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Antibiotic trajectories after cardiopulmonary bypass and in-hospital mortality across critical care databases

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Abstract

Background

Antibiotics are frequently administered around cardiopulmonary bypass (CPB), but conventional exposure definitions often reduce timing, antibacterial spectrum and treatment persistence to a single binary variable. This may obscure clinically distinct patterns, such as short perioperative prophylaxis, late escalation and sustained broad-spectrum treatment. We aimed to characterize early post-CPB antibiotic exposure trajectories across multiple critical care databases and examine their association with in-hospital mortality.

Methods

We conducted a retrospective multi-database cohort study of adults with a first extracorporeal circulation event, with mortality modelling focused on CPB patients from MIMIC-IV, INSPIRE and SICdb. Antibiotic records from day 0 to day 7 after CPB were harmonized by generic name, route and antibacterial spectrum. Local topical records were excluded, while inhaled antibiotics were retained. Rule-based trajectories classified patients into short prophylaxis, late escalation, persistent broad-spectrum therapy, early broad-spectrum de-escalation, anti-MRSA therapy without broad-spectrum exposure, persistent narrow-spectrum therapy and limited/no antibiotic exposure. The primary outcome was in-hospital mortality. Multivariable logistic regression was used to estimate associations between antibiotic trajectories and mortality, adjusting for age, sex, data source and source-standardized illness severity. Sensitivity analyses excluded deaths occurring within 48 hours and 72 hours after CPB and used leave-one-database-out validation.

Results

Among 14,966 CPB patients, 450 (3.0%) died before hospital discharge. The severity complete-case model included 14,521 patients and 427 deaths. Adding source-standardized severity to an age-, sex- and source-adjusted model improved apparent discrimination from 0.822 to 0.849 and reduced the Akaike information criterion from 3266.69 to 3117.38. Compared with short prophylaxis, persistent broad-spectrum therapy and late escalation showed the strongest adjusted associations with in-hospital mortality, with adjusted odds ratios of 11.26 (95% CI 7.34 to 17.28) and 10.37 (95% CI 6.99 to 15.38), respectively. These associations persisted after excluding deaths within 48 hours and 72 hours after CPB and remained elevated in leave-one-database-out analyses. In contrast, the association for early broad-spectrum de-escalation attenuated after excluding deaths within 72 hours, suggesting sensitivity to early fatal illness patterns.

Conclusions

In this multi-database cohort of CPB patients, persistent broad-spectrum therapy and late antibiotic escalation during the first postoperative week were reproducible markers of increased in-hospital mortality risk. These trajectories may capture clinically important postoperative states that are not

reflected by binary antibiotic exposure measures. However, because antibiotic trajectories are shaped by evolving infection suspicion, illness severity and postoperative complications, these findings should be interpreted as prognostic and hypothesis-generating rather than causal.

Introduction

Antibiotic treatment after cardiac surgery and CPB sits between two clinical imperatives: preventing procedure-related infection and avoiding unnecessary antimicrobial exposure. Perioperative prophylaxis is expected to be short, but postoperative instability, suspected infection, organ failure and reoperation can lead to broad-spectrum initiation, escalation or prolonged therapy. A single binary variable for any antibiotic use cannot distinguish these clinically different patterns [1-5].

Most retrospective database analyses also face a measurement problem. Antibiotic records are stored in different medication systems, routes and timing formats, while severity scores differ across databases. As a result, comparing post-CPB antibiotic exposure across cohorts requires not only drug-name normalization but also an exposure representation that preserves timing and spectrum without overfitting to one database's documentation style. This challenge is particularly important for multi-database analyses, where source composition can influence both treatment patterns and outcomes [6-9].

Trajectory-based exposure definitions provide a practical response to this problem. Instead of treating antibiotic exposure as a static covariate, a trajectory framework can separate early narrow prophylaxis from late broad-spectrum escalation, persistent broad-spectrum treatment and early de-escalation. These patterns are clinically interpretable, compatible with antimicrobial stewardship concepts and suitable for patient-level modelling. However, such trajectories need to be checked against daily exposure patterns and tested for stability across databases, because a strong pooled association may reflect source-specific practice rather than a reproducible clinical signal [10-14].

Here we built a multi-database CPB cohort from MIMIC-IV, INSPIRE and SICdb, with ECMO described in the parent extracorporeal cohort but excluded from mortality modelling because of sparse sample size. We extracted raw antibiotic records, excluded local topical exposure while retaining inhaled antibiotics, and created day 0-7 spectrum-based trajectories. We then evaluated the association between antibiotic trajectories and in-hospital mortality using source-adjusted and severity-adjusted logistic models, early-death exclusion, leave-one-database-out analyses and source-specific models. The central question was not whether antibiotics cause mortality, but whether post-CPB antibiotic trajectories can serve as reproducible risk markers across heterogeneous critical care databases.

Methods

Study design and data sources

We conducted a retrospective multi-database cohort study of adults receiving extracorporeal circulation. The source databases were MIMIC-IV, INSPIRE, SICdb and NWICU. Source-specific SQL queries identified

candidate CPB and ECMO events from procedure codes, operation records, procedure-event tables or device-related bedside records, depending on the structure of each database. The first qualifying extracorporeal event per patient was retained to avoid repeated-patient clustering and to define a single index time for antibiotic exposure assessment [6-8].

The first-event extracorporeal cohort contained 15,332 patients after eligibility filtering: 14,966 CPB patients and 366 ECMO patients. Because ECMO patients were few and trajectory categories were sparse, the current mortality analysis was restricted to CPB patients from MIMIC-IV, INSPIRE and SICdb. NWICU contributed ECMO patients only and was therefore not included in the CPB mortality models.

Cohort construction

Patients were eligible if they were aged 18 years or older, had a qualifying extracorporeal circulation event during the hospital admission and had a hospital length of stay greater than 24 hours. For MIMIC-IV, CPB was identified from ICD procedure codes (3961, 3966, 5A1221Z, 5A1221J), and ECMO was identified from ICD procedure codes or ICU procedure/chartevent items labelled as ECMO or extracorporeal membrane oxygenation. For INSPIRE, CPB was identified by non-missing and ordered CPB on/off times in the operation table. For SICdb, CPB was identified by positive heart surgery CPB duration, and ECMO was identified from ECMO pump, flow or FIO2 records. For NWICU, ECMO was identified from ICU procedure events labelled as ECMO or extracorporeal membrane oxygenation.

Within each database, all candidate events were enriched with admission timing, discharge timing, age, sex, hospital mortality and available ICU-stay information. Events were required to fall within the hospital admission when timestamp information was available. When more than one qualifying event was found for a patient, the earliest eligible event was retained.

Antibiotic extraction and classification

Antibiotic records were extracted from source-specific medication tables for the first-event extracorporeal cohort. Raw drug name, raw drug code, route, start time and stop time were preserved. Medication timing was converted to hours relative to the extracorporeal index time where possible. The raw extraction yielded 189,368 antibiotic-related medication rows. Classification retained the raw rows and added normalized generic drug names, antibacterial class, subclass, cephalosporin generation, route category and spectrum flags [10,15,16].

Drug normalization used a combined rule-based and ATC-informed approach. ATC J01 codes were used where available to support antibacterial class assignment. Name-based rules were used to standardize common generic names and combinations, including beta-lactam/beta-lactamase inhibitor combinations, cephalosporins, carbapenems, fluoroquinolones, glycopeptides, oxazolidinones, aminoglycosides, polymyxins, nitroimidazoles, macrolides, tetracyclines and other systemic antibacterial agents. Inactive combination components, such as tazobactam, sulbactam, clavulanate and cilastatin, were not counted as antibacterial agents by themselves.

