# Exploiting electronic health records to improve infection management


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# Abstract

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The main goal of effective infection management is to prescribe antimicrobials with an appropriate spectrum to combat the infecting pathogen and with dosing regimens that are optimally adjusted to the patient's characteristics to ensure efficacy. This first requires identifying the causative organism(s) and their antimicrobial susceptibilities to target therapy. However, this may be delayed due to the time taken to obtain culture results and then susceptibilities, or inconclusive if culture results are negative or only contaminating organisms are identified. Changing demographics, such as an ageing population and rising obesity rates, complicate dosing regimens, which are often developed from studies in healthy volunteers, leading to possible suboptimal outcomes.

The widespread adoption of electronic health records (EHR) offers a major opportunity to refine antimicrobial practices. This thesis aims to exploit electronic health records for improving infection management, focusing particularly on how they can be used to improve antimicrobial prescribing and tracking response to infection. I first evaluated the effectiveness of vancomycin prescribing guidelines at Oxford University Hospitals. The results showed that despite good compliance with the new guidelines (70-80%), the proportion of drug levels within the target range remained suboptimal (~30%). Using the real-world pharmacokinetic data, I developed updated dose recommendations to optimise drug levels, taking into account patient age, weight, and renal function. I then explored how routinely collected clinical parameters could guide treatment decisions in patients presenting with presumed bloodstream infections (BSI; based on having a blood culture taken), particularly when blood culture results are pending or negative. I found that how C-reactive protein and vital signs measurements changed over time after blood was taken for culture ("response trajectories") were associated with specific pathogen groups and infection sources in individuals with suspected BSI. Distinct patterns of clinical response trajectories were identified: early peaks (day 1 or 2) and typical recovery, slow recovery, a delayed peak (day 6), or persistently low levels. Centile reference charts were created based on the subgroups with "normal" responses to antibiotics as determined by latent class modelling to standardise the assessment of infection progression and treatment response in patients with suspected BSI; these could be used to guide management independently of microbiological test results. Finally, I examined the current clinical antibiotic prescribing patterns for suspected BSI and their association with the dynamics of these clinical parameters.

Overall, the thesis demonstrates the potential of EHR as a pivotal tool in enhancing the quality of antimicrobial management in clinical settings. By integrating data from EHR with patient-specific characteristics and real-time clinical responses, more personalised treatment recommendations can be developed to improve outcomes in patients with varying demographics and health profiles.

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## Ethics Statement for all Chapters

Ethical approval for analysis of de-identified electronic health record obtained from the Infections in Oxfordshire Research Database was obtained from the National Research Ethics Service South Central Oxford C Research Ethics Committee (19/SC/0403) and the National Confidentiality Advisory Group (19/CAG/0144).

## Declaration and attributions

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## Papers arising directly from this thesis

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# List of Abbreviations

| | |
|---|---|
| AIC | Akaike Information Criteria |
| AKI | Acute Kidney Injury |
| AMR | Antimicrobial Resistance |
| $AUC_{24}$ | Area Under 24-Hour Unbound Drug Plasma Concentration-Time Curve |
| BIC | Bayesian Information Criterion |
| BSI | Bloodstream Infections |
| CI | Confidence Interval |
| CNS | Central Nervous System |
| CRP | C-reactive Protein |
| DDD | Defined Daily Doses |
| eGFR | Estimated Glomerular Filtration Rate |
| ED | Emergency Department |
| EHR | Electronic Health Records |
| ENT | Ear, Nose and Throat |
| GIS | Geographic Information Systems |
| GAMLSS | Generalised Additive Models for Location Scale and Shape |
| ICU | Intensive Care Units |
| IORD | Oxfordshire Research Database |
| ITT | Intention to Treat |
| LCMM | Latent Class Mixed Model |
| LMS | Lambda-Mu-Sigma |
| MDRD | Modified Diet in Renal Disease |
| MIC | Minimum Inhibitory Concentration |
| MRSA | Methicillin-Resistant *Staphylococcus Aureus* |
| NEWS | National Early Warning Score |
| NLP | Natural Language Processing |

| | |
|---|---|
| OR | Odds Ratio |
| OUH | Oxford University Hospitals |
| PCT | Procalcitonin |
| PP | Per Protocol |
| ROC | Receiver Operating Characteristic |
| RRR | Relative-Risk Ratio |
| AUROC | Area Under the ROC curve |
| SABIC | Sample-size Adjusted BIC |
| SMD | Standardised Mean Difference |
| SOFA | Sequential Organ Failure Assessment |
| TDM | Therapeutic Drug Monitoring |
| WBC | White Blood Cell |
| WHO | World Health Organization |

# Chapter 1 Introduction

## 1.1 Current Infection Management Practices in Healthcare Settings

Infections persist as significant challenges for global healthcare systems, ranging from the recent COVID-19 pandemic caused by a novel virus to enduring bacterial infections. The complexity of managing these infections is exacerbated by the continuous evolution of pathogens and the alarming rise of antimicrobial resistance (AMR) [1]. AMR arises as microorganisms, including bacteria, fungi, viruses, and parasites, evolve mechanisms to survive exposure to the antimicrobials designed to obliterate them [2]. Consequent to this resistance, standard treatments lose effectiveness, allowing infections to persist and patients to potentially deteriorate, thus increasing the risk of morbidity and mortality at the population-level alongside escalating healthcare costs [1].

Efforts to combat AMR have led to the introduction of various strategies within healthcare settings aimed at enhancing infection management. Central to these initiatives is the establishment of antimicrobial stewardship programmes [3]. Such coordinated interventions aim to optimise antimicrobial usage, and typically involve implementing evidence-based prescribing guidelines, monitoring and assessing prescriber adherence, and providing ongoing education on the rational use of antimicrobials. Antimicrobial stewardship toolkits, such as the UK Health Security Agency's "Start Smart Then Focus" (**Figure** 1.1), advocate for critical procedures to ensure judicious use of antimicrobials [4]. Keys among these are microbiological

testing, initiating antimicrobial treatment promptly based on local guidelines, de-escalating empirical broad-spectrum antimicrobial therapy to targeted narrow-spectrum agents and stopping antimicrobial prescriptions if there is no evidence of infection. In addition to enhancing stewardship of antimicrobials, optimising antimicrobial administration to ensure adequate, but not excessive, drug exposure is another essential practice for effective infection treatment, which often involves the use of therapeutic drug monitoring (TDM) [5].

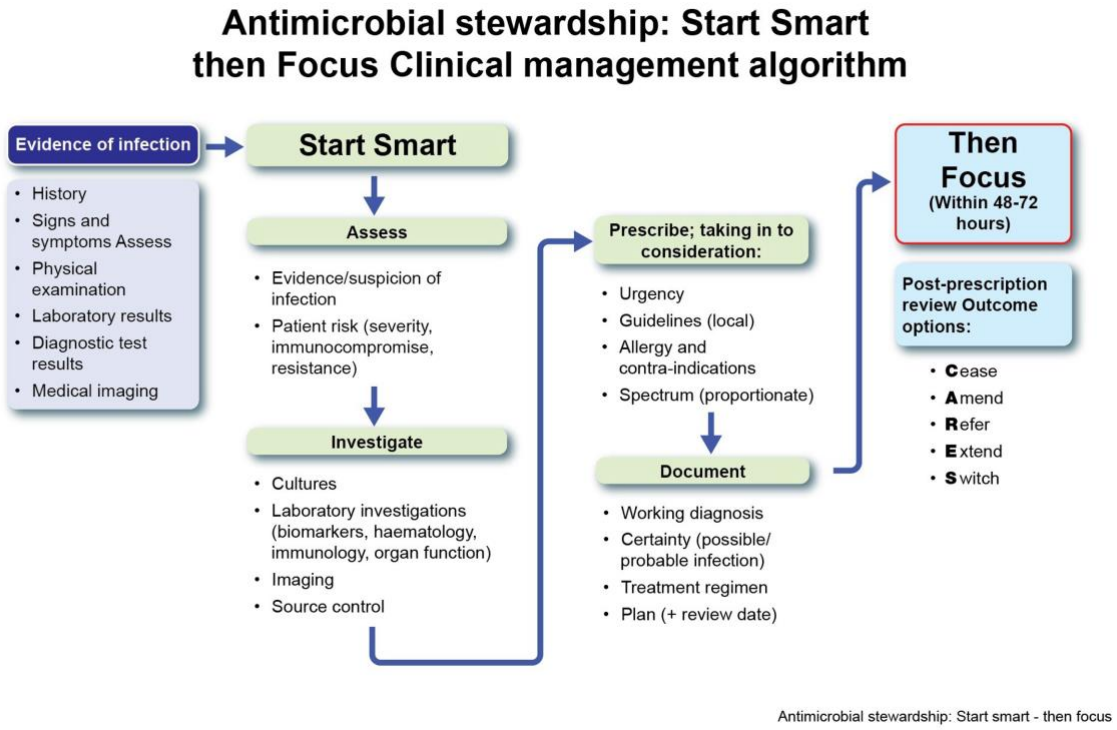


**Figure 1.1 Antimicrobial stewardship clinical management algorithm (UK Health Security Agency, 2015).**

### 1.1.1 Microbiological testing

Microbiological testing is considered to be the fundamental step in infection management, which involves identifying the causative pathogen(s) using various diagnostic methods, including blood cultures, tissue cultures, and advanced molecular techniques [6]. Blood culture remains the gold standard for diagnosis of bloodstream infections (BSI) due to its ease of use and high analytical sensitivity [7]. Ensuring blood cultures are taken as soon as possible is critical, as they help to identify the causative organisms and their antimicrobial susceptibility and assist in prescribing targeted antimicrobial therapy.

However, several key challenges complicate the effectiveness of blood culture diagnostics. One significant issue is the low number of organisms required to cause an infection, which can result in a low yield from blood cultures. Even small quantities of bacteria can make someone sick, making it difficult to detect the pathogen, especially if the sample volume is inadequate [8]. The prior use of community antimicrobials before arriving at hospitals can further reduce the yield of these cultures, leading to negative results even when an infection is present [8]. This low sensitivity of traditional culture methods often necessitates the use of broad-spectrum empirical therapy until specific pathogens can be identified, which will be discussed in the next section.

Another challenge is the slow turnaround time for traditional microbiological tests. Blood culture results typically take approximately 24 hours to identify the species and an additional 24-48 hours for antimicrobial susceptibility testing [7]. This delay can

contribute to increased morbidity and mortality, particularly in critically ill patients. Therefore, there is a pressing need for more rapid and sensitive diagnostic methods.

Faster, more reliable diagnostic modalities, such as multiplex PCR testing and biomarker-guided algorithms, are needed. In recent years, advances in rapid diagnostics have significantly improved the detection of viral pathogens such as influenza and SARS-CoV-2. These rapid diagnostic tests can provide results within hours, allowing for timely initiation of antiviral therapy and infection control measures [9–11]. However, equivalent rapid diagnostics for bacterial infections are not yet widely available due to cost constraints and their own limitations [12]. For example, the BioFire FilmArray blood culture identification panel costs approximately £150 per test [13], and its sensitivity, while better than traditional methods, is not perfect. This imperfection means that even if a pathogen is identified, there remains the possibility of missing other important pathogens, making it difficult to rule out the need for continued broad-spectrum antimicrobial therapy.

To address these challenges, ongoing research is focused on developing more rapid, sensitive, and comprehensive diagnostic tools for bacterial infections. These tools aim to not only identify the causative pathogens quickly but also provide detailed information on antimicrobial susceptibility, which is crucial for guiding effective treatment strategies [14].

### 1.1.2 Empirical antimicrobial therapy

In situations where immediate treatment is crucial, such as suspected sepsis, prompt empirical antimicrobial therapy should be applied before specific pathogens are identified. This approach involves administering antimicrobials that are likely to be effective against most suspected pathogens based on local epidemiology and resistance patterns. It requires a careful balance to ensure that patients receive immediate care while minimising the risk of inappropriate antimicrobial use [15].

Empirical antimicrobial therapy is particularly critical in the management of sepsis, a life-threatening condition that arises when the body's response to infection causes tissue damage, organ failure, and potentially death. Multiple studies have shown that delays in the administration of antimicrobials are associated with increased mortality in critical infections like sepsis [16–18]. For example, a study by Kumar et al. demonstrated that each hour of delay in administering effective antimicrobials was associated with an average decrease in survival of 7.6% [16]. Similarly, a meta-analysis by Sterling et al. found that delayed antimicrobial therapy was significantly associated with increased mortality in septic shock [17]. However, when administering empirical antimicrobials, clinicians face a trade-off. The goal is to use antimicrobials with an appropriate spectrum that is likely to be effective for patients based on local epidemiology and resistance patterns. How broad to go with the empirical treatment is a significant consideration. Using broad-spectrum antimicrobials indiscriminately can contribute to the development of AMR and disrupt the patient's microbiome, whereas using too narrow a spectrum may risk inadequate coverage of the causative pathogen [15].

A specific challenge in empirical therapy is translating hospital-level data on pathogen prevalence and resistance patterns to individual patients. Local epidemiological data provide general trends, but individual patient factors such as recent antimicrobial use, comorbid conditions, and history of resistant infections can significantly influence the likelihood of different pathogens and their resistance profiles. As highlighted by recent research showing conventional hospital antibiograms for *E. coli* and *Klebsiella* spp. have limited performance in predicting AMR for individual patients, applying broad population-level data to individual cases necessitates a nuanced approach that considers both general trends and individual patient characteristics [19].

### 1.1.3 De-escalation and escalation

Once pathogen-specific information is available, de-escalation becomes a key strategy. This process entails switching from a broad-spectrum empirical therapy to a more targeted one tailored to the identified pathogen and its susceptibility profile. De-escalation is a critical component of antimicrobial stewardship, as it helps minimise the development of antimicrobial resistance, reduce side effects, and conserve the efficacy of broad-spectrum agents for when they are truly needed [20,21].

As discussed above, empirical therapy often starts with broad-spectrum antibiotics because the specific pathogen causing the infection is unknown, and immediate treatment is crucial to prevent deterioration, especially in severe cases such as sepsis. These broad-spectrum agents are chosen based on local epidemiological data and resistance patterns to cover a wide range of potential pathogens. However, as soon as

microbiological test results become available, it is essential to reassess and narrow the antibiotic spectrum to target the identified pathogen.

This practice of de-escalation offers several benefits. It reduces the selection pressure on non-target bacteria, thereby minimising the development of resistance. It also reduces the risk of adverse drug reactions and side effects, which are more common with broad-spectrum antibiotics [21]. Furthermore, it preserves the efficacy of broad-spectrum antibiotics for future use, ensuring they remain effective for severe infections where other options may fail [20,21].

However, effective implementation of de-escalation is not without challenges. Delayed or negative microbiological test results may not assist in informing de-escalation decisions. This uncertainty can lead clinicians to continue broad-spectrum therapy longer than necessary, out of caution. Paradoxically, the clinical improvement of a patient can reduce the perceived urgency to de-escalate, leading to unnecessarily prolonged broad-spectrum antibiotic use [21,22].

Conversely, escalation is also an important concept in antimicrobial therapy. If the initial empirical therapy is found to be inadequate, either due to the emergence of new clinical information or the identification of a resistant pathogen, it may be necessary to escalate the treatment to a broader or more potent antibiotic. This ensures that the patient receives effective treatment and prevents the progression of the infection. Escalation, like de-escalation, requires careful consideration of the patient's clinical status and microbiological data to avoid both undertreatment and overtreatment.

The appropriate choice of duration of therapy is crucial to prevent relapse or recurrence of the infection. Traditional approaches have favoured longer courses of antimicrobials due to the fear of inadequate treatment leading to relapse or treatment failure [23,24]. However, there is growing evidence that shorter courses are equally effective for many infections while reducing the risk of resistance and side effects [23,25]. Uncertainty in the optimal duration often derives from a lack of high-quality, infection-specific data to guide clinicians [26]. Personal clinical experience and judgment still play a significant role in decision-making, leading to variability in practice [27].

### 1.1.4 Prescribing guidelines and personalised dosage adjustments

Antimicrobial prescribing decisions, whether for empirical broad-spectrum or de-escalated narrow-spectrum therapy, should ideally comply with evidence-based prescribing guidelines. These guidelines are intended to provide clinicians with a framework for choosing the most appropriate antimicrobial agent and dosing regimens, informed by the latest research and epidemiological data. However, the practical application of these guidelines often faces significant challenges. There is a notable lack of robust clinical trial data supporting many of these guidelines, and they frequently rely on expert consensus rather than high-quality evidence [28,29]. Additionally, the utility of hospital antibiograms, which are an important part of these guidelines, is limited due to their poor predictive value at the individual patient level [19]. This discrepancy highlights the gap between theoretical best practices and the complexities of real-world clinical settings.

