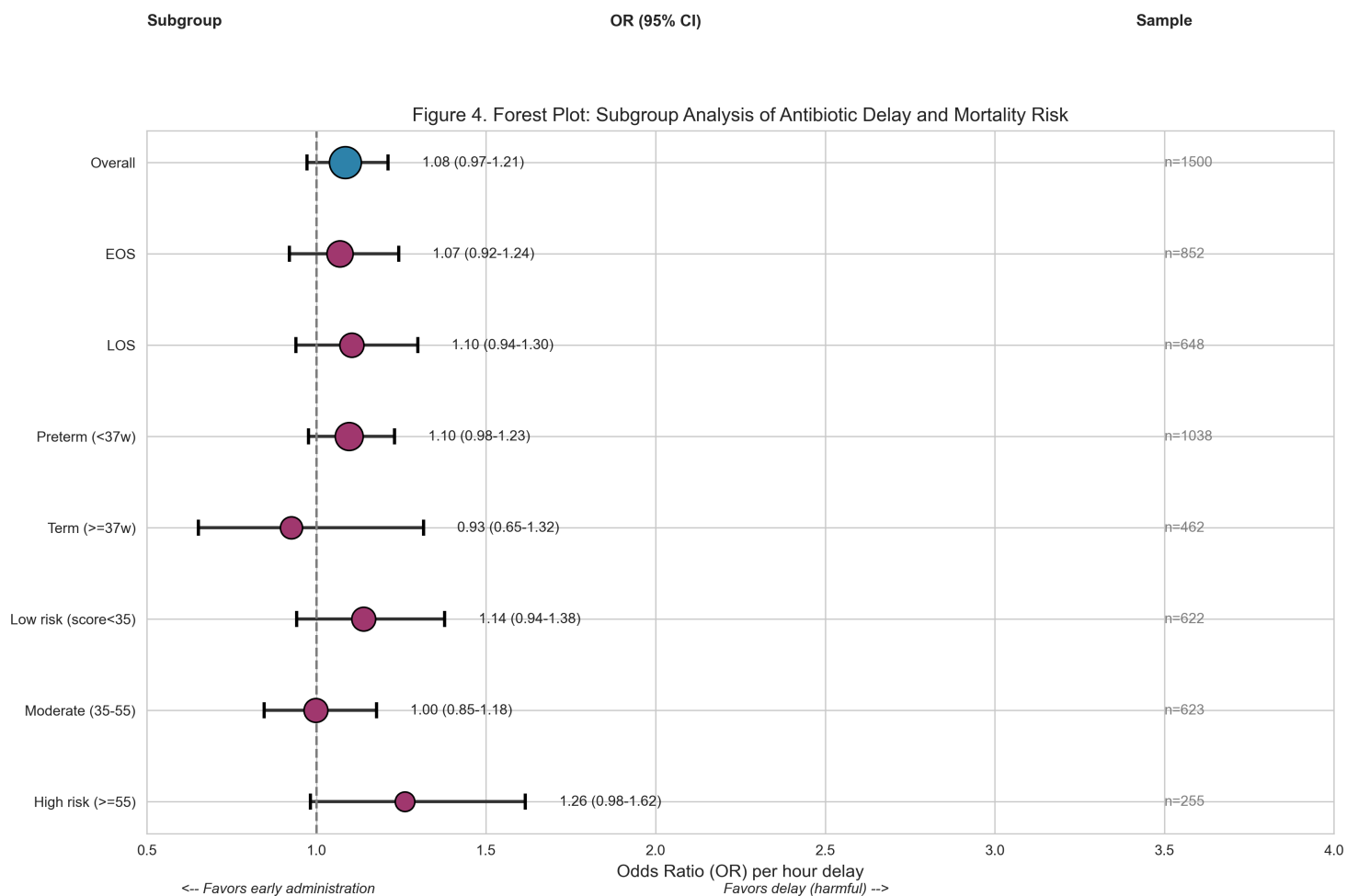


Figure 4

Adjusted associations between time-to-antibiotic delay and mortality across prespecified subgroups and overall population