Antibiotic spectrum indicators were prespecified. Broad-spectrum agents included antipseudomonal penicillins or beta-lactam/beta-lactamase inhibitor combinations, selected third-generation or later cephalosporins, carbapenems, aztreonam, fluoroquinolones, tigecycline and polymyxins. Separate indicators were generated for carbapenem, anti-MRSA, antipseudomonal and anaerobic coverage.

Route classification identified systemic, inhaled, local and unknown routes. Local topical records were excluded from the analytic exposure dataset, including ophthalmic, nasal, external and lock-route medications. Inhaled antibiotics were retained. After excluding local topical records, 179,746 medication rows remained for trajectory construction.

Antibiotic trajectory construction

The extracorporeal event defined day 0. Patient-day antibiotic features were generated from day -1 through day 7 relative to index. Day 0 represented 0-24 hours after index, day 1 represented 24-48 hours, and so on. A medication record was considered active on a patient-day when its start-stop interval overlapped that day; records with identical start and stop times were treated as point exposures on the corresponding day [12,13]. Trajectory assignment used all antibiotic records available within the day 0-7 window; for patients who died or were discharged before day 7, the trajectory therefore reflects the observed portion of that window.

For each patient-day, the pipeline created indicators for any systemic or inhaled antibacterial exposure, any inhaled antibacterial exposure, any broad-spectrum exposure, any carbapenem exposure, any anti-MRSA exposure, any antipseudomonal exposure and any anaerobic coverage. Patient-level features summarized exposure during 0-24 hours, 0-48 hours, 0-72 hours and 0-7 days after index.

The primary trajectory categories were rule-based and clinically prespecified: no antibiotic exposure from day 0 to day 7; short prophylaxis; late escalation; persistent broad-spectrum therapy; early broad-spectrum de-escalation; anti-MRSA therapy without broad-spectrum exposure; persistent narrow-spectrum therapy; limited narrow-spectrum exposure; and other antibiotic patterns.

The 0-48 hour definition of short prophylaxis was selected as the primary reference category because it is clinically compatible with perioperative cardiac-surgery prophylaxis and preserved a stable reference group. An exploratory 24 hour sensitivity definition, requiring day-0-only narrow exposure and no active exposure on days 1-7, was generated but was not selected as primary because it reduced the short-prophylaxis group to 120 patients [1,2,17,18].

Baseline covariates

Baseline covariates were extracted with source-specific SQL queries and merged one-to-one with the trajectory dataset by source database, patient identifier and admission identifier. Demographic covariates included age and sex. Clinical severity variables differed by source because each database captured different validated or operational scores. The primary severity score was first ICU day SOFA for MIMIC-IV,

ASA physical status for INSPIRE and SAPS3 for SICdb. NWICU had no populated formal severity score in the available local tables [19-21].

Because SOFA, ASA and SAPS3 are not exchangeable raw scales, the primary pooled models used a within-source and within-modality standardized severity score. This z score was calculated from the source-specific primary severity score within each source database and modality. The standardized score preserves local severity ranking while avoiding interpretation of raw SOFA, ASA and SAPS3 as a single common metric.

Additional source-specific covariates were extracted where available, including Charlson comorbidity index, body mass index, emergency surgery, admission urgency, sepsis on admission, CPB duration, aortic cross-clamp duration, baseline mechanical ventilation, vasopressor exposure and renal replacement therapy. Missingness was summarized by source and trajectory. The primary pooled mortality model used complete cases for the source-standardized severity score.

Outcome

The primary outcome was in-hospital mortality. Hospital death was derived from each source database's admission, patient or case death fields. For early-death sensitivity analyses, time from index to death was calculated from timestamp differences where available and from source-specific offset differences for INSPIRE and SICdb. MIMIC-IV CPB index timing was based on ICD procedure date and is therefore day-level approximate for CPB timing analyses.

Statistical analysis

The primary analysis estimated the association between antibiotic trajectory and in-hospital mortality among CPB patients. Logistic regression was used with short prophylaxis as the reference trajectory. The primary enhanced pooled model adjusted for age per 10 years, sex, source database and source-standardized severity score. Model outputs included adjusted odds ratios, 95% confidence intervals, Wald P values, sample size, deaths, events per parameter, apparent area under the receiver operating characteristic curve and AIC.

AUC was calculated by a rank-based estimator from fitted probabilities. AIC comparisons were treated as directly interpretable only when models used the same analytic sample. Specifically, AIC was compared between the minimal complete-case model and the enhanced core model; AIC values from early-death exclusion or leave-one-database-out analyses were retained only as descriptive diagnostics because the samples differed. Reported AUC values are apparent; they were not internally validated or optimism-corrected and should be interpreted as within-sample model comparisons rather than as estimates of external discrimination.

The model sequence included a minimal full-sample model adjusted for age, sex and source database; a minimal severity complete-case model using the same sample as the enhanced core model; the enhanced core model adding source-standardized severity; and a body-mass-index complete-case

sensitivity model adding BMI per 5 kg/m2. The enhanced core model included 14,521 CPB patients and 427 in-hospital deaths. Robustness of the principal trajectory associations to unmeasured confounding was summarized with E-values, computed on the risk-ratio scale after square-root conversion of the odds ratio [22].

Sensitivity and source-specific analyses

To assess reverse-causation risk from incomplete antibiotic trajectories among patients who died early after index, the enhanced core model was repeated after excluding known deaths within 48 hours and within 72 hours of index. These analyses were interpreted as sensitivity analyses because exclusions changed the risk set and outcome event count.

To evaluate database influence, the enhanced core model was repeated after excluding one source database at a time. Leave-one-database-out AIC values were considered descriptive only because the analyzed samples differed. Stability of the main trajectory signals was evaluated by comparing adjusted odds ratios across the full pooled model and each leave-one-database-out scenario.

Source-specific models were also fitted for MIMIC-IV, INSPIRE and SICdb. Because full categorical trajectory models within individual sources were sparse, source-specific analyses used one binary exposure at a time for key trajectory or exposure signals: persistent broad-spectrum trajectory, late escalation, early broad de-escalation, any broad-spectrum exposure during 0-48 hours, any carbapenem exposure during 0-7 days and any anti-MRSA exposure during 0-7 days.

All analyses were interpreted as adjusted associations rather than causal effects because antibiotic trajectories may reflect infection severity, clinician concern, postoperative complications and other sources of confounding by indication. More formally, the day 0-7 trajectory was analysed as a descriptive post-CPB exposure summary and a candidate prognostic marker, not as a baseline predictor or a causal treatment effect; the reported associations therefore describe how antibiotic management over the first postoperative week tracks with in-hospital mortality and should not be read as the effect of initiating or continuing broad-spectrum therapy.

Results

Study cohort and antibiotic trajectory distribution

We identified 14,966 adult patients who underwent a first CPB event and had a hospital stay longer than 24 h across MIMIC-IV, INSPIRE and SICdb. The cohort was dominated by MIMIC-IV (10,352 patients, 69.2%), with additional patients from INSPIRE (2,413, 16.1%) and SICdb (2,201, 14.7%). The median age was 68.0 years (IQR 60.0-75.0), 4,481 patients (29.9%) were female and 450 patients (3.0%) died before hospital discharge (**Table 1**).