Guidelines also encompass dosing recommendations, particularly for antibiotics with narrow therapeutic ranges such as vancomycin. These guidelines aim to guide clinicians on the appropriate dosing regimens to ensure therapeutic effectiveness while minimising toxicity. For instance, vancomycin dosing requires careful monitoring of blood levels to avoid nephrotoxicity and ensure adequate drug exposure [30]. However, these dosing guidelines often fail to account for patient-specific factors and comorbid conditions, which can significantly influence drug pharmacokinetics and pharmacodynamics, especially in special patient populations such as critically ill patients and obese patients [31,32]. This lack of personalisation can lead to suboptimal dosing, either resulting in insufficient therapeutic levels or an increased risk of adverse effects. Consequently, while dosing guidelines provide a valuable starting point, clinicians must frequently adjust regimens based on individual patient characteristics and dynamic clinical conditions, which can be challenging in busy clinical settings.

The complexity of optimal dosage adjustments arises from considering numerous patient-specific variables, including age, weight, organ function, etc [33]. Standard dosage regimens for antimicrobials are commonly established using pharmacokinetic data from clinical trials conducted in “average” patient populations, with particular cohorts, specifically the elderly and individuals with obesity, often underrepresented [34,35]. Consequently, the responses of these subgroups to antimicrobial therapy may not be adequately captured if there is underlying variability in absorption, metabolism and/or elimination. This variability, coupled with individual heterogeneity and differing pharmacokinetic/pharmacodynamic targets for various antimicrobials, can result in

suboptimal drug concentrations, potentially leading to therapeutic failure or resistance [36].

Careful consideration needs to be given to the appropriate adjustment of antimicrobial dosing for elderly patients, as physiological alterations associated with ageing can substantially impact pharmacokinetic and pharmacodynamic processes [37,38]. As individuals age, renal function often declines, manifesting in decreased glomerular filtration rate and reduced renal clearance [37]. Consequently, drugs excreted predominantly by the kidneys, such as many antibiotics, can accumulate to toxic levels if not appropriately dosed [37]. Age-related changes in body composition, including increased body fat, decreased lean body mass and total body water, also affect the distribution volume of hydrophilic and lipophilic drugs [38]. Moreover, polypharmacy, a common issue in this age group, raises the possibility of drug-drug interactions, altering the expected effects of antimicrobial agents [37].

Weight, more specifically obesity, also requires careful dose adjustment. Obesity can significantly affect the pharmacokinetics of drugs through alterations in absorption, distribution, metabolism, and excretion [39]. Increased body fat and altered blood flow to adipose tissues can lead to unpredictable distribution volumes for lipophilic and hydrophilic drugs [40]. Elevated renal clearance, a phenomenon sometimes observed in obesity, complicates the picture further by expediting drug elimination, thereby altering the half-life of renally-cleared agents and necessitating adjustments to dosage or administration frequency [34,41]. The routine methodologies, which typically draw on actual body weight or body surface area for dosage calculations, are problematic when

applied to obese patients, as they do not account for the distinct pharmacological landscape shaped by obesity. Clinical guidance on appropriate dosing for those living with obesity is currently insufficient, with recommendations often based on limited clinical data or pharmacokinetic modelling [36]. While large-scale clinical trials may not be necessary, robust pharmacokinetic data are essential to better understand and address these variations [34].

Moreover, the variability in local resistance patterns and the dynamic nature of microbial populations necessitate frequent updates to antimicrobial prescribing guidelines to remain relevant and effective. The lag in updating guidelines to reflect current data can result in outdated recommendations that do not align with the latest resistance trends or therapeutic insights. This issue is further compounded by the fact that many guidelines are not easily accessible or disseminated among clinicians, leading to inconsistent application in clinical practice [42].

Despite these challenges, adherence to prescribing guidelines remains a cornerstone of antimicrobial stewardship. The implementation of these practices requires robust institutional support, continuous education, and the integration of clinical decision support systems to aid clinicians in making informed decisions at the point of care [43]. Moreover, the development and adherence to guidelines must be accompanied by efforts to generate high-quality evidence through clinical trials and observational studies. Real-world data and post-implementation studies can provide valuable insights into the effectiveness of these guidelines and highlight areas for improvement.

Collaborative efforts among healthcare institutions, regulatory bodies, and researchers are essential to refine guidelines and ensure they are grounded in solid evidence.

### 1.1.5 Therapeutic Drug Monitoring (TDM)

TDM is another key component of effective infection management. This practice involves measuring drug concentrations in the blood to ensure they are within the therapeutic range and adjusting doses if they are not. TDM is particularly crucial for antibiotics with narrow therapeutic indices, such as vancomycin and aminoglycosides [5]. By monitoring drug levels and amending dosages accordingly, clinicians can achieve optimal therapeutic effects while minimising the risk of toxicity. This precision in dosing is vital, especially in patients with complex clinical conditions or altered pharmacokinetics [44].

Despite its benefits, TDM is not without challenges. One significant limitation is the availability and timing of drug level measurements, as delays can hinder timely dose adjustments [45]. Additionally, the interpretation of drug levels may require clinical expertise and a comprehensive understanding of pharmacokinetics and pharmacodynamics. There are also logistical challenges in implementing TDM in resource-limited settings, where access to the necessary laboratory facilities and trained personnel may be highly restricted [46].

Advances in technology and analytical methods are continually improving the feasibility and accuracy of TDM. For example, the development of point-of-care testing devices allows for rapid drug level measurements at the bedside, facilitating more timely dose

adjustments. Furthermore, integrating TDM with electronic health records (EHR) and clinical decision support systems can enhance the precision and efficiency of dosing adjustments, improving patient outcomes [47].

## 1.2 The Role of EHR in Infection Management

The advent of EHR has marked a paradigm shift in healthcare, particularly in the area of infectious diseases and epidemiology. The integration of EHR into healthcare has revolutionised the way clinical data is collected, stored, and utilised. This digital transformation provides new opportunities to manage infections more effectively and efficiently, ranging from early detection of outbreaks to optimising treatment protocols [48,49]. Through the aggregation of patient data, EHR enables the identification of emergent patterns, supports predictive modelling for infection spread, and ensures seamless data exchange with public health databases [49,50].

### 1.2.1 Surveillance for early detection of outbreaks

The early detection of infectious disease outbreaks is crucial for timely intervention and prevention of widespread transmission. EHR, with their extensive database of patient records and real-time data collection, offer a unique opportunity in this regard. They enable clinicians to quickly identify patterns indicative of an emerging outbreak, such as an unusual increase in certain diagnoses or prescription rates for specific antibiotics. For instance, by analysing data from multiple healthcare facilities, EHR can help recognise unusual spikes in cases of respiratory infections, which might suggest the beginning of an influenza outbreak or other respiratory pathogens [51,52]. This early warning system is not just limited to hospital settings but can extend to primary care

and outpatient settings, offering a comprehensive surveillance net [53]. Furthermore, integrating EHR with geographic information systems (GIS) can enhance outbreak detection by mapping the distribution of reported cases, thereby identifying potential hotspots and guiding targeted public health interventions [54].

### 1.2.2 Monitoring drug dose and blood levels

EHR can be instrumental in monitoring drug dosage and blood levels, improving adherence to clinical guidelines. Through EHR, clinicians can track the dosing, frequency, and duration of antibiotic prescriptions, ensuring they align with established guidelines. Clinical decision support systems integrated with EHR data can alert clinicians to potential allergies, suggest adjusted dosages based on patient-specific factors like body weight or renal function, and facilitate the automation of TDM requests [47,55]. These data can also identify patterns of non-compliance or deviations from recommended practices, informing improvements to guidelines or antimicrobial stewardship programs.

### 1.2.3 Tracking patient clinical response to inform infection management

The management of infectious diseases requires continuous evaluation and adjustment based on the patient's clinical response. Ideally, EHR could provide a comprehensive view of the patient's progress through routinely collected data such as inflammation markers (C-reactive protein [CRP] [56], procalcitonin [PCT] [57], white blood cell [WBC] count [58]), vital signs (heart rate, respiratory rate, temperature) ) [59], and established scoring systems such as the Sequential Organ Failure Assessment (SOFA) [60]. At least in theory, this real-time data allows clinicians to closely monitor the patient's response

to treatment, identify early signs of improvement or deterioration, and make informed decisions about therapeutic adjustments. For example, a decreasing trend in CRP levels and improvement in vital signs may suggest an effective response to antibiotics, potentially supporting a decision to de-escalate treatment. However, current EHR systems are often not optimally designed to provide this information easily, requiring significant navigation across different screens and systems. This can hinder the effective use of EHR in real-time decision-making.

### 1.2.4 Challenges in using EHR for research

While EHR offer major opportunities for managing infectious diseases, their effective exploitation is fraught with challenges. These challenges range from data accuracy and representativeness to the ethical considerations of using such data for research purposes.

One of the fundamental challenges in using EHR for research is ensuring data accuracy and completeness [61,62]. EHR data is primarily collected for clinical management and billing purposes (e.g., diagnostic codes), not research, which can lead to inconsistencies due to variations in data recording practices among different healthcare providers, and may differ from the codes most appropriate for research [63]. Additionally, hospital-based EHR may not capture all relevant patient information, especially from encounters outside of the primary healthcare system, such as home care. These inaccurate and incomplete data could bias the analysis, leading to biased conclusions and ineffective interventions.

Another significant challenge is the bias inherent in the data collected through EHR. In infectious disease management, there is often a bias in testing frequency – clinicians may not continue to request tests for patients who are doing well, while those with severe symptoms continue to be tested [64]. Additionally, there is a population bias, as individuals with more severe symptoms are more likely to seek care and therefore be included in EHR data. This scenario leads to an overrepresentation of severe cases in EHR, while milder cases, which constitute a substantial portion of the patient population, may be underrepresented [61,65]. This testing frequency bias must be accounted for when designing studies and interpreting data from EHR to ensure population generalisability.

EHR consist of a significant amount of unstructured data, such as physician's notes, radiology reports, and other free-text documents. Extracting meaningful information from this unstructured data is a complex task. Natural language processing (NLP) and other advanced data processing techniques are required to analyse this data effectively. However, these techniques are not universally implemented in current EHR systems due to various considerations, such as patient privacy, limiting the ability to fully utilise the wealth of information available in these records [66]. Additionally, unstructured data may contain nuanced clinical information that is difficult to standardise or categorise, leading to potential misinterpretation and loss of critical contextual details in patient records [66].

### 1.2.5 Ethical Considerations

The use of EHR data for research is associated with several ethical issues. These include concerns about patient consent, data privacy, and the potential for unintended consequences.

Patients have a fundamental right to control their personal health information. However, the use of EHR data in large-scale analyses often occurs without explicit patient consent, especially for public health purposes [67]. This raises ethical questions about the balance between individual privacy rights and the collective benefits of public health research. In the UK, the legal basis for research without consent is covered under Section 251 of the National Health Service Act 2006, with the justification being "a task in the public interest". This waiver of individual consent is managed through the Confidentiality Advisory Group.

The importance of confidentiality and privacy of patient data in EHR research cannot be overstated. While de-identification of data is a common practice to protect privacy, there are growing concerns about the re-identification of individuals through advanced data analysis techniques [67,68]. Ensuring robust data protection measures and continually updating these in line with technological advancements are imperative in maintaining patient trust and upholding ethical standards.

The use of EHR data for research can inadvertently lead to discrimination or stigmatisation of specific patient groups [67]. For instance, data indicating higher infection rates in specific communities could lead to negative stereotyping or discriminatory practices. Ethical use of EHR data involves not only protecting individual

data but also being cautious about how data interpretations might impact communities and ensuring that public health interventions are equitable and non-discriminatory.

## 1.3 Thesis Outline

The goal of this thesis is to exploit electronic health records for improving infection management, focusing particularly on how they can be used to improve antimicrobial prescribing and tracking response to infection.

I first evaluate the effectiveness of an antimicrobial guideline for vancomycin prescribing in Oxford University Hospitals (OUH) NHS Foundation Trust (Chapter 2). Here I examine factors associated with guideline compliance and drug levels, and explore whether doses and drug levels data in the EHR can be used to refine antimicrobial dosing recommendations. In Chapter 3, I focus on clinical parameters routinely collected in the EHR with the aim of studying the clinical response over time from infection in the broad population of patients with suspected BSI. Specifically, I aim to characterise population-level changes of inflammatory markers and physiological measurements by different clinical covariates and patient characteristics. The analyses in Chapter 3 reveal considerable variation in these inflammatory markers and physiological measurements across different pathogen groups, sources of infection and other clinical covariates; and that such population-level patterns of clinical response have the potential to be summarised and to inform the assessment of individual patient responses. Therefore, in Chapter 4, I examine underlying response patterns to identify those responding standardly to (effective) antibiotics, and to construct centile reference charts for expected clinical response in standard responders, which can be used to

identify deviations from typical recovery to inform individualised clinical decision-making. Building upon understanding of "normal" clinical response pattern in patients with suspected BSI, in Chapter 5 I aim to examine the current clinical antibiotic prescribing patterns for suspected BSI and their association with dynamics of clinical parameters, i.e., the relationship between rapid changes in CRP percentile levels and subsequent prescribing behaviours, as well as the effects of antibiotic adjustments on subsequent CRP centiles.

The thesis concludes with clinical implications of the current work and directions for future work.

# Chapter 2 Assessment of an institutional guideline for vancomycin dosing and identification of factors associated with dose and drug trough levels

The work presented in this Chapter was published in 2022 in the Journal of Infection [69]. Most of the tables and figures are the same as those published in the paper and its supplementary material.

## 2.1 Introduction

The widespread use of EHR provides a major opportunity to improve antimicrobial prescribing. Sophisticated prescribing aids can flag allergies, recommend dosages that adjust for patient factors such as weight or renal function, as well as automate requesting TDM. Web and smartphone-based apps can help disseminate guidelines. EHR data also provide an opportunity to review guideline compliance and (where measured) drug levels achieved and investigate factors associated with both. This chapter describes the impact of deploying a new vancomycin guideline supported by these approaches in OUH, and uses these findings to provide an example of how real-world pharmacokinetics based on EHR data can be used to improve dosing guidelines further.

Vancomycin is widely prescribed to treat infections caused by Gram-positive bacteria, including MRSA and *Enterococcus facium*. However, vancomycin's narrow therapeutic

index (requiring balancing efficacy against the risk of acute kidney injury (AKI)) and inter-personal variability in pharmacokinetics makes dosing difficult and necessitates TDM. International guidelines now recommend that vancomycin is monitored using the ratio of the area under the 24-hour unbound drug plasma concentration-time curve to minimum inhibitory concentration ($AUC_{24h}$/MIC) [70], targeting a ratio of 400–600 [2,3].

However, in practice, many hospitals still use vancomycin trough levels as a widely adopted but imperfect surrogate target for $AUC_{24h}$/MIC to simplify clinical management [71].

Institutional and national consensus guidelines can facilitate vancomycin dosing and monitoring [71–74]. However, guideline implementation has often been less effective than expected [75–80]. The need for individualised vancomycin dosing and TDM, alongside the logistical challenges of coordinating phlebotomy and drug administration in busy hospital settings, hinders implementation. Incomplete guideline compliance and failure to achieve levels despite following guidance contribute to sub-optimal dosing and may result in AMR and increased treatment failure [81], highlighting the need to investigate further the factors affecting vancomycin dosing and clinical outcomes.

OUH implemented a new vancomycin dosing guideline in August 2016 using vancomycin trough targets based on international guidelines from 2009 [71], including increasing the target trough level from 10–15 mg/L to 15–20 mg/L. The guidelines in OUH [82], delivered via a phone-based app and hospital computers, provide detailed instructions on loading and initial maintenance doses based on the patient's body

weight and renal function, and advise clinicians on adjusting subsequent maintenance doses based on TDM. Implementation is supported by a semi-automatic "powerplan" calculator within the hospital's EHR system, prompting clinicians to prescribe loading and initial maintenance doses based on the guidelines and automatically generate a request for the first vancomycin drug level. This chapter aimed to investigate the effectiveness of this new vancomycin dosing guideline, identify factors associated with dose and drug levels, and further optimise the guideline accordingly.

## 2.2 Methods

### 2.2.1 Research design and study population

Data were extracted from the Infections in Oxfordshire Research Database (IORD), containing data on all admissions to the OUH in Oxfordshire, United Kingdom, and associated characteristics, including antibiotics prescribed in the hospital. OUH contains 1000 beds in four hospitals, providing secondary care to a population of approximately 600,000 and specialist services to the surrounding region.