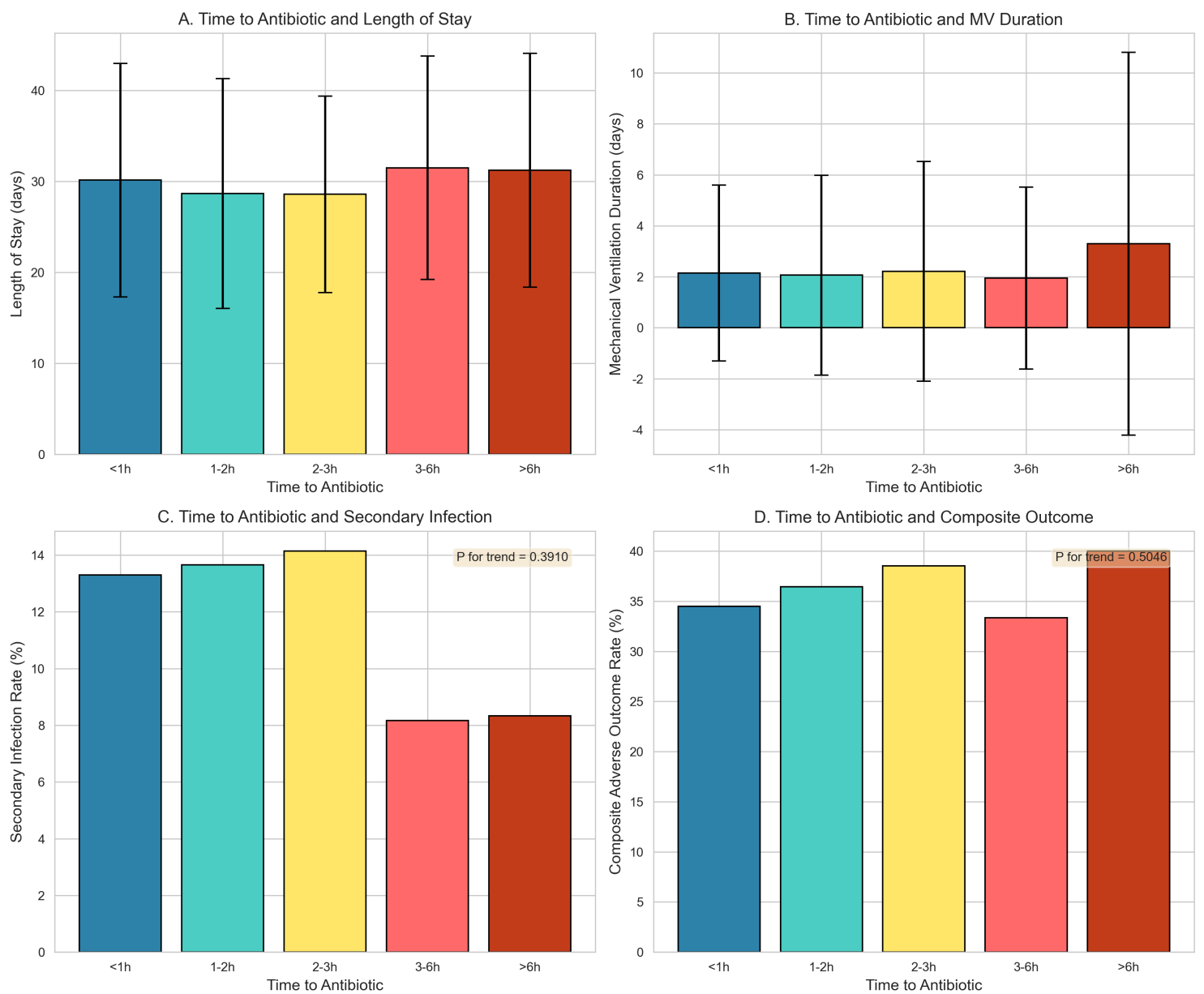


Figure 5

Secondary outcomes according to time-to-antibiotic categories (A) Hospital length of stay; (B) duration of mechanical ventilation; (C) secondary infection; (D) composite adverse outcome