Antibiotic exposure during the first 7 days after CPB separated into distinct treatment trajectories. Anti-MRSA use without concurrent broad-spectrum therapy was the largest group (5,052 patients, 33.8%),

followed by short prophylaxis (3,490, 23.3%) and persistent narrow-spectrum therapy (2,921, 19.5%). The main broad-spectrum trajectory groups were late escalation (1,243, 8.3%), persistent broad-spectrum therapy (882, 5.9%) and early broad-spectrum de-escalation (409, 2.7%). A further 891 patients (6.0%) received no systemic or inhaled antibacterial therapy from day 0 to day 7, and 78 (0.5%) had limited narrow-spectrum exposure. No patients met the residual “other” trajectory definition, so this category is not reported separately.

Baseline profile across antibiotic trajectories

Baseline characteristics differed across antibiotic trajectories. Compared with the short-prophylaxis group, patients receiving persistent broad-spectrum therapy or late escalation had higher source-standardized severity scores (median z score 0.45 in both groups versus -0.11 for short prophylaxis) and longer hospital stays (median 17.7 and 17.8 days versus 8.4 days). Crude in-hospital mortality was also higher in the persistent broad-spectrum and late-escalation groups (90 of 882, 10.2%; and 137 of 1,243, 11.0%, respectively) than in the short-prophylaxis group (42 of 3,490, 1.2%). Source composition varied by trajectory: INSPIRE contributed 34.5% of persistent broad-spectrum cases but only 13.9% of short-prophylaxis cases, whereas SICdb contributed 29.9% of short-prophylaxis cases but 6.0% of persistent broad-spectrum cases. These imbalances motivated severity-adjusted, source-adjusted and source-stratified analyses.

Daily exposure patterns support the trajectory definitions

Daily exposure profiles showed that the trajectory labels captured distinct antibiotic timing patterns (**Fig. 1**). In the short-prophylaxis group, broad-spectrum exposure remained 0% from day 0 through day 7, while systemic or inhaled antibacterial exposure was concentrated on days 0-1. In the persistent broad-spectrum group, broad-spectrum exposure was already common on day 0 (78%), peaked on day 2 (95%) and remained present in 48% of patients by day 7. Late escalation showed the opposite timing pattern, with no broad-spectrum exposure on days 0-1, followed by a rise from day 2 (32%) to day 7 (68%). Early broad-spectrum de-escalation was characterized by high day-0 broad-spectrum exposure (91%) followed by rapid decline by day 2 (5%) and near absence thereafter.

Enhanced mortality model performance

ECMO patients were not included in mortality modelling because the ECMO stratum was small and trajectory categories were sparse. The primary CPB enhanced model used the severity complete-case sample (14,521 patients; 427 deaths) and adjusted for antibiotic trajectory, age, sex, source database and source-by-modality standardized severity. Adding severity improved apparent discrimination from 0.822 in the same-sample minimal model to 0.849 in the enhanced model, with a lower AIC (3266.69 to 3117.38; **Fig. 2**). The severity-adjusted model retained adequate events per parameter (32.85), supporting its use as the primary model.

Antibiotic trajectories and in-hospital mortality

In the primary enhanced model, persistent broad-spectrum therapy and late escalation were the two strongest trajectory-level associations with in-hospital mortality, using short prophylaxis as the reference. Persistent broad-spectrum therapy was associated with an aOR of 11.26 (95% CI 7.34-17.28; 86 deaths among 851 patients in the model sample), and late escalation with an aOR of 10.37 (95% CI 6.99-15.38; 133 deaths among 1,200 patients). Early broad-spectrum de-escalation was also associated with mortality in the primary model (aOR 4.89, 95% CI 2.62-9.15), but this group had fewer events and required sensitivity analyses to assess the contribution of early postoperative deaths. Other non-reference trajectory groups showed smaller but still elevated associations, including anti-MRSA without broad-spectrum therapy (aOR 1.86, 95% CI 1.18-2.94), persistent narrow-spectrum therapy (aOR 1.80, 95% CI 1.20-2.71), no antibiotic exposure from day 0 to day 7 (aOR 3.88, 95% CI 2.24-6.71) and limited narrow-spectrum exposure (aOR 5.50, 95% CI 1.62-18.61; sparse, 3 deaths). The elevated estimate in the no-antibiotic group is unlikely to indicate harm from withholding antibiotics; it more plausibly reflects a prognostically distinct subset, including very early deaths preceding any antibiotic order, end-of-life care and incomplete medication capture.

Sensitivity analyses and source influence

The associations for persistent broad-spectrum therapy and late escalation were robust to early-death exclusion (**Fig. 3**). After excluding deaths within 48 h of the index event, the aORs were 15.55 (95% CI 9.63-25.12) for persistent broad-spectrum therapy and 14.49 (95% CI 9.24-22.72) for late escalation. After excluding deaths within 72 h, the corresponding aORs were 16.52 (95% CI 10.05-27.15) and 16.09 (95% CI 10.10-25.63). In contrast, the early broad-spectrum de-escalation association attenuated after early-death exclusion: the aOR decreased to 2.62 (95% CI 1.05-6.54) after excluding deaths within 48 h and to 1.00 (95% CI 0.23-4.29) after excluding deaths within 72 h, with fewer than 10 deaths remaining in the exposure group.

Leave-one-database-out analyses supported the stability of the persistent broad-spectrum and late-escalation signals(**Fig. 4**). Persistent broad-spectrum therapy remained associated with mortality after excluding MIMIC-IV (aOR 8.18, 95% CI 4.90-13.68), INSPIRE (aOR 8.93, 95% CI 5.41-14.74) or SICdb (aOR 21.81, 95% CI 10.40-45.76). Late escalation showed a similar pattern, with aORs of 5.64 (95% CI 3.55-8.96), 10.46 (95% CI 6.77-16.17) and 21.57 (95% CI 10.40-44.73), respectively. The larger estimates after excluding SICdb indicate that SICdb had a moderating influence on the pooled estimates, consistent with the source-specific analyses. Leave-one-database-out and source-specific estimates are not directly comparable in magnitude because they use different adjustment sets (minimal source-standardized adjustment versus richer source-specific covariates); the larger estimate after excluding SICdb is consistent with the near-null late-escalation association observed within SICdb diluting the pooled estimate.

Source-specific models further clarified transportability(**Fig. 5**). Persistent broad-spectrum therapy showed directionally consistent associations in all three databases and was significant in MIMIC-IV (aOR 3.33, 95% CI 2.09-5.32) and INSPIRE (aOR 2.80, 95% CI 1.76-4.44), but was imprecise in SICdb (aOR 1.44, 95% CI 0.63-3.30). Late escalation was strongly associated with mortality in MIMIC-IV (aOR 7.36, 95% CI

5.06-10.71), borderline in INSPIRE (aOR 1.55, 95% CI 0.98-2.47) and null in SICdb after adjustment (aOR 0.93, 95% CI 0.52-1.64). Early broad-spectrum de-escalation was not stable in source-specific models and was sparse across databases, supporting its interpretation as a sensitivity finding rather than a primary trajectory signal.

Taken together, these analyses identify persistent broad-spectrum therapy and late escalation as the most reproducible antibiotic trajectory signals associated with in-hospital mortality after CPB. The findings are associations rather than causal effects and remain vulnerable to confounding by indication, infection severity and postoperative complications, but their consistency across complementary sensitivity analyses supports their use as descriptive risk markers in this multi-database cohort.

Discussion

This multi-database study shows that early post-CPB antibiotic exposure can be represented as clinically interpretable trajectories and that two broad-spectrum patterns, persistent broad-spectrum therapy and late escalation, are reproducibly associated with in-hospital mortality. The main contribution is not a new claim that antibiotics directly increase mortality, but a data structure for separating short prophylaxis from sustained or delayed broad-spectrum treatment across heterogeneous clinical databases [10-12].