Vancomycin is the first-line glycopeptide antibiotic in OUH. The current adult dosing guideline for intravenous vancomycin was implemented on 1 August 2016 (**Table** 2.1, **Table** 2.2, **Table** 2.3). The patient's actual body weight and estimated glomerular filtration rate (eGFR) determine the loading and initial maintenance doses. The first drug trough level should be taken after 48 hours, i.e., before the fourth maintenance dose for twice-daily dosing and before the second maintenance dose for once-daily dosing. Recommendations are included for adjusting subsequent maintenance doses according to trough levels obtained. The target trough level is 15–20mg/L.

From 1 January 2016 to 1 June 2021, there were 7,355 inpatient treatment courses with intravenous vancomycin (**Figure** 2.1). I excluded 849 courses missing baseline characteristics, 365 courses for patients admitted to paediatrics, paediatric surgery, and renal medicine, and 427 courses for patients under 16 years, as the guideline was explicitly not applicable to these patients (**Figure** 2.1). I also excluded 1,995 courses which comprised less than 24 hours of intravenous vancomycin, most of which had only a single dose and no drug level measurements (typically used for surgical prophylaxis or initial empirical treatment; **Figure** 2.1). I then considered different outcomes with specific inclusion criteria, as shown in **Figure** 2.1. Variables considered and the type of regression for each outcome can be found in **Table** 2.4.

**Table 2.1 Recommended loading dose in OUH guidelines from 1 August 2016.**
Recommended loading dose for patients with eGFR ≥ 20mL/min/1.73m$^2$.

| Actual Body Weight (kg) | Dose |
|---|---|
| 35-49 | 1250mg |
| 50-64 | 1500mg |
| 65-100 | 2000mg |
| >100 | 2500mg |

Recommended loading dose for patients with eGFR < 20mL/min/1.73m$^2$.

| Actual Body Weight (kg) | Dose |
|---|---|
| <35 | 20mg/kg |
| 35-49 | 1000mg |
| 50-64 | 1250mg |
| >65 | 1500mg |

**Table 2.2 Recommended initial maintenance dose in OUH guidelines from 1 August 2016.**
Recommended initial maintenance dose for patients with eGFR ≥ 20mL/min/1.73m$^2$.

| | | eGFR (mL/min/1.73m$^2$) | | | | |
|---|---|---|---|---|---|---|
| | | 20-29 | 30-44 | 45-59 | 60-89 | >90 |
| Actual Body Weight (kg) | 35-49 | 500mg Once daily | 500mg Once daily | 750mg Once daily | 500mg Twice daily | 750mg Twice daily |
| | 50-64 | 500mg Once daily | 750mg Once daily | 1000mg Once daily | 750mg Twice daily | 1000mg Twice daily |
| | 65-84 | 750mg Once daily | 1000mg Once daily | 1250mg Once daily | 1000mg Twice daily | 1250mg Twice daily |
| | 85-100 | 750mg Once daily | 1250mg Once daily | 1500mg Once daily | 1250mg Twice daily | 1500mg Twice daily |
| | >100 | 1000mg Once daily | 750mg Twice daily | 1000mg Twice daily | 1500mg Twice daily | 2000mg Twice daily |

Recommended initial maintenance dose for patients with eGFR < 20mL/min/1.73m$^2$.

| Actual Body Weight (kg) | Dose |
|---|---|
| <35 | 20mg/kg Once only then re-check level |
| ≥35 | 1000mg Once only then re-check level |

**Table 2.3 Interpretation of vancomycin levels and recommended maintenance dose adjustments.**

| Trough level | Action required |
|---|---|
| Less than 10mg/L | Increase maintenance dose by two weight bands (see **Table 2.2**). |
| 10-14mg/L | Increase maintenance dose by one weight bands (see **Table 2.2**). |
| 15-20mg/L | Target trough level. Continue with current dose. |
| 21-25mg/L | Reduce maintenance dose by one weight band (see **Table 2.2**). |
| Over 25mg/L | In patients with normal renal function, check the time the sample was taken against time of drug administration. If the sample time does not account for high level, then:<br>1. Omit further doses.<br>2. Monitor level daily until it reaches 20mg/L or below.<br>3. Re-start IV vancomycin at two weight bands lower than before (see **Table 2.2**). |

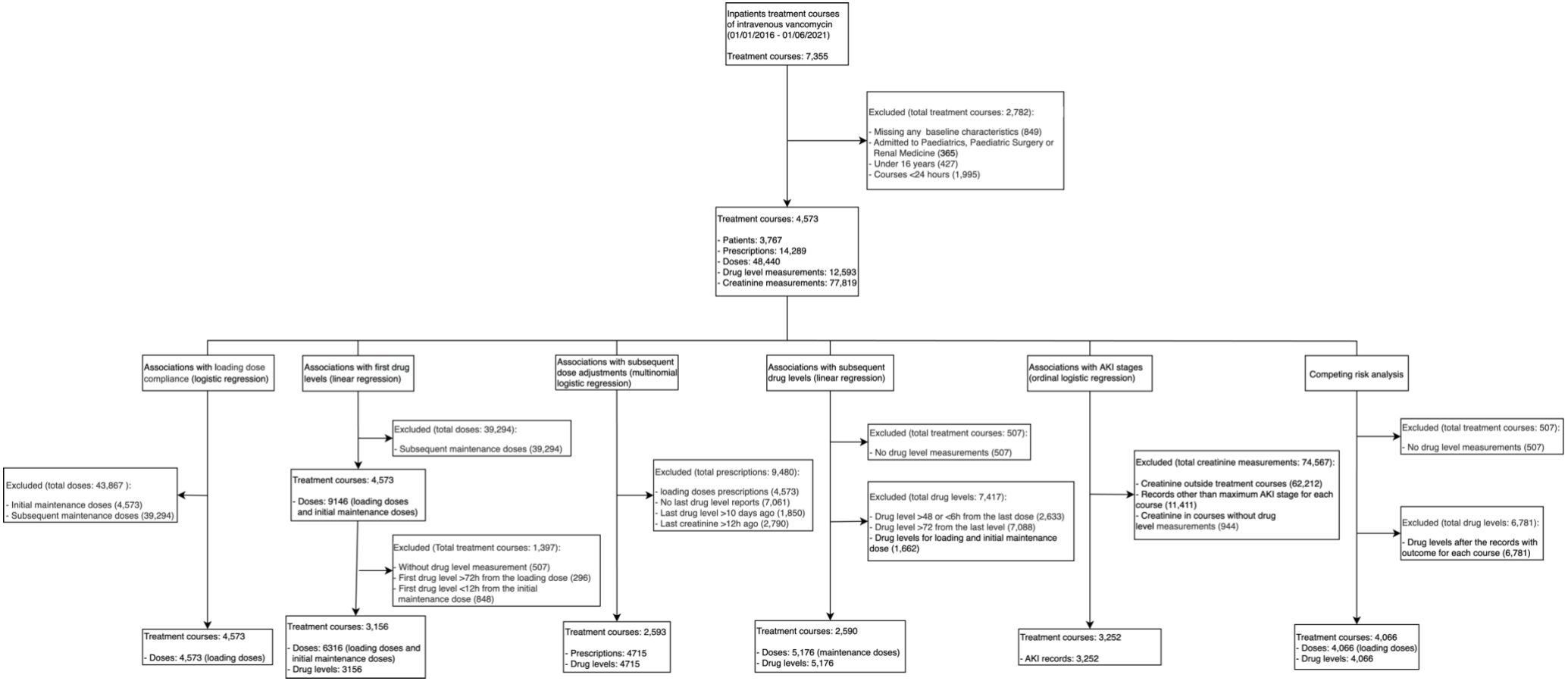


**Figure 2.1 Flowchart of the dataset selection and generation for each outcome investigated.**

**Table 2.4 Outcomes considered in regression models together with explanatory variables considered.**

| Variables | Loading Dose Compliance (logistic) | First Drug Levels (linear) | Dose Change Direction (multinomial) | Subsequent Drug Levels (linear) | Reaching drug level target or stopping drug (competing risks) | AKI Stage (ordered logistic) |
|---|---|---|---|---|---|---|
| Weight (kg) | Weight | * | Weight | * | * | * |
| Age at admission (years) | Age | Age | Age | Age | Age | Age |
| Sex | Sex | Sex | Sex | Sex | Sex | Sex |
| Charlson Score | Charlson Score | Charlson Score | Charlson Score | Charlson Score | Charlson Score | Charlson Score |
| Elixhauser Score | Elixhauser Score | Elixhauser Score | Elixhauser Score | Elixhauser Score | Elixhauser Score | Elixhauser Score |
| eGFR (pre-treatment , mL/min/1.73 $m^2$) | eGFR (pre-treatment) | eGFR (pre-treatment) | eGFR (pre-treatment) | eGFR (pre-treatment) | eGFR (pre-treatment) | eGFR (pre-treatment) |
| eGFR (most recent, mL/min/1.73 $m^2$) | | | eGFR (most recent) | | | |
| Drug Level (mg/L) | | | Preceding Drug Level within/above/below Target Range | | | Drug Level (time-average) ** |
| Daily Dose (mg/kg/day) | | | | Daily Dose (most recent) | | Daily Dose (time-average )** |
| Actual Loading Dose (mg/kg) | | Actual Loading Dose | | | Actual Loading Dose | |
| Actual Initial Maintenance Dose (mg/kg/day) | | Actual Initial Maintenance Dose | | | | |
| Dosing Interval | | Dosing Interval (initial maintenance dose) | | Dosing Interval (most recent dose) | | |
| Guideline Compliance | | Guideline Compliance (both loading dose and initial maintenance dose) | Guideline Compliance (both loading dose and initial maintenance dose) | | | |
| Time Since Loading Dose | | Time Since Loading Dose | | | | |
| Time Since Preceding Dose | | Time Since Preceding Dose (initial maintenance dose) | | Time Since Preceding Dose | | |
| Time Since Preceding Drug Level Measurement | | | | Time Since Preceding Drug Level Measurement | | |
| Dose Change ( mg/kg/day) | | | | Dose Change | | |
| Loading dose Prescription characteristics | Prescription day of year, day of week, minute of day | | | | | |
| Specialty admitted to | Specialty | | | | | |
| Calendar date and pre/post implementation | Calendar date and pre/post implementation | | | | | |
| Results | Detailed estimates in **Table** 2.7 | Detailed estimates in **Table** 2.9 | Detailed estimates in **Table** 2.11 | Detailed estimates in **Table** 2.13 | Detailed estimates in **Table** 2.15 | Detailed estimates in **Table** 2.18 |

Note: Shading indicates explanatory variables that are not applicable (e.g., occur after the outcome, are co-linear with or mediate the effects of other variables, or are not potential confounders for this outcome). *Weight not included as daily dose in mg/kg included instead. **Calculated by averaging over time up to the record with maximum AKI stage for each course using the trapezoidal rule.

I included inpatient treatment courses with intravenous vancomycin lasting ≥24 hours, defining new treatment courses by >14 days between successive doses. Each treatment course contained at least one prescription plus records of individual drug administrations. I extracted patient characteristics (age, weight, sex, ethnicity, Charlson and Elixhauser scores) and information related to the prescription, administration and monitoring of vancomycin (date and time of prescription and administration, dose, drug trough levels and serum creatinine measurements). Pre-treatment creatinine was defined as the mean over all measurements within two weeks before each treatment course. eGFR was calculated using the Modified Diet in Renal Disease (MDRD) equation [83], imputing non-black ethnicity where this was unknown.

### 2.2.2 Statistical analyses

Regression analyses of different outcomes investigated the new guideline's effectiveness and examined factors associated with doses and drug levels (**Table** 2.4).

Descriptive analysis was used to demonstrate the changes in the proportion of loading doses, initial maintenance doses, guideline compliance and first drug trough levels before and after guideline implementation. To investigate the compliance of loading doses with the new guideline, I calculated the recommended dose and dosing interval for loading and initial maintenance doses and compared them to the actual doses. Non-compliance was defined as the actual dose failing >10% beyond the recommended dose range. Logistic regression was used to examine factors associated with guideline compliance. For each course, the first drug level was matched with patient characteristics and records of the loading and initial maintenance doses. Linear

regression was conducted to investigate the association between the baseline characteristics, doses and initial trough levels.

I also used descriptive analysis to demonstrate changes in subsequent maintenance doses and drug levels during the study. Multinomial logistic regression was used to investigate the effects of several baseline characteristics and drug levels on dose adjustments. A further linear regression analysis was performed to examine whether dose adjustments for subsequent maintenance doses contributed to a higher likelihood of achieving the target drug level.

Ordered logistic regression was used to investigate the risk of nephrotoxicity at different doses and drug levels and changes in the probability of AKI before and after implementing the guidelines. AKI was defined using the Kidney Disease Improving Global Outcomes guideline [84], with AKI stages 1, 2 and 3 defined as 1.5–1.9-fold or ≥26.5μmol/l increase from baseline, 2.0–2.9-fold increase, and ≥3-fold increase or serum creatinine ≥353.6μmol/l, respectively. Changes in serum creatinine were calculated by comparing with the pre-treatment creatinine values. I extracted the records with the maximum AKI stage for each course and calculated average drug levels and doses (averaged over time up to that record) using the trapezoidal rule.

Competing risks analysis was conducted to investigate the effects of different ranges of loading dose on the cumulative incidence of reaching the target level over time, allowing for the competing risk of stopping vancomycin before reaching the target level. I also

examined the probability of achieving the target conditional on remaining on vancomycin for different loading dose groups.

To optimise the recommended maintenance dose, I used a simplified linear model, incorporating three baseline characteristics (i.e., age, eGFR, weight) and the actual initial maintenance dose, to estimate their relationship with the first drug trough level. With this model, I predicted the first drug trough level resulting from all possible combinations of age, eGFR, weight and daily dose, which simulated the relationship between dose and drug levels in different patient groups. I then filtered out combinations with trough levels in the target range (15–20mg/L) to obtain the potential doses required to achieve target levels in patients of different ages, renal function and body weight. I evaluated the probable impact of these updated guidelines using pharmacokinetic models. TDMx, which simulates six population pharmacokinetic models [85], was used to predict trough levels and $AUC_{24h}$/MIC ratios.

In all models, continuous explanatory variables were truncated at 1% and 99% to reduce the influence of outliers. Potential non-linear associations were investigated using natural cubic splines. The number of knots was determined based on Akaike Information Criteria (AIC) in univariate models. Then, this degree of non-linearity was retained in multivariable models only where it improved model fit ($p<0.05$). Two-way interactions were included in models where the interaction $p<0.05$.

## 2.3 Results

From 1 January 2016 to 1 June 2021, there were 4,573 inpatient vancomycin treatment courses lasting ≥24h in 3,767 patients ≥16 years (**Figure** 2.1). The median age, weight and eGFR at the start of each course were 62.5 (IQR 48.9–73.2) years, 80.0 (IQR 67.2–93.7) kg, and 90.8 (IQR 70.1–112.2) mL/min/1.73 $m^2$, respectively; 58.1% of courses were in males (**Table** 2.5). Patients had relatively few comorbidities, with most admitted to Trauma and Orthopaedics (57.5%), Neurosurgery (10.5%) and Clinical Haematology (8.7%).

**Table 2.5 Patient characteristics at the start of vancomycin courses.**

| Variable | Overall (N=4573) |
|---|---|
| Age at admission (years) | |
| Median (Q1, Q3) | 62.5 (48.9, 73.2) |
| Sex | |
| Male | 2658 (58.1%) |
| Female | 1915 (41.9%) |
| Weight (kg) | |
| Median (Q1, Q3) | 80.0 (67.2, 93.7) |
| eGFR (mL/min/1.73 $m^2$) | |
| Median (Q1, Q3) | 90.8 (70.1, 112.2) |
| Ethnicity | |
| White | 3567 (78.0%) |
| Black | 70 (1.5%) |
| Asian | 123 (2.7%) |
| Other | 74 (1.6%) |
| Unknown | 739 (16.2%) |
| Charlson score | |
| Median (Q1, Q3) | 1 (0, 1) |
| Elixhauser score | |
| Median (Q1, Q3) | 2 (1, 3) |
| Specialty admitted to | |
| Trauma and Orthopaedics | 2630 (57.5%) |
| Neurosurgery | 482 (10.5%) |
| Clinical Haematology | 397 (8.7%) |
| General Surgery | 260 (5.7%) |
| General Internal Medicine | 139 (3.0%) |
| Geriatric Medicine | 104 (2.3%) |
| Gastroenterology | 83 (1.8%) |
| Infectious Diseases | 82 (1.8%) |
| Cardiology | 68 (1.5%) |
| Emergency Medicine | 7 (0.2%) |
| Other Medical specialties | 135 (3.0%) |
| Other Surgical specialties | 166 (3.6%) |
| Other | 20 (0.4%) |

Note: Characteristics are shown per treatment course at the initial prescription for each vancomycin treatment course between 01 January 2016 and 01 June 2021.