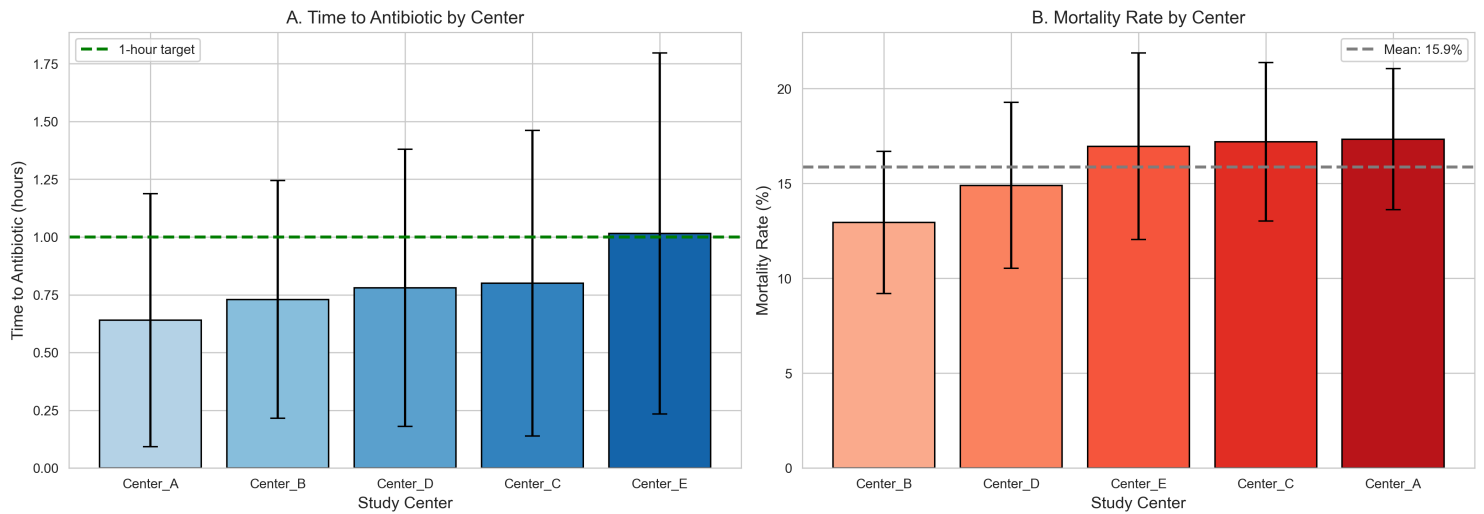


Figure 6

Center-level variation in time-to-antibiotic administration and in-hospital mortality

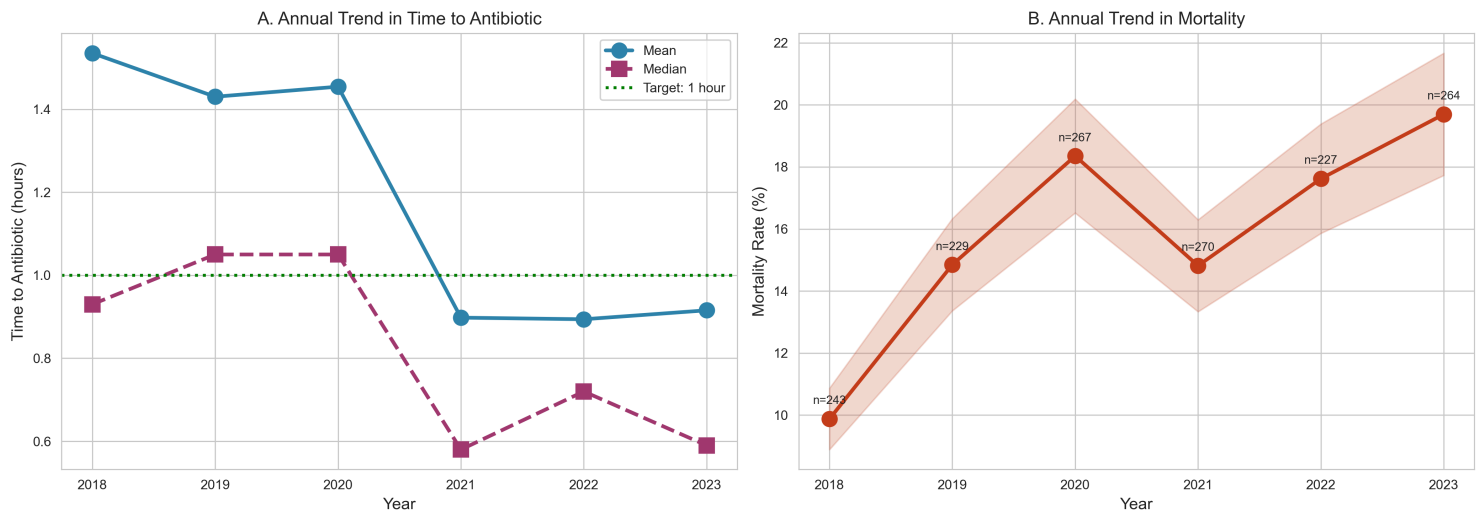


Figure 7

Temporal trends in time-to-antibiotic administration and in-hospital mortality from 2018 to 2023

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [supptable1pathogens.csv](#)
- [supptable2sensitivity.csv](#)
- [table1baselinecharacteristics.csv](#)
- [table2mortalitybytime.csv](#)

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- [table4subgroupanalysis.csv](#)