The strongest finding was the stability of the persistent broad-spectrum and late-escalation signals. Both trajectories had higher crude mortality than short prophylaxis, remained strongly associated with mortality after adjustment for source and source-standardized severity, and stayed elevated after excluding deaths within 48 h or 72 h. This robustness argues that these patterns are not merely artefacts of very early deaths truncating antibiotic observation. Clinically, persistent broad-spectrum therapy may mark patients with ongoing infection concern, prolonged instability or complex postoperative courses, whereas late escalation may mark a transition from expected perioperative care to suspected postoperative deterioration [4,5,23-26].

The attenuation of early broad-spectrum de-escalation after excluding deaths within 72 h is important for interpretation. In the main model, early broad-spectrum de-escalation appeared associated with mortality, but the signal disappeared after removing early deaths and became sparse. This pattern is consistent with reverse causation or early fatal illness: some patients may receive broad empirical therapy immediately because they are already critically ill and then die before a full 7-day trajectory can form. For this reason, early broad-spectrum de-escalation should remain a sensitivity finding rather than a primary risk marker [13,14,27-30].

Because trajectory classification requires observation across the postoperative week, very early deaths could in principle truncate trajectory assignment and raise the possibility of immortal-time or time-alignment bias. The 48-hour and 72-hour early-death exclusions function as approximate landmark analyses for this concern: the persistent broad-spectrum and late-escalation associations were unchanged or strengthened, whereas the early broad-spectrum de-escalation association attenuated to the null. The de-escalation result behaves as expected for a reverse-causation artefact and serves as an

internal falsification check, indicating that these sensitivity analyses can detect and remove such artefacts when they are present; the stability of the two broad-spectrum signals under the same procedure therefore argues against an immortal-time or early-death explanation. The increase in odds ratios after early-death exclusion partly reflects the preferential removal of early deaths from lower-risk reference groups, and a formal day-7 landmark or time-varying exposure model was not implemented, so residual time-alignment bias cannot be fully excluded; landmark and time-dependent analyses are a priority for future work.

The modelling strategy also highlights a practical issue in multi-database critical care research. Severity information was available in different forms across sources: SOFA in MIMIC-IV, ASA physical status in INSPIRE and SAPS3 in SICdb. Treating these raw scales as interchangeable would be clinically and statistically difficult. Source-by-modality standardization provided a pragmatic pooled adjustment strategy, and adding this standardized severity measure improved model discrimination and AIC within the same complete-case sample. Nevertheless, this approach assumes that one local standard deviation has comparable prognostic meaning across sources, an assumption that should be tested in future external validation [19-21].

Source-specific analyses indicate that trajectory associations were not fully uniform. Persistent broad-spectrum therapy was directionally consistent across all databases and significant in MIMIC-IV and INSPIRE, whereas late escalation was strongest in MIMIC-IV, borderline in INSPIRE and null in SICdb after source-specific adjustment. This heterogeneity may reflect differences in surgical populations, documentation, antimicrobial practice, baseline severity measurement or timing precision. It supports reporting pooled estimates together with source-specific and leave-one-database-out diagnostics rather than relying only on a single pooled model [6-9].

Several limitations define the scope of the findings. First, the study is observational, and antibiotic trajectories are likely confounded by indication, suspected infection, culture results, clinician concern, reoperation, shock, organ failure and other postoperative complications. Second, the exposure model used drug names, routes and spectrum flags, but did not incorporate dose, therapeutic drug monitoring, microbiology, appropriateness of therapy or time-varying clinical indications. Third, the databases differed in timing precision and covariate availability; for example, MIMIC-IV CPB timing was based on ICD procedure date, and CPB duration was unavailable there. Fourth, ECMO was excluded from mortality modelling because the available sample was too small for stable trajectory models. Finally, the trajectory definitions were clinically informed and reproducible, but still rule-based; future work should compare them with data-driven trajectory models and stewardship-oriented spectrum scores [10-12].

To quantify how susceptible the principal findings are to unmeasured confounding, E-values were calculated for the two main signals after square-root conversion of the odds ratio. An unmeasured confounder would need to be associated with both antibiotic trajectory and mortality by a risk ratio of approximately 6.2 for persistent broad-spectrum therapy and 5.9 for late escalation, and of approximately 4.9 and 4.7 respectively to move the lower confidence limits to the null, to fully explain the observed

associations. Confounders of this strength would have to exceed the prognostic contribution of the measured severity scores, suggesting the two broad-spectrum signals are unlikely to be entirely attributable to unmeasured confounding, although confounding by indication remains the most important limitation.

These limitations do not weaken the descriptive value of the trajectory framework, but they set boundaries around interpretation. Persistent broad-spectrum therapy and late escalation should be understood as post-CPB risk markers that identify patients with high mortality risk and complex clinical courses. The next analytic step is to incorporate infection diagnoses, microbiology, postoperative complications and time-varying severity to separate treatment response, clinical deterioration and confounding by indication.

Conclusion

This study addresses the measurement of post-CPB antibiotic exposure by converting heterogeneous medication records into clinically interpretable day 0-7 trajectories. Across three CPB data sources, persistent broad-spectrum therapy and late escalation were the most reproducible trajectory markers associated with in-hospital mortality after adjustment for age, sex, source database and source-standardized severity. The findings support trajectory-based antibiotic exposure as a descriptive risk stratification tool for multi-database critical care research, but they should not be interpreted as causal treatment effects. Future analyses should incorporate infection diagnoses, microbiology, postoperative complications and time-varying severity to distinguish antimicrobial response, clinical deterioration and confounding by indication.

Declarations

Ethics approval and consent to participate

All critical-care databases analyzed in this study are de-identified and publicly available to credentialed researchers through PhysioNet (https://physionet.org). The project was approved by the Institutional Review Boards of Beth Israel Deaconess Medical Center (BIDMC) and the Massachusetts Institute of Technology (MIT). The waiver of informed consent was approved by the Institutional Review Board of BIDMC due to the de-identification of all protected health information. One author (Z.F., Zhao-kun Fan) completed the online course on Data or Specimens Only Research and gained access to the database for data extraction after passing the Collaborative Institutional Training Initiative (CITI) exam (Record ID: 74444440).

Consent for publication

Not applicable.

Availability of data and materials

This study was based on four publicly available or access-controlled de-identified clinical databases: MIMIC-IV, INSPIRE, the Salzburg Intensive Care database (SICdb), and the Northwestern ICU database (NWICU). MIMIC-IV, SICdb, and NWICU can be accessed through PhysioNet after completion of the required training, credentialing procedures, and data use agreements, where applicable. INSPIRE is a publicly available perioperative medicine dataset. The authors do not have permission to redistribute the original patient-level data. The derived analytic code, cohort-selection algorithms, antibiotic-exposure definitions, outcome definitions, and variable-harmonization table are provided in the Supplementary Material and are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Clinical trial number

Not applicable.

Authors' contributions

Z.F. and Y.S. conceptualized the study. Z.F. designed the analytical framework, extracted the data, performed the statistical analyses, and drafted the manuscript. D.Z. and R.Y. contributed to antibiotic exposure harmonization, trajectory classification, and validation of the analytic dataset. W.C. and C.L. contributed to cohort construction, database-specific variable checking, and clinical interpretation of the findings. Z.Z. and D.Z. contributed to figure preparation, result verification, and manuscript revision. Y.S. supervised the study and critically revised the manuscript for important intellectual content. All authors reviewed and approved the final version of the manuscript.(Z.F., Zhao-kun Fan; Y.S., Ying-ying Shen; D.Z., Ding Zhang; R.Y., Ru-qin Yi; W.C., Wei Chen; C.L., Cheng-en Li; Z.Z., Zhi-rong Zhang.)