### 2.3.1 Changes in doses following new guideline implementation

Following the implementation of the new vancomycin dosing guideline in August 2016, there were notable shifts in loading doses from predominantly 1000mg (66% before August 2016) to 2000mg (57% after August 2016), and in initial maintenance doses, which were more varied with the new guideline (**Figure** 2.2**A/B/D/E**). Guideline compliance continued to increase slightly over 2017–2021 for both loading and initial maintenance doses (to 84% and 70%, respectively) (**Figure** 2.2**G/H**).

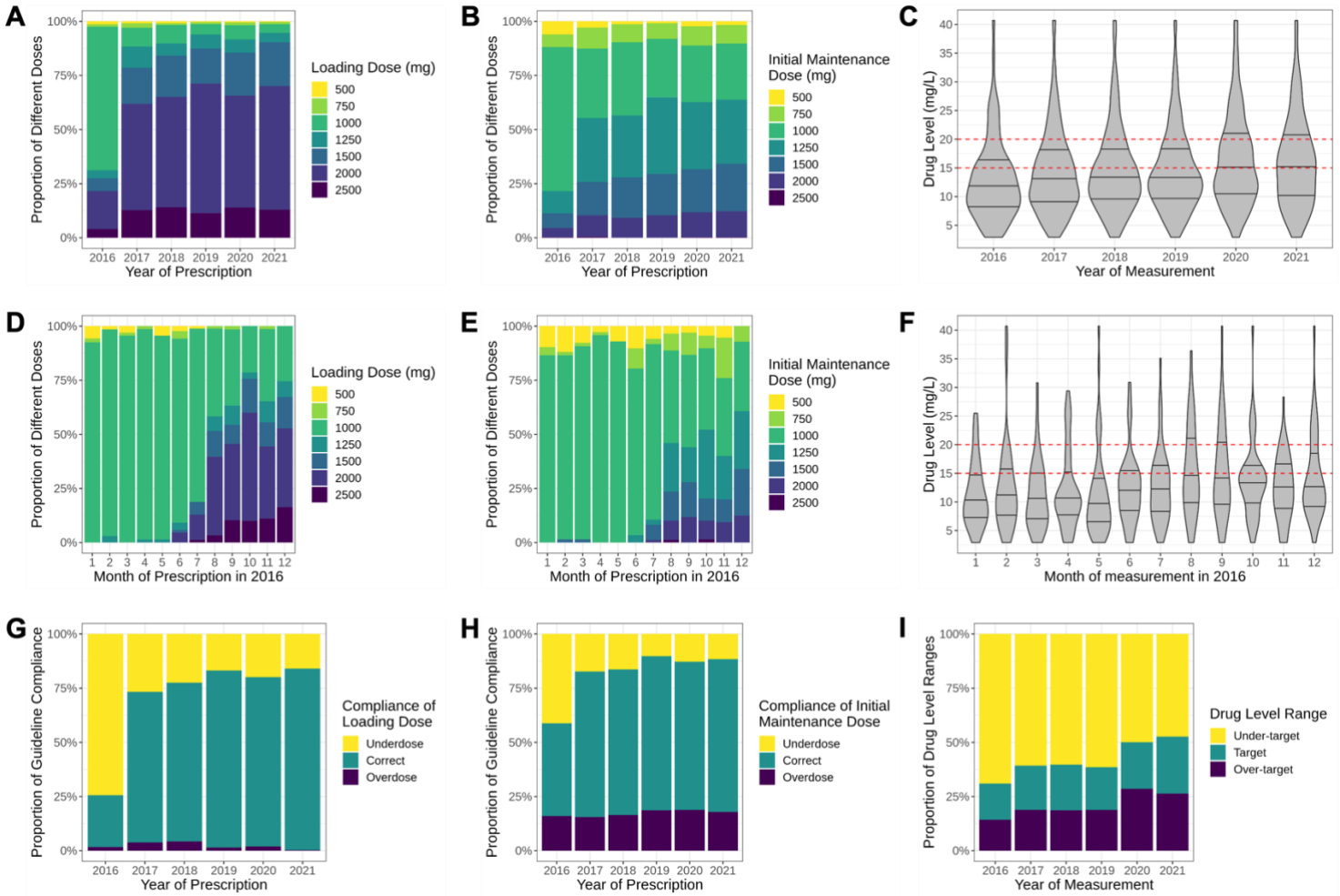


**Figure 2.2 Vancomycin doses and compliance with guidelines.**
Loading doses, initial maintenance doses and first drug trough levels are shown in panels A–C, by year for 2016 to 2021, and panels D–F by months in 2016. Panels G and H show the proportion of loading and initial maintenance doses compliant (±10%) with the guidelines by year, and panel I shows the proportion of drug levels in the range (15–20mg/L). The dashed red lines in panels C and F indicate the target vancomycin trough level ranges.

Multiple independent factors were associated with loading doses complying with the guideline (**Table** 2.6, **Table** 2.7). Guideline compliance independently increased with patient age (odds ratio (OR)=1.14 per 10 years older [95% confidence interval (CI) 1.09,1.20]) and eGFR (OR=1.05 per 10mL/min/1.73 $m^2$ higher [1.03,1.08]) but decreased with higher Elixhauser scores (OR=0.91 per unit higher [0.84,0.98]) (an EHR-based measure of illness acuity). Compliance was independently lower in those admitted to Trauma and Orthopaedics (OR=0.30 [0.18,0.49]) and Cardiology (OR=0.37 [0.17,0.78]) compared to General Internal Medicine. Compliance increased significantly in the months before the formal implementation of the guidelines (OR=4.41 per month [1.96,9.91]) and continued to increase after implementation but at a much slower rate (OR=1.02 per month [1.02,1.03]). Compliance rose slightly from the beginning of August (the annual start time for each new cohort of junior doctors) to the end of the following July (OR=1.04 per month [1.02,1.06]). Additionally, compliance was higher for prescriptions written around midday than at midnight (**Figure** 2.3) and was lower for prescriptions written on Mondays (OR=0.58 vs Wednesday [0.45,0.74]).

**Table 2.6 Characteristics of loading dose prescriptions by compliance with the guideline (N=4573).**

| Variable | Incorrect (N=1547) | Correct (N=3026) | Total (N=4573) | p value |
|---|---|---|---|---|
| Age at admission (years) | | | | **0.02** |
| Median (Q1, Q3) | 61.2 (47.8, 73.0) | 63.0 (49.4, 73.3) | 62.5 (48.9, 73.2) | |
| Sex | | | | 0.08 |
| Male | 927 (59.9%) | 1731 (57.2%) | 2658 (58.1%) | |
| Female | 620 (40.1%) | 1295 (42.8%) | 1915 (41.9%) | |
| Weight (kg) | | | | 0.76 |
| Median (Q1, Q3) | 79.7 (66.5, 96.7) | 80.0 (68.0, 92.7) | 80.0 (67.2, 93.7) | |
| eGFR (mL/min/1.73 $m^2$) | | | | **<0.0001** |
| Median (Q1, Q3) | 88.5 (68.2, 110.0) | 91.8 (71.6, 113.4) | 90.8 (70.1, 112.2) | |
| Ethnicity | | | | 0.11 |
| White | 1184 (76.5%) | 2383 (78.8%) | 3567 (78.0%) | |
| Black | 32 (2.1%) | 38 (1.3%) | 70 (1.5%) | |
| Asian | 38 (2.5%) | 85 (2.8%) | 123 (2.7%) | |
| Other | 25 (1.6%) | 49 (1.6%) | 74 (1.6%) | |
| Unknown | 268 (17.3%) | 471 (15.6%) | 739 (16.2%) | |
| Charlson score | | | | 0.45 |
| Median (Q1, Q3) | 1 (0, 1) | 1 (0, 1) | 1 (0, 1) | |
| Elixhauser score | | | | 0.82 |
| Median (Q1, Q3) | 2 (1, 3) | 2 (1, 3) | 2 (1, 3) | |
| Specialty admitted to | | | | **<0.0001** |
| General Internal Medicine | 39 (2.5%) | 100 (3.3%) | 139 (3.0%) | |
| General Surgery | 85 (5.5%) | 175 (5.8%) | 260 (5.7%) | |
| Trauma and Orthopaedics | 1000 (64.6%) | 1629 (53.8%) | 2629 (57.5%) | |
| Neurosurgery | 112 (7.2%) | 371 (12.3%) | 483 (10.6%) | |
| Emergency Medicine | 2 (0.1%) | 5 (0.2%) | 7 (0.2%) | |
| Gastroenterology | 14 (0.9%) | 69 (2.3%) | 83 (1.8%) | |
| Clinical Haematology | 99 (6.4%) | 298 (9.8%) | 397 (8.7%) | |
| Cardiology | 32 (2.1%) | 36 (1.2%) | 68 (1.5%) | |
| Infectious Diseases | 29 (1.9%) | 53 (1.8%) | 82 (1.8%) | |
| Geriatric Medicine | 30 (1.9%) | 74 (2.4%) | 104 (2.3%) | |
| Other Medical specialty | 44 (2.8%) | 91 (3.0%) | 135 (3.0%) | |
| Other Surgical specialty | 59 (3.8%) | 107 (3.5%) | 166 (3.6%) | |
| Other | 2 (0.1%) | 18 (0.6%) | 20 (0.4%) | |
| Prescription day of week | | | | **<0.0001** |
| Sun | 283 (6.2%) | 87 (5.6%) | 196 (6.5%) | |
| Mon | 634 (13.9%) | 268 (17.3%) | 366 (12.1%) | |
| Tue | 640 (14.0%) | 215 (13.9%) | 425 (14.0%) | |
| Wed | 977 (21.4%) | 304 (19.7%) | 673 (22.2%) | |
| Thu | 695 (15.2%) | 219 (14.2%) | 476 (15.7%) | |
| Fri | 981 (21.5%) | 345 (22.3%) | 636 (21.0%) | |
| Sat | 363 (7.9%) | 109 (7.0%) | 254 (8.4%) | |

**Table 2.7 Factors independently associated with compliance with the new guideline loading dose.**

| Factors | OR | 95% CI | p value |
|---|---|---|---|
| Age (per 10 years) | 1.14 | 1.09 – 1.20 | **<0.0001** |
| Sex | | | |
| Male | Reference | | |
| Female | 1.04 | 0.89 – 1.22 | 0.59 |
| Weight (per 10 kg) | 1.03 | 0.99 – 1.07 | 0.16 |
| eGFR (per 10 mL/min/1.73 $m^2$) | 1.05 | 1.03 – 1.08 | **0.0001** |
| Charlson score | 1.05 | 0.94 – 1.17 | 0.37 |
| Elixhauser score | 0.91 | 0.84 – 0.98 | **0.01** |
| Specialty admitted to | | | |
| General Internal Medicine | Reference | | |
| General Surgery | 0.53 | 0.30 – 0.92 | 0.03 |
| Trauma and Orthopaedics | 0.30 | 0.18 – 0.48 | **<0.0001** |
| Neurosurgery | 1.20 | 0.68 – 2.06 | 0.52 |
| Emergency Medicine | 1.03 | 0.15 – 20.18 | 0.98 |
| Gastroenterology | 2.15 | 0.89 – 5.72 | 0.11 |
| Clinical Haematology | 1.10 | 0.61 – 1.95 | 0.74 |
| Cardiology | 0.37 | 0.17 – 0.78 | **0.009** |
| Infectious Diseases | 0.51 | 0.25 – 1.06 | 0.07 |
| Geriatric Medicine | 0.93 | 0.45 – 1.92 | 0.84 |
| Other Medical specialty | 1.02 | 0.51 – 2.07 | 0.95 |
| Other Surgical specialty | 0.50 | 0.27 – 0.91 | **0.02** |
| Other | 8.08 | 1.27 – 123.72 | 0.06 |
| Prescription day of week | | | |
| Wed | Reference | | |
| Sun | 0.88 | 0.61 – 1.30 | 0.52 |
| Mon | 0.58 | 0.45 – 0.74 | **<0.0001** |
| Tue | 0.77 | 0.60 – 0.99 | **0.04** |
| Thu | 0.83 | 0.65 – 1.07 | 0.15 |
| Fri | 0.74 | 0.59 – 0.93 | **0.01** |
| Sat | 1.00 | 0.71 – 1.43 | 0.98 |
| Prescription minute of day | See **Figure 2.3** | | 0.10 |
| Prescription day of year (from 1 August, per 30 days) | 1.04 | 1.02 – 1.06 | **0.0004** |
| Guideline implementation (post vs pre) | 9.18 | 3.93 – 22.09 | **<0.0001** |
| Days before guideline implementation (per 30 days) | 4.41 | 2.23 – 11.41 | **0.0003** |
| Days after guideline implementation (per 30 days) | 1.02 | 1.02 – 1.03 | **<0.0001** |

Note: See **Table 2.6** for the distribution of characteristics. Potential confounding variables (i.e., weight, sex, Charlson score, time of the year, week and day when the prescription was written) were included in the analysis regardless of significance, see **Table 2.4**. The day of the year when the prescription was written was counted from 01 August to reflect the annual start time for each new cohort of junior doctors. Natural cubic splines were used with 4 knots at the 10th, 33rd, 67th and 90th percentiles to allow for non-linearity in the effects of time of the day of the prescription on guideline compliance. There was no evidence of interaction between factors in the model ($p>0.05$).

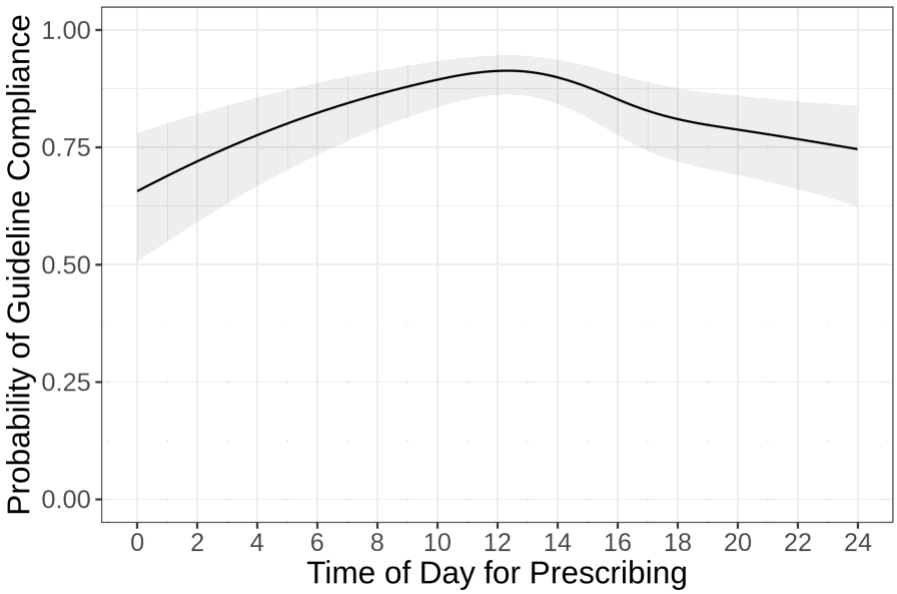


**Figure 2.3 Associations between the time of day of the prescription and guideline compliance of the loading dose.**
Other factors were held constant at their mean (for continuous variables) or reference levels (for categorical variables).

There were 3156 (69%) treatment courses that had a drug level taken within 72 hours of starting intravenous vancomycin (median 43.0h (IQR 36.9–47.4) [range 19.6,71.9]). The substantial shifts in loading and initial maintenance dose over time (**Figure** 2.2**A/B/D/E**) had relatively small effects on the first drug trough levels (**Figure** 2.2**C/F**), with only a modestly increasing trend over 2016–2021 and a limited increase in the proportion of first drug levels reaching the target range (from 17% to 26%, **Figure** 2.2**I**). Notably, even in those following the guideline-recommended loading and initial maintenance dose, only 20% of first drug levels reached the target range.

First drug trough levels were independently associated with several baseline factors (**Table** 2.8, **Table** 2.9) with the strongest effects from eGFR and age rather than dose per kg or dosing compliance. Drug levels were independently lower in those with higher eGFR (0.74mg/L lower for every ten mL/min/1.73m$^2$ higher [95% CI 0.62,0.86]). Drug levels were higher in older individuals when initial maintenance doses were

administered twice daily (1.12mg/L per 10 years older [0.95,1.28]), with no evidence of an effect of age with once-daily administration (-0.01mg/L per 10 years older [-0.47,0.45, interaction p<0.0001]). Drug levels were also higher in those with higher Elixhauser scores (0.81mg/L per unit higher [0.58,1.03]). As expected for levels obtained ~48h into treatment, the initial maintenance dose had a stronger effect (0.23mg/L higher per 1mg/kg/day higher [0.16,0.29]) than the effect of the loading dose (-0.06mg/L lower per 1mg/kg/day higher [-0.11,0.01]). Underdosing compared to guideline recommendations in the loading dose and initial maintenance dose resulted in lower drug levels (-0.92mg/L [-1.47,-0.37] and -0.67mg/L [-1.45,0.11], respectively) and conversely overdosing in higher drug levels (1.73mg/L [0.14,3.32] and 1.11mg/L [0.37,1.84], respectively).