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Table

Table 1 | Baseline characteristics of cardiopulmonary bypass patients by antibiotic trajectory

Characteristic	Overall n=14,966	Short prophylaxis n=3,490	Persistent broad-spectrum n=882	Late escalation n=1,243	Early broad de-escalation n=409	Other trajectories n=8,942
Demographics and anthropometry						
Age, years	68.0 [60.0, 75.0]	67.0 [60.0, 75.0]	66.0 [57.2, 75.0]	70.0 [60.0, 75.0]	70.0 [60.0, 76.0]	67.0 [60.0, 75.0]
Female sex	4,481 (29.9)	916 (26.2)	356 (40.4)	401 (32.3)	212 (51.8)	2,596 (29.0)
Body-mass index, kg/m²	27.6 [24.2, 31.5]	27.4 [24.2, 31.0]	25.7 [22.2, 30.7]	26.8 [22.9, 31.5]	27.5 [23.4, 31.4]	27.9 [24.7, 31.9]
Illness severity						
Source-standardized severity, z	−0.09 [−0.82, 0.45]	−0.11 [−0.82, 0.45]	0.45 [−0.50, 1.00]	0.45 [−0.45, 1.00]	0.28 [−0.82, 0.64]	−0.09 [−0.82, 0.45]
SOFA score (MIMIC-IV)	5.0 [3.0, 7.0]	5.0 [3.0, 6.0]	6.0 [3.0, 8.0]	6.0 [4.0, 9.0]	5.0 [3.0, 8.0]	5.0 [3.0, 7.0]
ASA physical status (INSPIRE)	3.0 [2.0, 3.0]	3.0 [2.0, 3.0]	3.0 [2.0, 3.0]	3.0 [2.0, 3.0]	3.0 [2.0, 3.0]	3.0 [2.0, 3.0]
SAPS3 score (SICdb)	43.0 [37.0, 50.0]	40.0 [35.0, 46.0]	57.0 [46.0, 66.0]	53.0 [46.0, 62.0]	44.5 [40.8, 57.2]	44.0 [38.0, 51.0]
Procedure						
Cardiopulmonary bypass duration, min	155 [108, 210]	125 [92, 175]	220 [165, 270]	205 [155, 265]	186 [125, 228]	155 [112, 207]
Aortic cross-clamp duration, min	70 [51, 97]	65 [48, 89]	108 [78, 138]	91 [60, 124]	68 [55, 113]	72 [52, 100]
Hospital course						
Hospital length of stay, days	9.1 [6.1, 14.7]	8.4 [5.6, 13.0]	17.7 [10.8, 31.0]	17.8 [10.8, 29.8]	10.1 [7.6, 14.6]	8.7 [5.9, 13.0]
ICU length of stay, days	2.0 [1.2, 3.3]	1.8 [1.2, 3.0]	3.4 [1.7, 6.8]	4.5 [1.9, 8.9]	2.1 [1.3, 3.4]	1.6 [1.2, 3.0]
Peri-operative and clinical status						
Emergency surgery (INSPIRE)	258 (10.7)	23 (4.7)	99 (32.6)	29 (7.8)	12 (14.8)	95 (8.1)

Elective admission (SICdb)	1,478 (67.2)	772 (74.1)	25 (47.2)	82 (55.4)	9 (50.0)	590 (62.8)
Urgent admission (SICdb)	290 (13.2)	74 (7.1)	13 (24.5)	29 (19.6)	3 (16.7)	171 (18.2)
Sepsis on admission (SICdb)	30 (1.4)	6 (0.6)	7 (13.2)	3 (2.0)	3 (16.7)	11 (1.2)
Baseline mechanical ventilation	7,530 (75.8)	1,384 (72.7)	357 (70.7)	554 (80.9)	226 (76.4)	5,009 (76.5)
Baseline vasopressor exposure	6,539 (65.8)	990 (52.0)	328 (65.0)	491 (71.7)	209 (70.6)	4,521 (69.0)
Renal replacement therapy	274 (2.3)	22 (0.7)	25 (4.5)	80 (9.6)	9 (2.9)	138 (1.8)
Data source						
MIMIC-IV	10,352 (69.2)	1,962 (56.2)	525 (59.5)	721 (58.0)	310 (75.8)	6,834 (76.4)
INSPIRE	2,413 (16.1)	486 (13.9)	304 (34.5)	374 (30.1)	81 (19.8)	1,168 (13.1)
SICdb	2,201 (14.7)	1,042 (29.9)	53 (6.0)	148 (11.9)	18 (4.4)	940 (10.5)
Outcome						
In-hospital death	**450 (3.0)**	**42 (1.2)**	**90 (10.2)**	**137 (11.0)**	**17 (4.2)**	**164 (1.8)**

Data are median [Q1, Q3] for continuous variables and n (%) for categorical variables; group sizes are shown in the column headers. Percentages use non-missing denominators, which differ by variable because of source-specific data availability, so absolute n need not sum to the column size. Source-restricted variables are labelled in parentheses: SOFA (MIMIC-IV), ASA physical status (INSPIRE), and SAPS3, cardiopulmonary bypass and aortic cross-clamp duration, admission urgency and sepsis on admission (SICdb), and emergency surgery (INSPIRE). The source-standardized severity score is the within-source, within-modality z score of the primary severity measure (SOFA, ASA or SAPS3). Crude outcome differences are descriptive and are not adjusted for severity or data source. ASA, American Society of Anesthesiologists; ICU, intensive care unit; IQR, interquartile range; SAPS3, Simplified Acute Physiology Score 3; SOFA, Sequential Organ Failure Assessment.

Table 1. *Baseline characteristics of CPB patients by antibiotic trajectory. Baseline characteristics are shown for the full cardiopulmonary bypass (CPB) cohort and for the four key antibiotic trajectory groups: short*

prophylaxis, persistent broad-spectrum therapy, late escalation and early broad-spectrum de-escalation. Remaining trajectory groups are pooled as other trajectories. Continuous variables are summarized as median [interquartile range] with available sample size. Binary and categorical variables are summarized as n/N (%), using the non-missing denominator. The source-standardized severity score is the within-source and within-modality z score of the primary source-specific severity measure (SOFA for MIMIC-IV, ASA physical status for INSPIRE and SAPS3 for SICdb). Crude outcome differences are descriptive and should not be interpreted as adjusted trajectory effects.

Figures

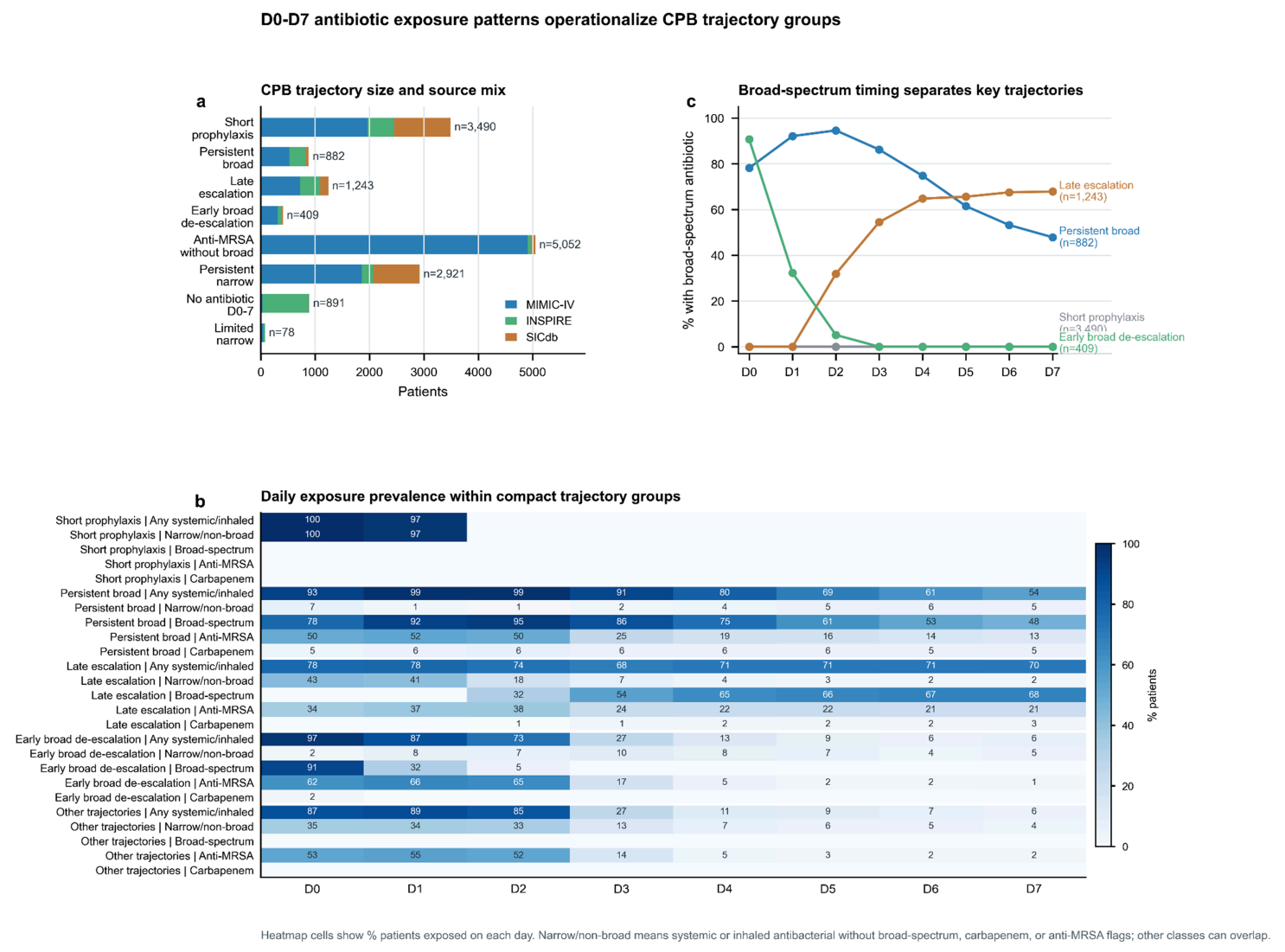


Figure 1

D0-D7 antibiotic exposure patterns operationalize CPB trajectory groups. a, Size and source composition of the main CPB antibiotic trajectory groups. Bars show patient counts from MIMIC-IV, INSPIRE and SICdb; labels show total patients per trajectory. b, Daily exposure heatmap for compact trajectory groups from day 0

to day 7 after CPB. Cells show the percentage of patients exposed on each day. Narrow/non-broad denotes systemic or inhaled antibacterial exposure without broad-spectrum, carbapenem or anti-MRSA flags. c, Broad-spectrum exposure curves for the four key trajectory groups. Persistent broad-spectrum therapy shows early and sustained broad-spectrum exposure, late escalation shows delayed broad-spectrum initiation after day 1, early broad-spectrum de-escalation shows rapid decline after day 0 and short prophylaxis shows no broad-spectrum exposure. CPB, cardiopulmonary bypass; D0-D7, days 0-7 after the index CPB event.

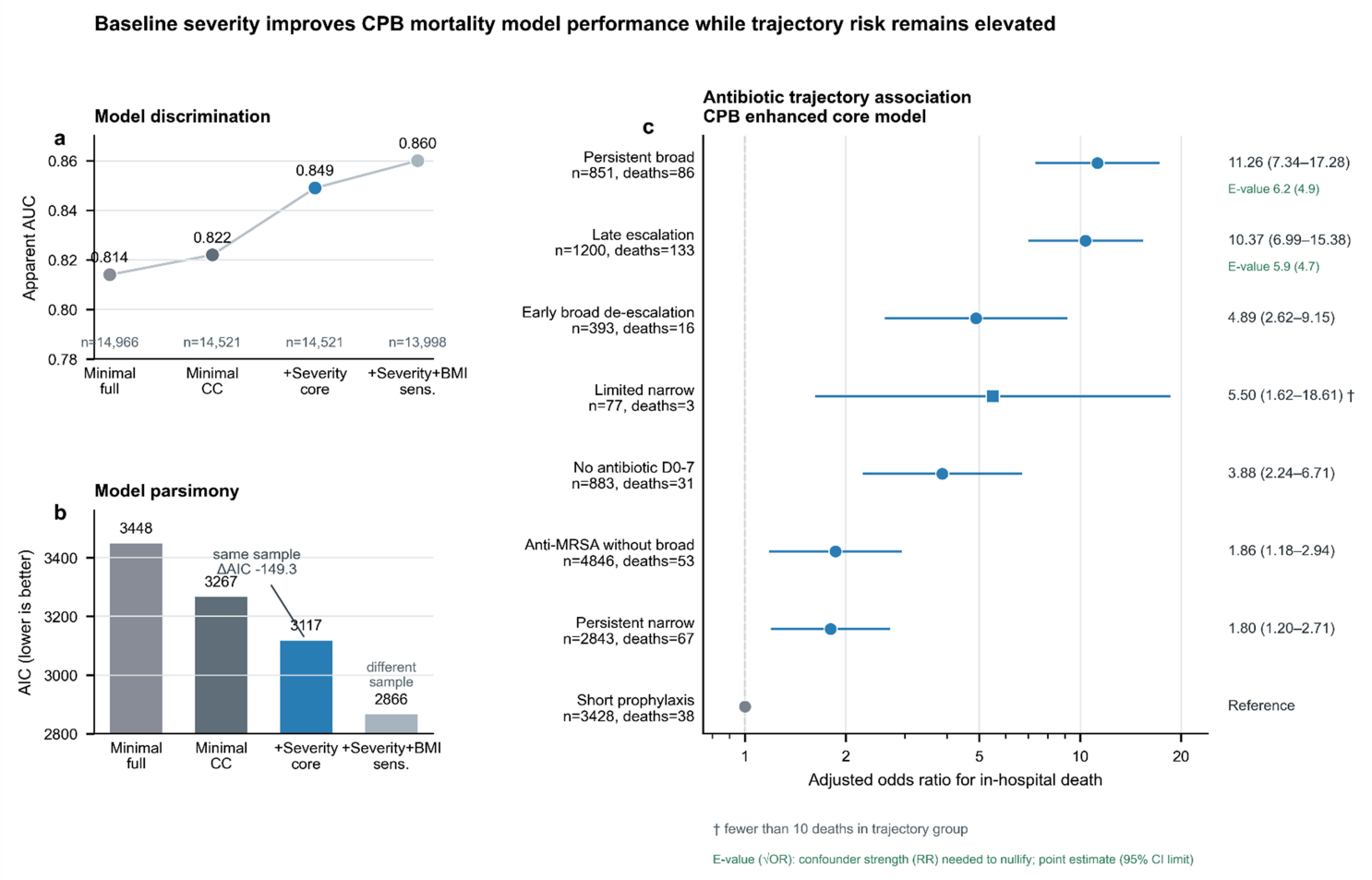


Figure 2

Source-standardized severity improves CPB mortality model performance and identifies broad-spectrum trajectory signals. a, Apparent area under the receiver operating characteristic curve (AUC) across the CPB mortality model sequence. The minimal full model adjusts for trajectory, age, sex and source database; the minimal complete-case model uses the same severity complete-case sample as the enhanced model; the enhanced core model adds source-by-modality standardized severity; the BMI sensitivity model additionally adjusts for body mass index among complete cases. b, Akaike information criterion (AIC) for the same model sequence. AIC is directly comparable for the minimal complete-case and enhanced core models because they use the same sample; the BMI sensitivity model uses a smaller complete-case sample. c, Adjusted odds ratios for in-hospital mortality from the enhanced core model by antibiotic trajectory, using short prophylaxis as the reference. Points show adjusted odds ratios and horizontal lines show 95%

confidence intervals. Square markers denote trajectory groups with fewer than 10 deaths. The enhanced core model included 14,521 CPB patients and 427 deaths. In c, the green annotations report E-values for persistent broad-spectrum therapy and late escalation (point estimate, with the 95% CI limit in parentheses), computed on the risk-ratio scale after square-root conversion of the odds ratio; larger values indicate greater robustness to unmeasured confounding (VanderWeele and Ding, Annals of Internal Medicine 2017).