**Table 2.8 Characteristics of inpatient vancomycin treatment courses by whether the first drug level reached the target trough level (N=3156).**

| Variable | Under-target (N=1871) | Target (N=642) | Over-target (N=643) | Total (N=3156) | p value |
|---|---|---|---|---|---|
| Age at admission (years) | | | | | **<0.0001** |
| Median (Q1, Q3) | 57.0 (43.2, 69.2) | 69.0 (60.2, 77.0) | 68.3 (57.6, 76.7) | 62.9 (49.1, 72.8) | |
| Sex | | | | | **<0.0001** |
| Male | 1138 (60.8%) | 346 (53.9%) | 327 (50.9%) | 1811 (57.4%) | |
| Female | 733 (39.2%) | 296 (46.1%) | 316 (49.1%) | 1345 (42.6%) | |
| Weight (kg) | | | | | **<0.0001** |
| Median (Q1, Q3) | 79.0 (66.9, 92.0) | 80.5 (69.5, 96.0) | 83.5 (70.0, 101.2) | 80.0 (68.0, 94.6) | |
| eGFR (mL/min/1.73 $m^2$) | | | | | **<0.0001** |
| Median (Q1, Q3) | 99.0 (81.5, 120.5) | 84.8 (67.1, 102.9) | 77.2 (62.0, 99.0) | 92.2 (73.2, 113.5) | |
| Ethnicity | | | | | **0.002** |
| White | 1428 (76.3%) | 526 (81.9%) | 526 (81.8%) | 2480 (78.6%) | |
| Black | 29 (1.5%) | 3 (0.5%) | 5 (0.8%) | 37 (1.2%) | |
| Asian | 57 (3.0%) | 12 (1.9%) | 24 (3.7%) | 93 (2.9%) | |
| Other | 41 (2.2%) | 6 (0.9%) | 10 (1.6%) | 57 (1.8%) | |
| Unknown | 316 (16.9%) | 95 (14.8%) | 78 (12.1%) | 489 (15.5%) | |
| Charlson score | | | | | **<0.0001** |
| Median (Q1, Q3) | 1 (0, 1) | 1 (0, 1) | 1 (0, 2) | 1 (0, 1) | |
| Elixhauser score | | | | | **<0.0001** |
| Median (Q1, Q3) | 1 (0, 2) | 2 (1, 3) | 2 (1, 3) | 2 (1, 3) | |
| Loading dose (mg/kg) | | | | | 0.09 |
| Median (Q1, Q3) | 24.7 (21.4, 27.6) | 24.0 (20.9, 27.0) | 24.3 (21.6, 27.2) | 24.4 (21.4, 27.4) | |
| Initial maintenance dose (mg/kg/day) | | | | | **<0.0001** |
| Median (Q1, Q3) | 30.6 (25.1, 33.7) | 28.6 (23.9, 32.9) | 29.0 (25.0, 34.1) | 29.9 (25.0, 33.6) | |
| Maintenance dosing interval (hour) | | | | | **0.0002** |
| 12 | 1720 (91.9%) | 555 (86.4%) | 576 (89.6%) | 2851 (90.3%) | |
| 24 | 151 (8.1%) | 87 (13.6%) | 67 (10.4%) | 305 (9.7%) | |
| Loading dose compliance | | | | | **0.0002** |
| Underdose | 584 (31.2%) | 170 (26.5%) | 153 (23.8%) | 907 (28.7%) | |
| Correct | 1250 (66.8%) | 460 (71.7%) | 465 (72.3%) | 2175 (68.9%) | |
| Overdose | 37 (2.0%) | 12 (1.9%) | 25 (3.9%) | 74 (2.3%) | |
| Initial maintenance dose compliance | | | | | **<0.0001** |
| Underdose | 384 (20.5%) | 109 (17.0%) | 64 (10.0%) | 557 (17.6%) | |
| Correct | 1280 (68.4%) | 409 (63.7%) | 391 (60.8%) | 2080 (65.9%) | |
| Overdose | 207 (11.1%) | 124 (19.3%) | 188 (29.2%) | 519 (16.4%) | |

**Table 2.9 Factors independently associated with first drug level.**

| Factors | Coefficients | 95% CI | p value |
|---|---|---|---|
| (Intercept) | 9.36 | 6.91 – 11.82 | **<0.0001** |
| Age (per 10 years) | 1.12 | 0.95 – 1.28 | **<0.0001** |
| Sex | | | |
| Male | Reference | | |
| Female | 0.76 | 0.28 – 1.24 | **0.002** |
| eGFR (per 10 mL/min/1.73 $m^2$) | -0.74 | -0.86 – -0.62 | **<0.0001** |
| Charlson score | -0.22 | -0.55 – 0.10 | 0.18 |
| Elixhauser score | 0.81 | 0.58 – 1.03 | **<0.0001** |
| Loading dose (mg/kg) | -0.06 | -0.11 – -0.01 | **0.02** |
| Initial maintenance dose (mg/kg/day) | 0.23 | 0.16 – 0.29 | **<0.0001** |
| Loading dose compliance | | | |
| Correct | Reference | | |
| Underdose | -0.92 | -1.47 – -0.37 | **0.001** |
| Overdose | 1.73 | 0.14 – 3.32 | **0.03** |
| Initial maintenance dose compliance | | | |
| Correct | Reference | | |
| Underdose | -0.67 | -1.45 – 0.11 | 0.09 |
| Overdose | 1.11 | 0.37 – 1.84 | **0.003** |
| Maintenance dosing interval (hour) | | | |
| 12 | Reference | | |
| 24 | 8.20 | 4.76 – 11.65 | **<0.0001** |
| Time since loading doses (hour) | -0.05 | -0.10 – 0.01 | 0.09 |
| Time since initial maintenance doses (hour) | 0.04 | -0.01 – 0.10 | 0.12 |
| Age : Maintenance dosing interval of 24h | -0.11 | -0.16 – -0.06 | **<0.0001** |

Note: See **Table** 2.8 for the distribution of characteristics. Weight was not considered as dose in mg/kg/day was included instead. There was strong evidence of an interaction between age and dosing interval for the initial maintenance dose so this was included ($p<0.0001$), but no evidence of interaction between other factors in the model ($p>0.05$). Potential confounding variables (i.e., Charlson score, time since loading doses and time since initial maintenance doses) were included in the analysis regardless of significance.

### 2.3.2 Changes in maintenance doses after initial drug levels

Compared to changes in loading and initial maintenance doses, there were minor changes in the subsequent maintenance doses after guideline implementation (**Figure** 2.4**A/B**). Subsequent maintenance doses increased slightly from August 2016 and remained high over 2017–2021. Proportionally, doses within 30–40mg/kg/day rose by about 17%, while doses within 10–20mg/kg/day fell by about 7% (**Figure** 2.4**C**).

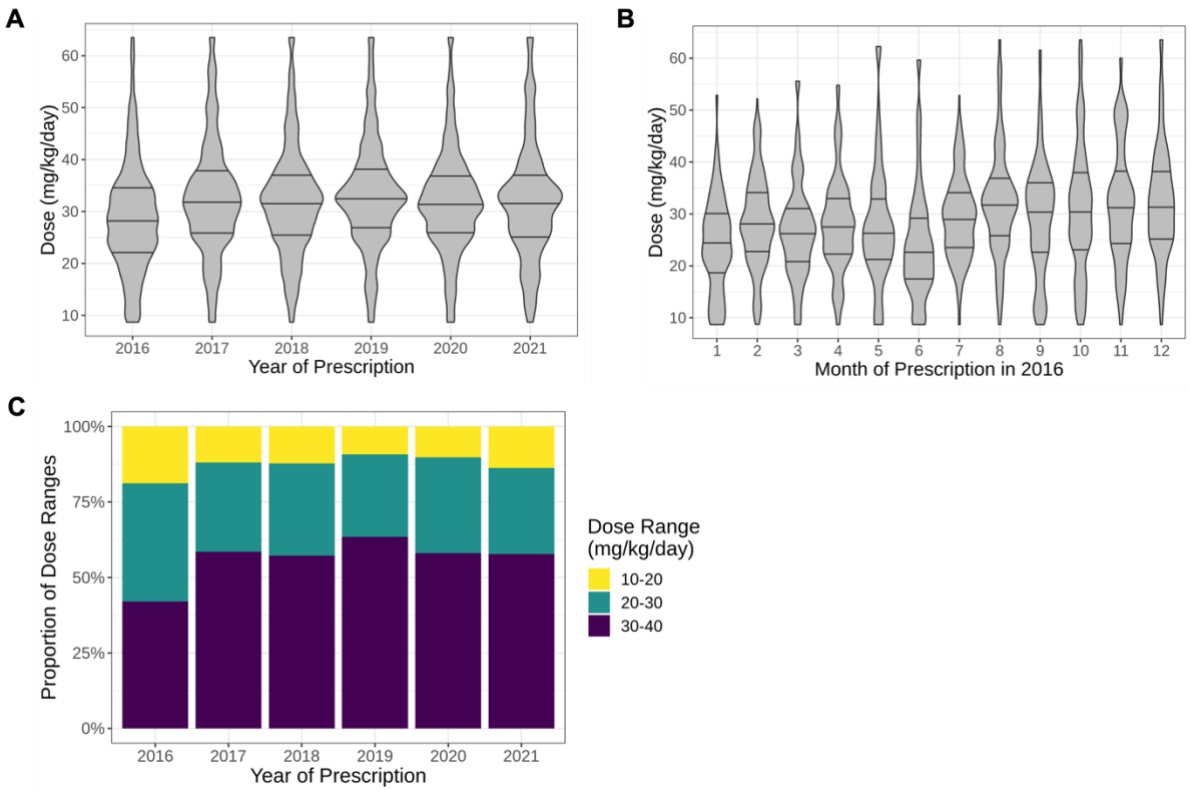


**Figure 2.4 Subsequent vancomycin maintenance doses.**
Panel A shows doses by years between 2016 and 2021, and panel B by month in 2016. Panel C shows the proportion of doses in three dose ranges (10–20mg/kg/day., 20–30mg/kg/day, 30–40mg/kg/day) over 2016-2021.

For maintenance dose prescriptions issued following measured drug levels (N=4715), 833 (21%) followed a trough level within the target range. Following below target drug levels, 2076/2927 (71%) maintenance dose prescriptions increased the dose, and following above target drug levels 706/955 (74%) lowered the dose. The median dose changes (mg/day) following measured drug levels <10mg/L, 10–15mg/L, 15–20mg/L and >20mg/L were 500 (IQR 200–1000), 500 (IQR 0–500), 0 (IQR -250–0), -500 (IQR -500–0), respectively (**Figure** 2.5, also shows percentage changes). Examining the effects of drug levels on subsequent dose adjustments using multinomial logistic regression (**Table** 2.10, **Table** 2.11), the strongest associations were with most recent eGFR, but these varied according to the previous drug level (**Figure** 2.6). When the previous drug level was below target (<15mg/L), maintenance doses were generally (72–77% of the

time) increased in patients with normal renal function (eGFR≥80mL/min/1.73m$^2$), while the likelihood of maintaining or even lowering the current dose increased with lower eGFR. Conversely, high drug levels (>20mg/L) generally (78–80% of the time) led to lower subsequent maintenance doses, although this decreased at higher eGFR (≥80mL/min/1.73m$^2$). Effects of other factors were much smaller. For example, the odds of reducing maintenance doses were higher in patients with higher pre-treatment eGFR (relative-risk ratio (RRR)=1.10 per 10mL/min/1.73 m$^2$ higher [1.05,1.16]), higher body weight (RRR=1.09 per 10kg higher [1.04,1.14]) and in older individuals (RRR=1.07 per 10 years higher [1.01,1.13]).

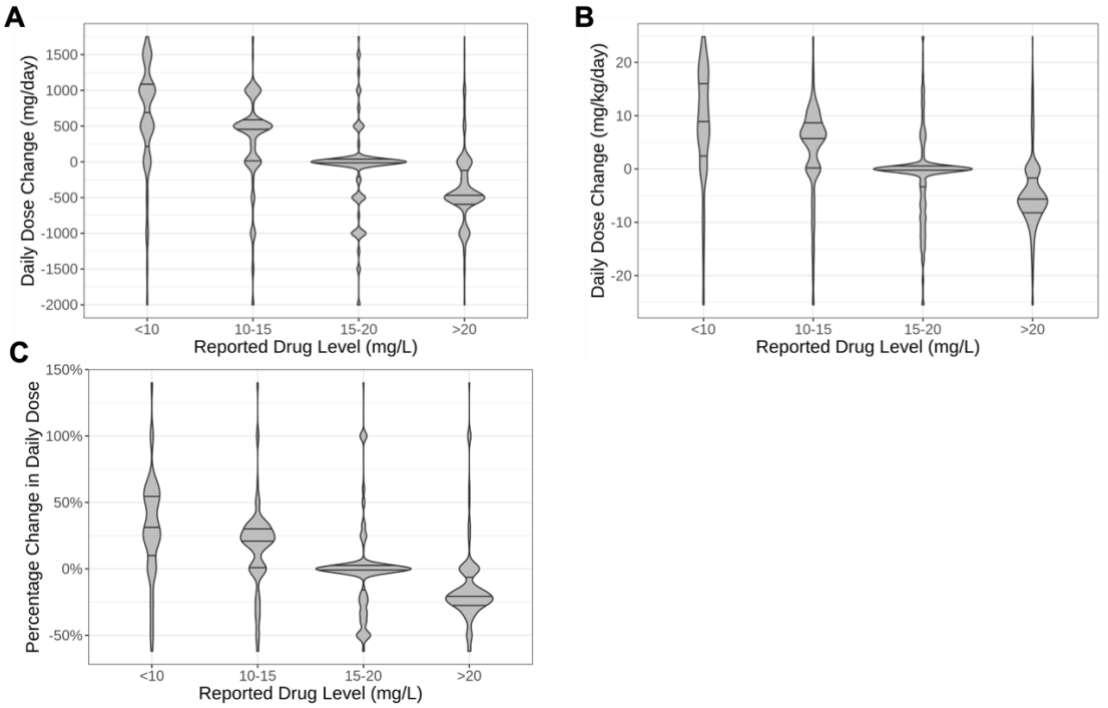


**Figure 2.5 Maintenance dose adjustment following measured drug levels.**
Panel A shows daily maintenance dose change (mg/day) following measured drug trough levels at different ranges (<10mg/L, 10–15mg/L, 15–20mg/L, >20mg/L), panel B daily maintenance dose change by body weight (mg/kg/day) and panel C percentage change in daily maintenance dose. The median daily maintenance dose change (mg/day) following measured drug level at <10 mg/L, 10–15mg/L, 15–20mg/L and >20mg/L were 500 (IQR 200–1000), 500 (IQR 0–500), 0 (IQR -250–0), -500 (IQR -500–0), respectively; the median daily maintenance dose change by body weight (mg/kg /day) were 8.7 (IQR 2.1–16.8), 6.0 (IQR 0–8.6), 0 (IQR -3.3–0) and -5.7 (IQR -7.9–-0.4).