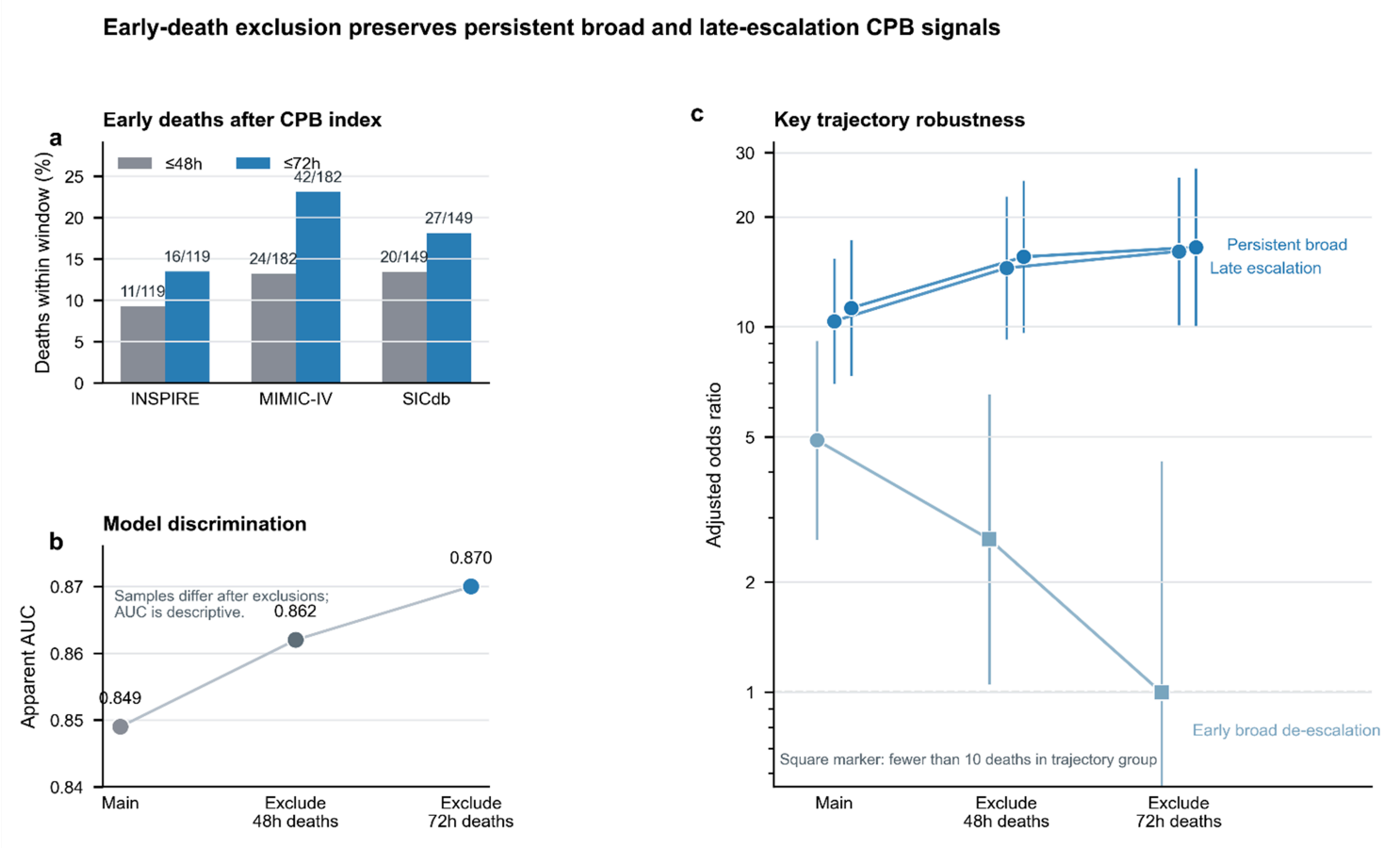


Figure 3

Persistent broad-spectrum therapy and late escalation remain elevated after early-death exclusion. a, Proportion of in-hospital deaths occurring within 48 h and 72 h of the CPB index event by source database. Labels show early deaths over total hospital deaths. b, Apparent AUC for the enhanced core model in the main analysis and after excluding deaths within 48 h or 72 h of the index event. These AUC values are descriptive across exclusion scenarios because the analysed samples differ. c, Adjusted odds ratios for persistent broad-spectrum therapy, late escalation and early broad-spectrum de-escalation across the main model and early-death exclusion scenarios. Points show adjusted odds ratios and vertical lines show 95% confidence intervals. Persistent broad-spectrum therapy and late escalation remain elevated after excluding early deaths, whereas early broad-spectrum de-escalation attenuates after 72 h exclusion and becomes sparse. The reference group is short prophylaxis.

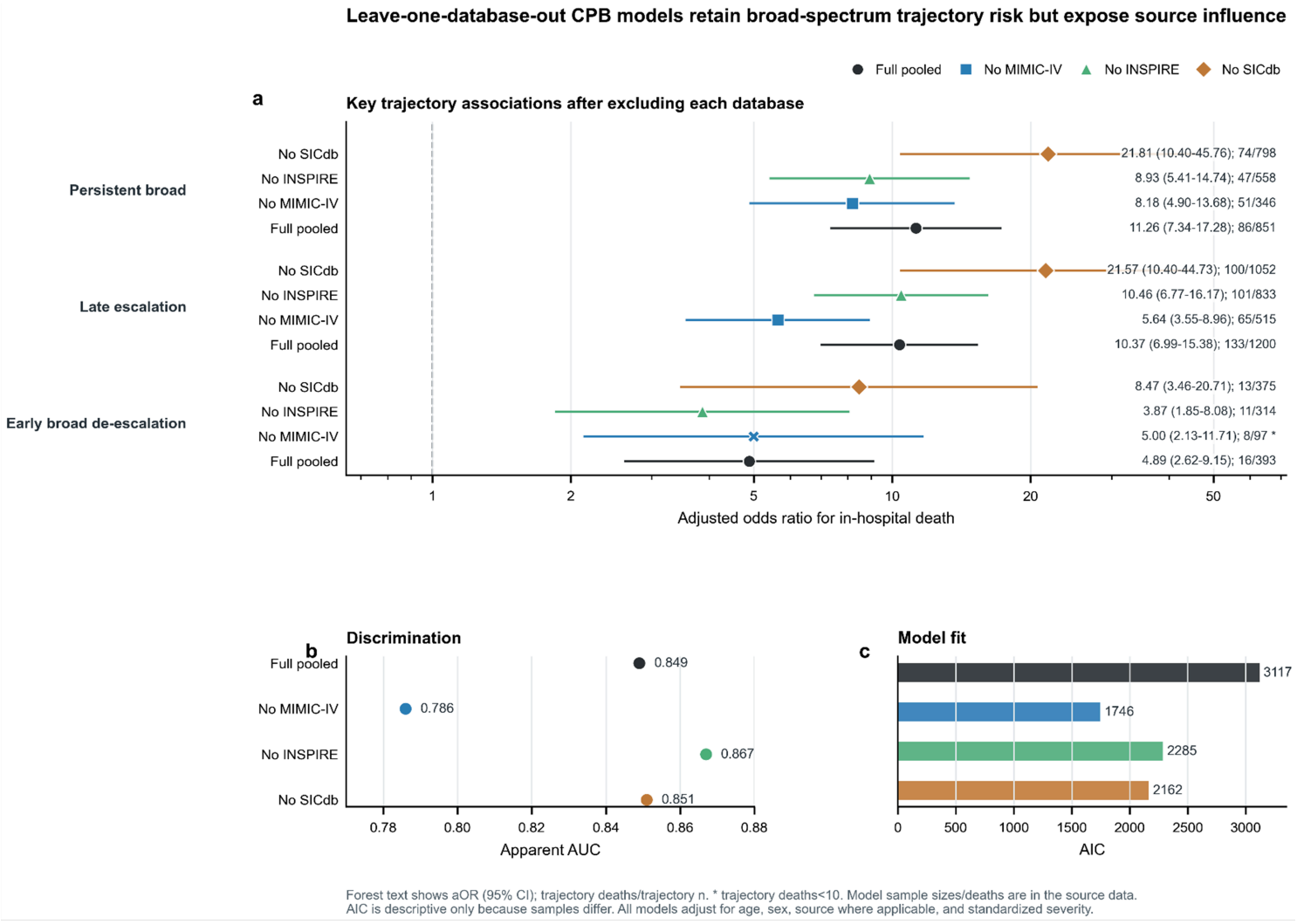


Figure 4

Leave-one-database-out models retain the main broad-spectrum signals but expose source influence. a, Adjusted odds ratios for the three key trajectory signals in the full pooled model and after excluding MIMIC-IV, INSPIRE or SICdb. Points show adjusted odds ratios and horizontal lines show 95% confidence intervals; labels show adjusted odds ratio (95% CI) and exposed deaths/exposed patients. Asterisks denote sparse trajectory groups. b, Apparent AUC for each leave-one-database-out model. c, AIC for each model. Because each leave-one-database-out analysis uses a different source composition and sample size, AIC is shown as descriptive only. Persistent broad-spectrum therapy and late escalation remain elevated across leave-one-database-out analyses, whereas early broad-spectrum de-escalation is less stable and sparse in some scenarios.

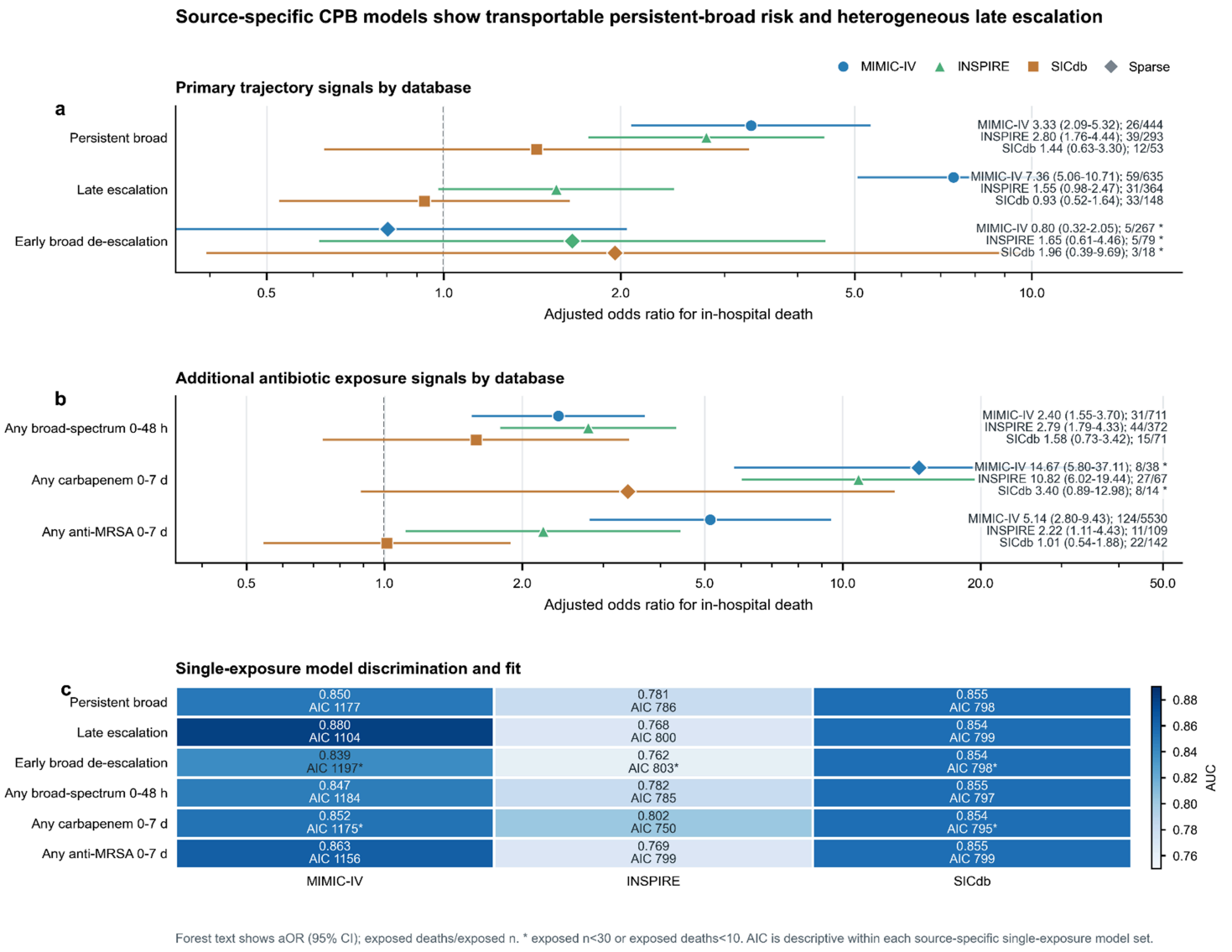


Figure 5

Source-specific binary exposure models for key antibiotic trajectory and exposure signals. Source-specific logistic models were fitted separately in MIMIC-IV, INSPIRE and SICdb using one binary exposure at a time because full categorical trajectory models were sparse within individual databases. Primary exposures were persistent broad-spectrum therapy, late escalation and early broad-spectrum de-escalation. Secondary exposures were any broad-spectrum exposure during 0-48 h, any carbapenem exposure during 0-7 d and any anti-MRSA exposure during 0-7 d. Points show adjusted odds ratios and horizontal lines show 95% confidence intervals. Source-specific adjustment sets differed according to covariate availability: MIMIC-IV adjusted for age, sex, SOFA, Charlson comorbidity index, BMI, mechanical ventilation, vasopressor exposure and renal replacement therapy; INSPIRE adjusted for age, sex, ASA physical status, emergency surgery, CPB duration and BMI; SICdb adjusted for age, sex, SAPS3, admission urgency, sepsis on admission, CPB duration, aortic cross-clamp duration, BMI and renal replacement therapy. AUC and AIC are shown as model diagnostics and should be compared descriptively because models are non-nested.