**Table 2.10 Characteristics of prescriptions of maintenance doses by direction of dose change (N=4715).**

| Variable | Increased (N=2277) | Maintained (N=1126) | Reduced (N=1312) | Total (N=4715) | p value |
|---|---|---|---|---|---|
| Age at admission (years) | | | | | **<0.0001** |
| Median (Q1, Q3) | 56.7 (42.5, 69.1) | 63.7 (49.6, 74.4) | 66.0 (53.3, 76.0) | 61.0 (46.7, 72.7) | |
| Sex | | | | | **<0.0001** |
| Male | 1411 (62.0%) | 633 (56.2%) | 717 (54.6%) | 2761 (58.6%) | |
| Female | 866 (38.0%) | 493 (43.8%) | 595 (45.4%) | 1954 (41.4%) | |
| Weight (kg) | | | | | **<0.0001** |
| Median (Q1, Q3) | 78.0 (65.3, 90.0) | 77.8 (66.0, 91.9) | 80.0 (67.0, 96.2) | 78.7 (66.0, 92.0) | |
| eGFR (pre-treatment, mL/min/1.73 $m^2$) | | | | | **<0.0001** |
| Median (Q1, Q3) | 99.3 (79.1, 124.4) | 86.9 (59.4, 110.1) | 83.7 (62.5, 110.1) | 92.9 (69.0, 117.3) | |
| eGFR (most recent, mL/min/1.73 $m^2$) | | | | | **<0.0001** |
| Median (Q1, Q3) | 109.8 (88.4, 140.1) | 94.8 (67.9, 121.9) | 88.5 (64.9, 116.2) | 101.4 (77.0, 130.2) | |
| Ethnicity | | | | | 0.49 |
| White | 1711 (75.1%) | 878 (78.0%) | 1013 (77.2%) | 3602 (76.4%) | |
| Black | 40 (1.8%) | 15 (1.3%) | 17 (1.3%) | 72 (1.5%) | |
| Asian | 83 (3.6%) | 29 (2.6%) | 35 (2.7%) | 147 (3.1%) | |
| Other | 37 (1.6%) | 15 (1.3%) | 18 (1.4%) | 70 (1.5%) | |
| Unknown | 406 (17.8%) | 189 (16.8%) | 229 (17.5%) | 824 (17.5%) | |
| Charlson score | | | | | **<0.0001** |
| Median (Q1, Q3) | 1 (0, 1) | 1 (0, 2) | 1 (0, 2) | 1 (0, 1) | |
| Elixhauser score | | | | | **<0.0001** |
| Median (Q1, Q3) | 1 (0, 2) | 2 (1, 3) | 2 (1, 3) | 2 (1, 3) | |
| Range of reported drug level | | | | | **<0.0001** |
| Under-target (<15mg/L) | 2076 (91.2%) | 462 (41.0%) | 389 (29.6%) | 2927 (62.1%) | |
| Target (15–20mg/L) | 123 (5.4%) | 493 (43.8%) | 217 (16.5%) | 833 (17.7%) | |
| Over-target (>20mg/L) | 78 (3.4%) | 171 (15.2%) | 706 (53.8%) | 955 (20.3%) | |
| Loading dose compliance | | | | | 0.13 |
| Underdose | 740 (32.5%) | 322 (28.6%) | 395 (30.1%) | 1457 (30.9%) | |
| Correct | 1482 (65.1%) | 769 (68.3%) | 885 (67.5%) | 3136 (66.5%) | |
| Overdose | 55 (2.4%) | 35 (3.1%) | 32 (2.4%) | 122 (2.6%) | |
| Initial maintenance dose compliance | | | | | **<0.0001** |
| Underdose | 555 (24.4%) | 207 (18.4%) | 214 (16.3%) | 976 (20.7%) | |
| Correct | 1432 (62.9%) | 690 (61.3%) | 796 (60.7%) | 2918 (61.9%) | |
| Overdose | 290 (12.7%) | 229 (20.3%) | 302 (23.0%) | 821 (17.4%) | |

**Table 2.11 Factors independently associated with changes in maintenance doses following drug levels.**

| | Dose Change: Increased | | | Dose Change: Reduced | | |
|---|---|---|---|---|---|---|
| **Factors** | **RRR[1]** | **95% CI[1]** | **p value** | **RRR[1]** | **95% CI[1]** | **p value** |
| Age (per 10 years) | 1.04 | 0.99 – 1.10 | 0.15 | 1.07 | 1.01 – 1.13 | **0.03** |
| Sex | | | | | | |
| Male | Reference | | | Reference | | |
| Female | 0.91 | 0.76 – 1.09 | 0.29 | 1.11 | 0.92 – 1.33 | 0.28 |
| Weight (per 10 kg) | 0.95 | 0.91 – 1.00 | **0.04** | 1.09 | 1.04 – 1.14 | **0.0005** |
| eGFR (pre-treatment, per 10 mL/min/1.73 $m^2$) | 0.99 | 0.95 – 1.04 | 0.70 | 1.10 | 1.05 – 1.16 | **0.0001** |
| eGFR (most recent) | See | | **<0.0001** | See | | **<0.0001** |
| Charlson score | 0.88 | 0.79 – 0.99 | **0.04** | 0.95 | 0.84 – 1.07 | 0.38 |
| Elixhauser score | 0.95 | 0.88 – 1.04 | 0.25 | 1.01 | 0.93 – 1.10 | 0.76 |
| Range of reported drug level | | | | | | |
| Target | Reference | | | Reference | | |
| Under-target | 14.55 | 9.38 – 22.58 | **<0.0001** | 1.55 | 1.11 – 2.15 | **0.01** |
| Over-target | 1.59 | 0.79 – 3.21 | 0.20 | 6.26 | 4.39 – 8.92 | **<0.0001** |
| Loading dose compliance | | | | | | |
| Correct | Reference | | | Reference | | |
| Underdose | 1.20 | 0.98 – 1.45 | 0.07 | 1.10 | 0.90 – 1.35 | 0.37 |
| Overdose | 0.89 | 0.53 – 1.48 | 0.65 | 0.85 | 0.49 – 1.46 | 0.56 |
| Initial maintenance dose compliance | | | | | | |
| Correct | Reference | | | Reference | | |
| Underdose | 1.20 | 0.96 – 1.50 | 0.11 | 0.85 | 0.66 – 1.08 | 0.19 |
| Overdose | 0.82 | 0.64 – 1.04 | 0.11 | 1.18 | 0.94 – 1.49 | 0.16 |
| eGFR (most recent) : Range of reported drug level | See **Figure 2.6** | | **<0.0001** | See | | **<0.0001** |

[1]RRR = Relative-Risk Ratio, CI = Confidence Interval

Note: See **Table** 2.10 for the distribution of characteristics. Natural cubic splines were used with 4 knots at the 10th, 33rd, 67th and 90th percentiles to allow for non-linearity in the effects of the most recent eGFR on dose adjustments. There was strong evidence of an interaction between the range of the last drug level and the most recent eGFR, so this was included (p<0.0001), but no evidence of interaction between other factors in the model (p>0.05).

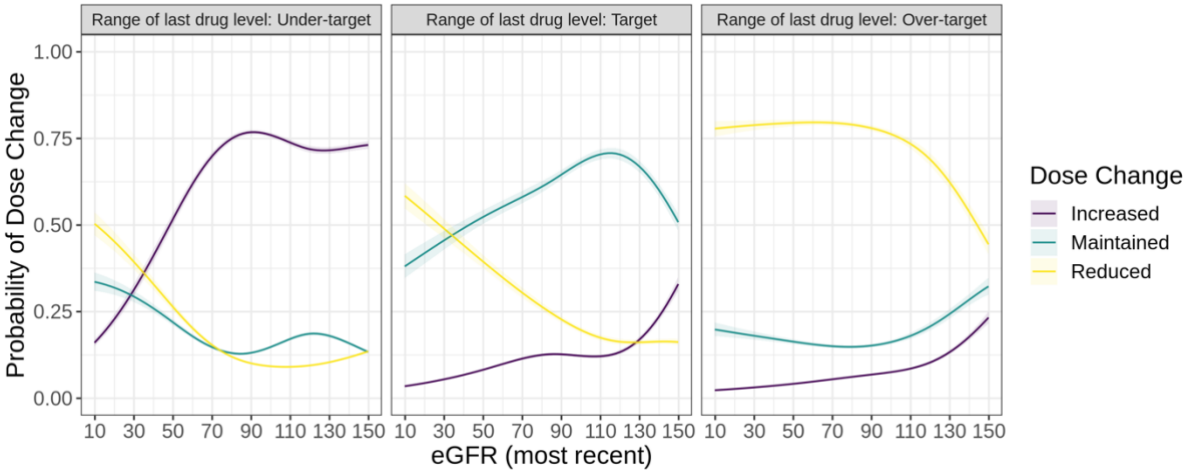


**Figure 2.6 Probability of different changes in vancomycin prescriptions occurring following a drug level by drug level (panels) and renal function (x-axis).**

Under-target, target and over-target are drug levels <15mg/L, 15-20mg/L and >20mg/L respectively. Effects shown are marginalised over the levels of all other factors.

### 2.3.3 Subsequent drug levels

Like first drug trough levels, there was also a slightly increasing trend in subsequent drug levels from 2016 to 2021 (**Figure** 2.7), with an increasing percentage of subsequent drug levels within the target range (from 28% to 32%).

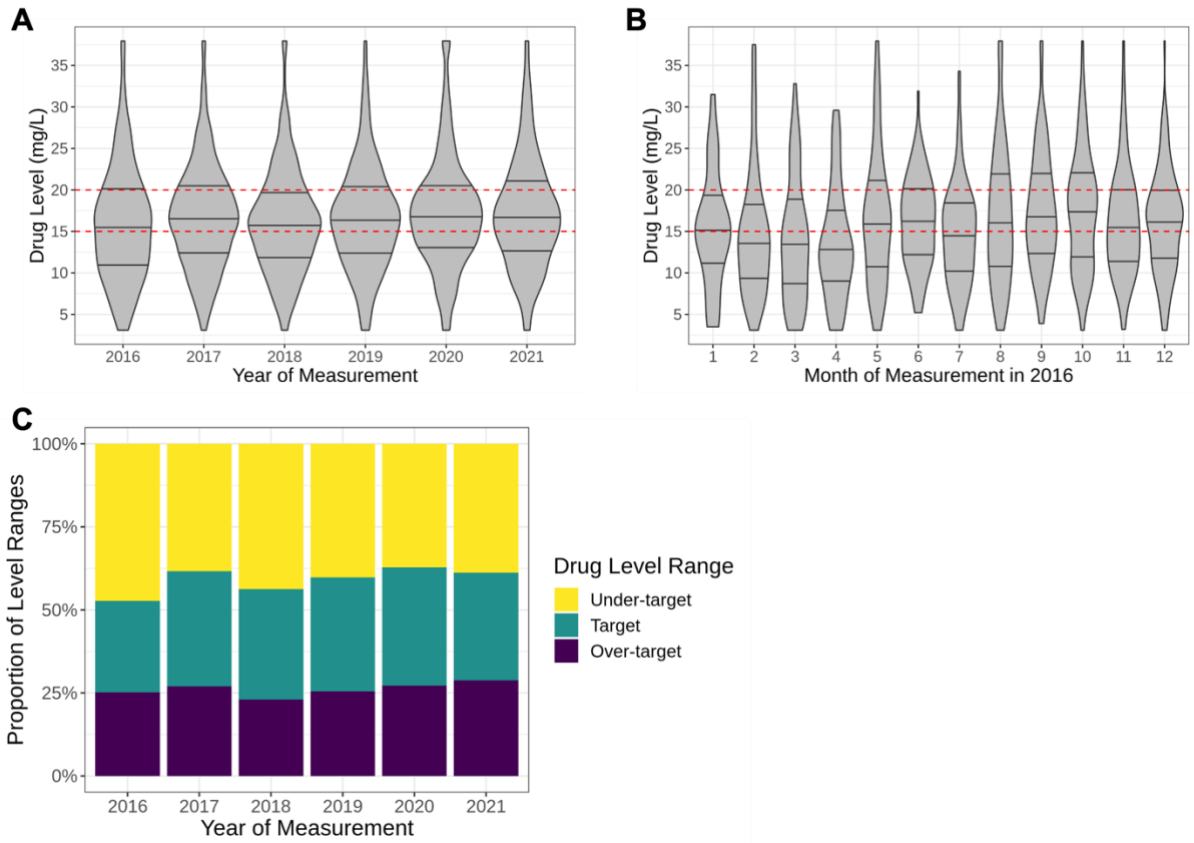


**Figure 2.7 Subsequent vancomycin drug levels.**
Panel A shows drug levels by years between 2016 and 2021, panel B by months in 2016. Panel C shows the proportion of levels in different drug level ranges (under-target, target, over-target) over 2016-2021. The dashed red lines in panels A and B indicate the target drug range (15–20 mg/L).

Subsequent drug levels (N=5176) were most strongly associated with maintenance doses and dose adjustments as expected (**Table** 2.12, **Table** 2.13). Drug levels increased non-linearly with total daily doses **(Figure** 2.8**A**), with 20–60mg/kg/day associated with mean levels in range (for twice daily dosing only and at the reference category for other effects). Adjustments made to maintenance doses in response to

drug levels were typically more successful at reducing levels than increasing them: reducing maintenance doses (by a median 7mg/kg/day [IQR 6–12]) typically brought the drug levels within the target range, while increasing doses (by a median 9mg/kg/day [IQR 6–13]) did not (**Figure** 2.8**B**). Like initial drug levels, drug levels were higher in older adults when maintenance doses were administered twice daily (1.14mg/L per 10 years older [95%CI 1.03,1.25], with no evidence of an association with age with once-daily dosing (-0.04mg/L [-0.33,0.24, interaction p<0.0001]; **Figure** 2.8**C**). Drug levels were lower in those with higher eGFR (0.46 mg/L lower per 10 mL/min/1.73m$^2$ higher [0.40,0.52]) and were higher in those with higher Elixhauser scores (0.72mg/L per unit higher [0.57,0.88]). As expected, drug levels were lower the longer the time from the last dose to the drug level measurement (**Figure** 2.8**D**), with significant variability in the timing of trough levels, which did not always follow the recommended timeframe (12h for twice-daily dosing, 24h for once-daily dosing).

**Table 2.12 Characteristics of maintenance doses by whether the subsequent drug levels reached the target trough level (N=5176).**

| Variable | Under-target (N=2127) | Target (N=1712) | Over-target (N=1337) | Total (N=5176) | p value |
|---|---|---|---|---|---|
| Age at admission (years) | | | | | **<0.0001** |
| Median (Q1, Q3) | 55.3 (41.0, 68.0) | 67.3 (55.3, 76.1) | 68.7 (57.3, 77.9) | 63.4 (49.9, 74.1) | |
| Sex | | | | | **<0.0001** |
| Male | 1338 (62.9%) | 950 (55.5%) | 733 (54.8%) | 3021 (58.4%) | |
| Female | 789 (37.1%) | 762 (44.5%) | 604 (45.2%) | 2155 (41.6%) | |
| Weight (kg) | | | | | **0.0002** |
| Median (Q1, Q3) | 79.0 (67.0, 92.4) | 79.0 (68.2, 92.3) | 81.2 (68.4, 96.6) | 80.0 (68.0, 93.2) | |
| eGFR (mL/min/1.73 $m^2$) | | | | | **<0.0001** |
| Median (Q1, Q3) | 100.5 (80.8, 125.1) | 87.7 (68.8, 108.3) | 75.5 (58.0, 100.0) | 90.8 (68.9, 114.3) | |
| Ethnicity | | | | | **<0.0001** |
| White | 1586 (74.6%) | 1381 (80.7%) | 1042 (77.9%) | 4009 (77.5%) | |
| Black | 43 (2.0%) | 13 (0.8%) | 12 (0.9%) | 68 (1.3%) | |
| Asian | 78 (3.7%) | 48 (2.8%) | 39 (2.9%) | 165 (3.2%) | |
| Other | 40 (1.9%) | 24 (1.4%) | 13 (1.0%) | 77 (1.5%) | |
| Unknown | 380 (17.9%) | 246 (14.4%) | 231 (17.3%) | 857 (16.6%) | |
| Charlson score | | | | | **<0.0001** |
| Median (Q1, Q3) | 1 (0, 1) | 1 (0, 1) | 1 (0, 2) | 1 (0, 1) | |
| Elixhauser score | | | | | **<0.0001** |
| Median (Q1, Q3) | 1 (0, 2) | 2 (1, 3) | 2 (1, 3) | 2 (1, 3) | |
| Maintenance dose (mg/kg/day) | | | | | **<0.0001** |
| Median (Q1, Q3) | 32.5 (26.4, 39.2) | 30.7 (23.1, 37.9) | 27.6 (20.3, 35.5) | 31.2 (23.7, 37.8) | |
| Maintenance dosing interval (hour) | | | | | **<0.0001** |
| 12 | 1967 (92.5%) | 1516 (88.6%) | 1089 (81.5%) | 4572 (88.3%) | |
| 24 | 160 (7.5%) | 196 (11.4%) | 248 (18.5%) | 604 (11.7%) | |
| Dose change amount (mg/kg/day) | | | | | **<0.0001** |
| Median (Q1, Q3) | 0.0 (0.0, 6.0) | 0.0 (0.0, 0.0) | 0.0 (0.0, 0.0) | 0.0 (0.0, 0.0) | |
| Time from last dose to current drug level measurement (hour) | | | | | **<0.0001** |
| Median (Q1, Q3) | 11.5 (10.3, 14.2) | 11.0 (9.9, 12.7) | 11.1 (9.7, 18.3) | 11.2 (10.0, 14.0) | |
| Time from last drug level measurement to current one (hour) | | | | | **<0.0001** |
| Median (Q1, Q3) | 33.7 (22.8, 48.2) | 37.9 (23.6, 48.5) | 27.5 (22.2, 47.8) | 34.7 (22.9, 48.2) | |

**Table 2.13 Factors independently associated with subsequent drug levels.**

| Factors | Coefficients | 95% CI | p value |
|---|---|---|---|
| (Intercept) | 12.48 | 11.29 – 13.67 | **<0.0001** |
| Age (per 10 years) | 1.14 | 1.03 – 1.25 | **<0.0001** |
| Sex | | | |
| Male | Reference | | |
| Female | 0.26 | -0.07 – 0.58 | 0.12 |
| eGFR (per 10 mL/min/1.73 $m^2$) | -0.46 | -0.52 – -0.40 | **<0.0001** |
| Charlson score | -0.10 | -0.32 – 0.13 | 0.40 |
| Elixhauser score | 0.72 | 0.57 – 0.88 | **<0.0001** |
| Maintenance dose (mg/kg/day) | See **Figure** 2.8**A** | | **<0.0001** |
| Maintenance dosing interval (hour) | | | |
| 12 | Reference | | |
| 24 | 0.87 | 0.69 – 1.06 | **<0.0001** |
| Dose change amount (mg/kg/day) | See **Figure** 2.8**B** | | **<0.0001** |
| Time from last dose to current drug level measurement (hour) | See **Figure** 2.8**D** | | **<0.0001** |
| Time from last drug level measurement to current one (hour) | -0.01 | -0.02 – 0.00 | 0.05 |
| Age : Maintenance dosing interval | See **Figure** 2.8**C** | | **<0.0001** |

Note: See **Table** 2.12 for the distribution of characteristics. Weight was not considered as dose in mg/kg/day was included instead. Natural cubic splines were used with 4 knots at the 10th, 33rd, 67th and 90th percentiles to allow for non-linearity in the effects of maintenance doses and time from the last dose to current drug level measurement on subsequent drug levels. Potential confounding variables (i.e., Charlson score, time from preceding doses and time from preceding drug level measurements) were included in the analysis. There was strong evidence of an interaction between the age and the dosing interval so this was included ($p<0.0001$), but no evidence of interaction between other factors in the model ($p>0.05$).

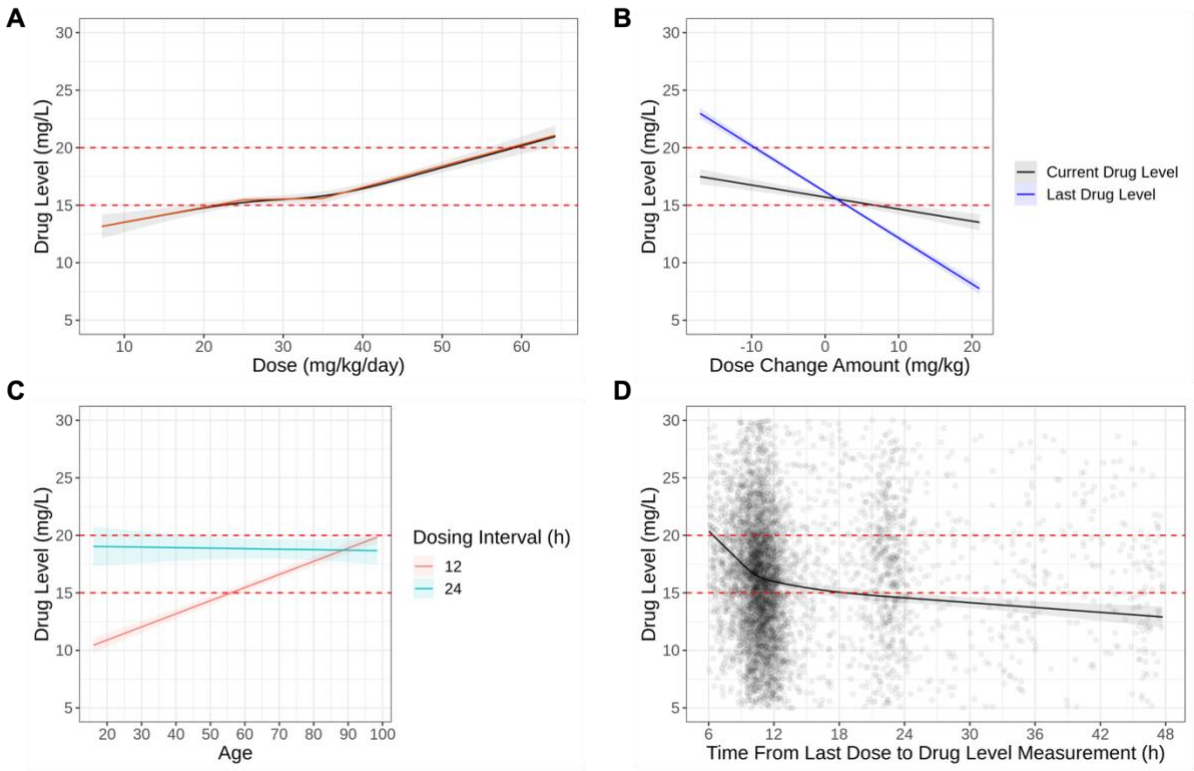


**Figure 2.8 The associations between subsequent drug levels and post-initial maintenance doses (given twice daily) (panel A), dose change (panel B), age (panel C), time from the last dose to drug level measurement (panel D).**
(A) Non-linear associations between drug levels and subsequent doses (black line) are approximated with piecewise linear splines (red line). (B) The blue line represents the drug level measured before dose adjustment and is estimated separately. (D) The data points represent the actual time of blood sampling versus drug levels. The red dashed line represents the target trough level range recommended in the dosing guideline (15-20mg/L). Other factors were held constant at their mean (for continuous variables) or reference levels (for categorical variables).

### 2.3.4 Time to reach therapeutic levels

There was no evidence that higher loading doses per kg led to a higher cumulative incidence of reaching the target level within 72 hours (p=0.47; **Table** 2.14, **Table** 2.15, **Figure** 2.9**A**), although they did appear to increase the early probability of reaching target levels (within 40 hours). Over the longer term, the probability of reaching the target before stopping vancomycin was higher in the low (10-20 mg/kg) and medium (20-30 mg/kg) loading dose groups (p=0.002). Higher loading doses (30-40 mg/kg) were also associated with a higher cumulative incidence of vancomycin discontinuation (p=0.0001).

In those remaining on vancomycin, the conditional probability of achieving target levels at 5 days was 55–63%; it was similar in the medium and high loading dose groups at 10 days (89–90%), slightly higher than the low dose group (85%) (**Figure** 2.9**B**).

**Table 2.14 Characteristics of vancomycin treatment courses by the trough level outcome.**

| Variable | Target achieved before 72h whilst on vancomycin (N=1109) | Course stopped before 72h and before observing a drug level in the target range (N=796) | On vancomycin at 72h without having achieved the target (N=2369) | Total (N=4066) | p value |
|---|---|---|---|---|---|
| Age at admission (years) | | | | | **<0.0001** |
| Median (Q1, Q3) | 68.5 (58.1, 76.8) | 58.8 (44.9, 71.3) | 59.9 (46.2, 71.5) | 62.7 (49.0, 73.2) | |
| Sex | | | | | **0.0004** |
| Male | 560 (53.0%) | 421 (59.4%) | 1385 (60.2%) | 2366 (58.2%) | |
| Female | 496 (47.0%) | 288 (40.6%) | 916 (39.8%) | 1700 (41.8%) | |
| Weight (kg) | | | | | 0.25 |
| Median (Q1, Q3) | 80.0 (68.7, 95.2) | 80.0 (68.0, 94.4) | 80.0 (67.1, 93.5) | 80.0 (67.7, 94.0) | |
| eGFR (mL/min/1.73 $m^2$) | | | | | **<0.0001** |
| Median (Q1, Q3) | 85.5 (65.0, 104.6) | 90.6 (71.8, 111.8) | 94.3 (73.0, 116.9) | 91.3 (70.9, 112.7) | |
| Ethnicity | | | | | **0.008** |
| White | 851 (80.6%) | 564 (79.5%) | 1769 (76.9%) | 3184 (78.3%) | |
| Black | 6 (0.6%) | 11 (1.6%) | 41 (1.8%) | 58 (1.4%) | |
| Asian | 24 (2.3%) | 17 (2.4%) | 75 (3.3%) | 116 (2.9%) | |
| Other | 12 (1.1%) | 19 (2.7%) | 37 (1.6%) | 68 (1.7%) | |
| Unknown | 163 (15.4%) | 98 (13.8%) | 379 (16.5%) | 640 (15.7%) | |
| Charlson score | | | | | **0.0002** |
| Median (Q1, Q3) | 1 (0, 2) | 1 (0, 1) | 1 (0, 1) | 1 (0, 1) | |
| Elixhauser score | | | | | **<0.0001** |
| Median (Q1, Q3) | 2 (1, 3) | 1 (0, 2) | 1 (1, 2) | 2 (1, 3) | |
| Loading dose (mg/kg) | | | | | **0.006** |
| Median (Q1, Q3) | 24.1 (21.2, 27.3) | 24.8 (21.5, 28.6) | 24.4 (21.0, 27.4) | 24.4 (21.2, 27.6) | |

**Table 2.15 Factors independently associated with reaching the target, treating stopping vancomycin before 72h and before observing a drug level in the target range as a competing risk.**

| Factors | HR* | 95% CI | p value |
|---|---|---|---|
| Age (per 10 years) | 1.26 | 1.21 – 1.31 | **<0.0001** |
| Sex | | | |
| Male | Reference | | |
| Female | 1.18 | 1.04 – 1.33 | **0.01** |
| eGFR (per 10 mL/min/1.73 $m^2$) | 0.98 | 0.96 – 1.00 | **0.04** |
| Charlson score | 1.04 | 0.96 – 1.13 | 0.36 |
| Elixhauser score | 1.00 | 0.94 – 1.06 | 0.91 |
| Loading dose (mg/kg) | 1.00 | 0.99 – 1.01 | 0.47 |

*HR = Hazard Ratio.

Note: See **Table** 2.14 for the distribution of characteristics. Weight was not included, as the loading dose in mg/kg was included instead. There was no evidence of interaction between factors in the model (p>0.05).

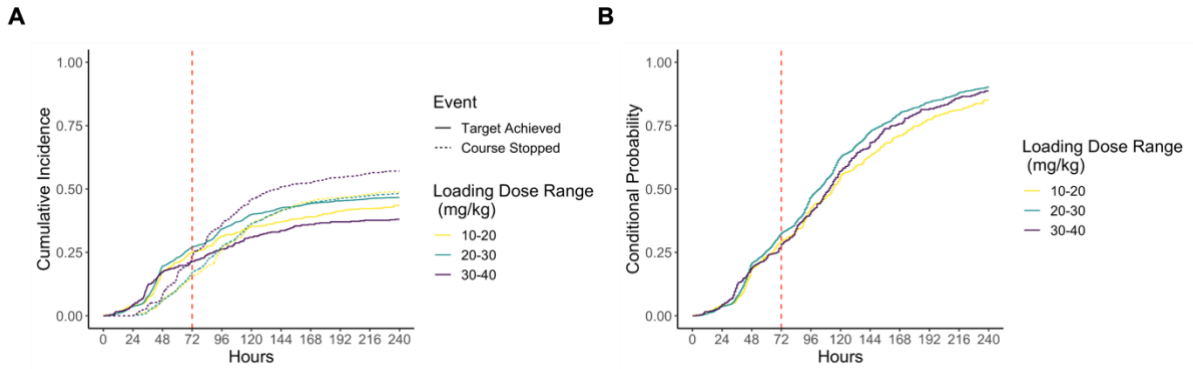


**Figure 2.9 Cumulative incidence of achieving the target trough level.**
Panel A shows the cumulative incidence of achieving the target trough level (solid line) versus stopping vancomycin before being observed to reach the target (dashed line). Panel B shows the probability of achieving the target conditional on remaining on vancomycin. Both plots are shown according to loading dose 10-20mg/kg (yellow), 20-30mg/kg (green), 30-40mg/kg (purple). Follow-up time was censored at 240 hours.

### 2.3.5 Acute kidney injury

The risk of nephrotoxicity was relatively low, with only 147 (4.5%), 29 (0.9%) and 9 (0.3%) Stage 1, Stage 2 and Stage 3 AKI cases, and no stage 4 cases, respectively, in 3252 courses with post-treatment creatinine measurements (**Table** 2.16). Where AKI occurred (n=185), at the end of treatment 50% (93/185) patients had recovered to ≤1.5 times their pre-treatment creatinine level; for those cases with data recorded within six months (n=101), 88% had recovered (89/101). Higher average drug levels were linearly associated with an increased odds of AKI, such that there was no clear "cut-off"

threshold value for AKI. However predicted probabilities of AKI with trough levels of 15–20mg/L were not substantially higher than at 10–15mg/L (**Figure** 2.10**A/B**, **Table** 2.18). Observed AKI incidence in patients with time-averaged trough levels of 15–20 mg/L was still relatively low (5.5%, 33/596; **Table** 2.17). AKI risk was higher in those with lower pre-treatment eGFR and higher Elixhauser scores (**Figure** 2.11, **Table** 2.18). There was no evidence of a change in AKI rate over calendar time after guideline implementation after adjusting for baseline characteristics (odds ratio=1.09 per year, 95%CI=0.97–1.22, p=0.14).

**Table 2.16 Characteristics of vancomycin treatment courses by highest acute kidney injury stage (N=3252).**

| Variable | None (N=3067) | Stage 1 (N=147) | Stage 2 (N=29) | Stage 3 (N=9) | Total (N=3252) | p value |
|---|---|---|---|---|---|---|
| Age at admission (years) | | | | | | 0.07 |
| Median (Q1, Q3) | 62.5 (49.0, 73.1) | 65.1 (51.0, 74.8) | 60.9 (53.5, 68.2) | 54.4 (34.9, 58.5) | 62.6 (49.1, 73.2) | |
| Sex | | | | | | **0.04** |
| Male | 1789 (58.3%) | 69 (46.9%) | 19 (65.5%) | 5 (55.6%) | 1882 (57.9%) | |
| Female | 1278 (41.7%) | 78 (53.1%) | 10 (34.5%) | 4 (44.4%) | 1370 (42.1%) | |
| Weight (kg) | | | | | | 0.44 |
| Median (Q1, Q3) | 79.7 (67.0, 93.5) | 77.5 (66.2, 90.6) | 77.6 (66.0, 87.7) | 95.0 (80.0, 101.0) | 79.4 (67.0, 93.4) | |
| eGFR (mL/min/1.73 $m^2$) | | | | | | **<0.0001** |
| Median (Q1, Q3) | 92.1 (71.4, 114.2) | 67.4 (31.1, 110.3) | 85.5 (75.9, 115.8) | 102.1 (85.7, 105.7) | 91.6 (70.1, 113.8) | |
| Ethnicity | | | | | | 0.98 |
| White | 2373 (77.4%) | 114 (77.6%) | 21 (72.4%) | 8 (88.9%) | 2516 (77.4%) | |
| Black | 47 (1.5%) | 4 (2.7%) | 0 (0.0%) | 0 (0.0%) | 51 (1.6%) | |
| Asian | 93 (3.0%) | 4 (2.7%) | 1 (3.4%) | 0 (0.0%) | 98 (3.0%) | |
| Other | 46 (1.5%) | 2 (1.4%) | 0 (0.0%) | 0 (0.0%) | 48 (1.5%) | |
| Unknown | 508 (16.6%) | 23 (15.6%) | 7 (24.1%) | 1 (11.1%) | 539 (16.6%) | |
| Charlson score | | | | | | **<0.0001** |
| Median (Q1, Q3) | 1 (0, 1) | 1 (1, 2) | 1 (1, 2) | 1 (0, 1) | 1 (0, 1) | |
| Elixhauser score | | | | | | **<0.0001** |
| Median (Q1, Q3) | 2 (1, 3) | 2 (1, 4) | 2 (1, 3) | 2 (1, 2) | 2 (1, 3) | |
| Average dose (mg/kg)* | | | | | | 0.36 |
| Median (Q1, Q3) | 16.7 (14.3, 18.9) | 16.7 (14.2, 18.9) | 15.6 (12.2, 18.4) | 18.4 (15.9, 21.9) | 16.7 (14.3, 18.9) | |
| Average drug level (mg/L)* | | | | | | **<0.0001** |
| Median (Q1, Q3) | 10.8 (7.3, 15.1) | 12.3 (9.2, 17.6) | 13.6 (11.4, 18.5) | 15.3 (10.9, 35.4) | 10.9 (7.4, 15.2) | |

*Average drug levels and doses calculated as a time-average over all values up to and including the creatinine measurement defining the worst acute kidney injury stage, using the trapezoidal rule.

**Table 2.17 Incidence of the highest acute kidney injury stage in vancomycin treatment courses with different average drug levels.**

| Trough Level (average, mg/L)* | <10 mg/L (N=1382) | 10-15 mg/L (N=1001) | 15-20 mg/L (N=596) | >20 mg/L (N=273) | Total (N=3252) | p value |
|---|---|---|---|---|---|---|
| AKI stage | | | | | | **<0.0001** |
| None | 1330 (96.2%) | 937 (93.6%) | 563 (94.5%) | 237 (86.8%) | 3067 (94.3%) | |
| Stage 1 | 44 (3.2%) | 53 (5.3%) | 23 (3.9%) | 27 (9.9%) | 147 (4.5%) | |
| Stage 2 | 6 (0.4%) | 9 (0.9%) | 9 (1.5%) | 5 (1.8%) | 29 (0.9%) | |
| Stage 3 | 2 (0.1%) | 2 (0.2%) | 1 (0.2%) | 4 (1.5%) | 9 (0.3%) | |
| Any Stage | 52 (3.8%) | 64 (6.4%) | 33 (5.5%) | 36 (13.2%) | 185 (5.7%) | |

*Average trough levels calculated as a time-average over all values up to and including the creatinine measurement defining the worst acute kidney injury stage, using the trapezoidal rule.

**Table 2.18 Factors independently associated with the maximum acute kidney injury stage per vancomycin course.**

| Factors | OR | 95% CI | p value |
|---|---|---|---|
| Age (per 10 years) | 0.92 | 0.83 – 1.01 | 0.08 |
| Sex | | | |
| Male | Reference | | |
| Female | 1.28 | 0.94 – 1.75 | 0.11 |
| eGFR (per 10 mL/min/1.73 $m^2$) | See **Figure** 2.11 | | **<0.0001** |
| Charlson score | 1.06 | 0.87 – 1.29 | 0.55 |
| Elixhauser score | 1.17 | 1.01 – 1.34 | **0.03** |
| Average dose (mg/kg) | 1.04 | 1.00 – 1.09 | **0.04** |
| Average drug level (mg/L) | 1.06 | 1.03 – 1.08 | **<0.0001** |

Note: See **Table** 2.16 for the distribution of characteristics. Weight was not included, as the average dose in mg/kg was included instead. Natural cubic splines were used with 3 knots at the 10th, 50th and 90th percentiles to allow for non-linearity in the effects of eGFR on the probability of different stages of AKI. No evidence of interaction between factors in the model (p>0.05). The model predictions are based on the variables' mean and reference level; therefore, there is a difference between the observed frequencies in **Table** 2.17 and the predicted values.

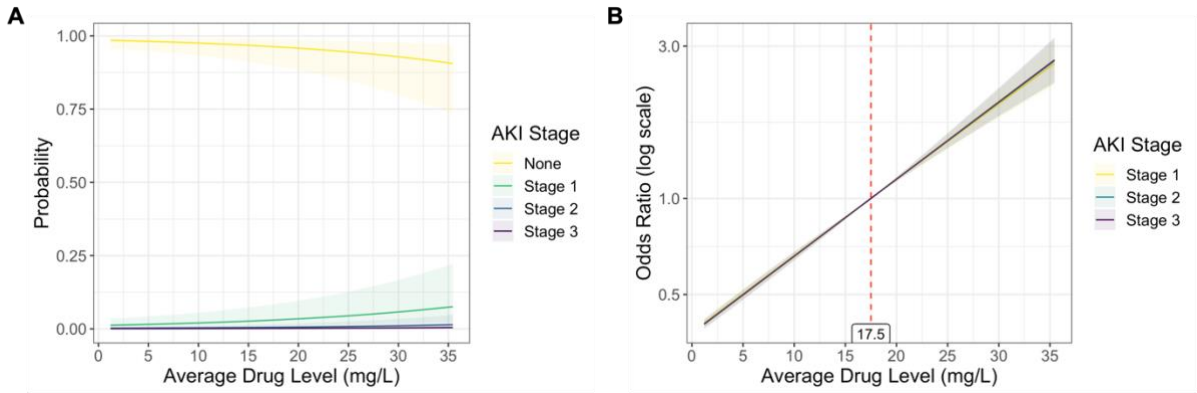


**Figure 2.10 Associations between the probability of different stages of AKI and average drug levels.** Panel A shows the probability of stage 1, 2 and 3 AKI, and panel B the odds ratios for AKI (centred at 17.5mg/L). Other factors were held constant at their mean (for continuous variables) or reference levels (for categorical variables). There was no evidence of non-linearity between drug levels and the risk of AKI (p=0.34).

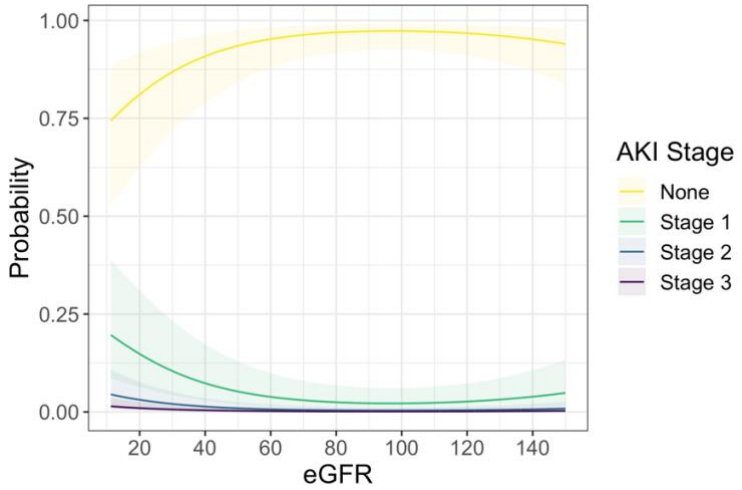


**Figure 2.11 The associations between the probability of different stages of AKI and pre-treatment eGFR.**
Other factors were held constant at their mean (for continuous variables) or reference levels (for categorical variables).

### 2.3.6 Proposed guideline update

Based on a regression model for the relationship between initial maintenance doses (total daily dose, both once and twice daily) and first drug trough levels in patients of different ages, eGFR and body weight (**Table** 2.19), the initial maintenance dose required to achieve the target drug levels in the younger patients (40–60 years) was predicted to be 500–1500 mg higher than the daily dose recommended by the current guideline (**Figure** 2.12). The predicted optimal dose for patients aged 60–80 years was similar to the current guideline recommendation in patients with eGFR below 90 mL/min/1.73 $m^2$, but was higher than the guideline dose in patients with eGFR above 90 mL/min/1.73 $m^2$. For patients 60–80 years and ≥110 kg, the predicted optimal dose was lower than the current guideline-recommended dose. New initial maintenance dosing recommendations, based on the current loading dose, are presented in **Table** 2.20. Estimates from pharmacokinetic models[85] supported that my updated guidelines were likely to increase the number of patients achieving trough levels of 15–20mg/L

(**Table** 2.21), with all but one age-eGFR-weight group predicted to achieve levels of 14–20mg/L. Estimated $AUC_{24h}$/MIC ratios were 400–700 for nearly all groups.

**Table 2.19 Associations between first drug trough levels and age, eGFR, weight and initial maintenance doses.**

| Factors | Coefficients | 95% CI | p value |
|---|---|---|---|
| (Intercept) | 16.70 | 12.39 – 21.00 | **0.001** |
| Age (per 10 years) | -0.59 | -1.15 – -0.02 | **0.04** |
| eGFR (mL/min/1.73 $m^2$) | Non-linear term | | **<0.0001** |
| Weight (kg) | Non-linear term | | 0.85 |
| Initial maintenance dose (per 100 mg/day) | 0.09 | -0.09 – 0.28 | 0.32 |
| Age : Initial maintenance dose | $5.36x10^{-5}$ | $2.36x10^{-5}$ – $8.36x10^{-5}$ | **0.0005** |
| Age : eGFR | Non-linear term | | 0.20 |
| eGFR : Weight | Non-linear term | | **0.007** |
| Age : Weight | Non-linear term | | 0.16 |

Note: Natural cubic splines were used with two knots at 80 and 105 to allow for non-linearity in the effects of eGFR, two knots at 72 and 89 for weight. Two-way interactions between age, eGFR, weight and initial maintenance doses were included.

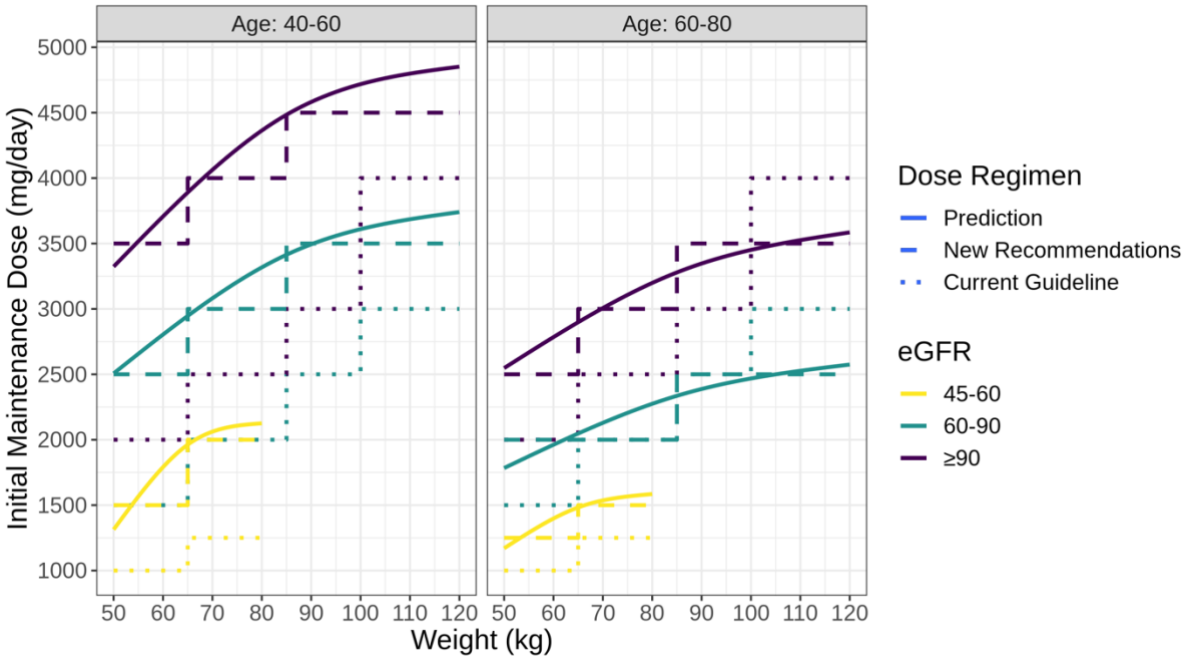


**Figure 2.12 Proposed updated initial maintenance doses by age group, weight and renal function.** Model predictions are shown as a solid line, dosing recommendations rounded to doses that can be reliably administered are shown as a dashed line. The current guideline is shown as a dotted line. Dose predictions were not made for patients aged under 40 years, with eGFR less than 45 mL/min/1.73 $m^2$ and in some weight ranges due to insufficient data.

**Table 2.20 Optimised dosing recommendations for initial maintenance dose for patients aged 40–60 and 60–80.**

| Age: 40-60 years | | eGFR (mL/min/1.73m$^2$) | | |
|---|---|---|---|---|
| | | 45-60 | 60-90 | >90 |
| Actual Body Weight (kg) | 50-65 | 750mg Twice daily | 1250mg Twice daily | 1750mg Twice daily |
| | 65-85 | 1000mg Twice daily | 1500mg Twice daily | 2000mg Twice daily |
| | 85-100 | * | 1750mg Twice daily | 2250mg Twice daily |
| | >100 | * | 1750mg Twice daily | 2250mg Twice daily |

| Age: 60-80 years | | eGFR (mL/min/1.73m$^2$) | | |
|---|---|---|---|---|
| | | 45-60 | 60-90 | >90 |
| Actual Body Weight (kg) | 50-65 | 1250mg Once daily | 1000mg Twice daily | 1250mg Twice daily |
| | 65-85 | 750mg Twice daily | 1000mg Twice daily | 1500mg Twice daily |
| | 85-100 | * | 1250mg Twice daily | 1750mg Twice daily |
| | >100 | * | 1250mg Twice daily | 1750mg Twice daily |

*Dose predictions were not made for patients in some weight and eGFR ranges due to insufficient observed data.

**Table 2.21 Predicted mean trough levels and $AUC_{24h}$/MIC based on the optimised dosing regimens.**

| Age: 60-80 years | | eGFR (mL/min/1.73m$^2$) | | |
|---|---|---|---|---|
| | | 45-60 | 60-90 | >90 |
| Actual Body Weight (kg) | 50-65 | 11.1 mg/L<br>404 | 16.3 mg/L<br>561 | 15.8 mg/L<br>585 |
| | 65-85 | 14.8 mg/L<br>434 | 14.2 mg/L<br>478 | 14.5 mg/L<br>546 |
| | 85-100 | * | 16.4 mg/L<br>510 | 17.1 mg/L<br>596 |
| | >100 | * | 14.5 mg/L<br>434 | 14.7 mg/L<br>497 |

*Dose predictions were not made for patients in some weight and eGFR ranges due to insufficient observed data.
Note: First trough levels at 48h and $AUC_{24–48h}$/MIC (area under the concentration-time curve on day 2 divided by MIC of 1mg/L) were estimated by TDMx, which uses automated multimodel approaches to simulate individual PK profiles based on six population pharmacokinetic models.

## 2.4 Discussion

The analysis of vancomycin data over a five-year period revealed that implementing new guidelines increased prescribed doses successfully, but had a more limited impact on achieving therapeutic drug levels. Several previous studies have reported limited vancomycin dosing guideline compliance [75–79]. In contrast and supporting the value of the electronic prescribing aids and web/phone app implementation, loading and initial maintenance dose prescriptions in OUH hospitals showed rapid and good compliance with the new guidelines (reaching 70–80% compliance). Subsequent maintenance doses also adhered well to the guideline recommendations (with 72% of prescriptions correctly adjusting the dose when the drug level was outside the target range). Some variation in practice remained, e.g., with lower compliance in some specialties or when each new cohort of junior doctors started work. However, despite the high levels of compliance achieved and the guidelines being tailored to patients' weight and eGFR, the proportion of drug levels reaching the target range was suboptimal (26% initial trough levels and 32% subsequent trough levels). Similar to previous reports [86], only 20% of first drug levels achieved the target even when the guideline was followed, with most patients under-dosed, suggesting that current guidelines may need revision or to account for other patient factors, including age in particular. Drug levels were independently lower and more likely to be below target in younger patients, those without morbidities, those with normal renal function, and those with lower acuity of illness (Elixhauser score), likely due to higher renal clearance.

The real-world pharmacokinetic data collected from EHR data allowed me to propose updated guidelines. Although current consensus recommendations suggest $AUC_{24h}$/MIC ratio-based dosing, many hospitals still use trough levels to guide dosing for logistical reasons (difficulty in getting multiple drug levels to calculate $AUC_{24}$, lack of identification of causative pathogen) and the existence of current competency in this approach. I therefore proposed updates to better achieve trough levels of 15-20 mg/L. Theoretically, higher loading doses may help initial control of infection and more rapidly achieve the minimum vancomycin concentrations (e.g., 10mg/L) needed to prevent the emergence of AMR [87]. However, trough drug levels at steady state are more related to initial maintenance doses [86]. I found no evidence that higher loading doses increased the percentage achieving target levels by 72 hours, although there was some evidence of increased levels within 40 hours. Therefore, while maintaining the current loading dose, I propose updating initial maintenance dosing to optimise drug levels and account for the impact of patient age, which is not considered at present. Using regression model predictions suggests patients 40–60 years should receive higher maintenance doses than currently recommended (by 500–1500 mg per day) and higher doses than those 60-80 years. Based on my model simulations, the updated guideline achieved trough levels of 15–20 mg/L and $AUC_{24h}$/MIC of 400–700 in most cases. The latter is within the $AUC_{24h}$/MIC range recommended by some authors [88], but higher than the target of 400–600 in US guidelines [71,72]. There was insufficient data to produce recommendations for patients <40 or >80 years; careful implementation of recommendations for 40–60 and 60–80 years for these groups could be considered. Further changes such as thrice-daily administration may be required in younger patients, e.g., a retrospective study of 151 patients revealed that 40% of patients under

40 years of age eventually required more frequent dosing (every 8h) and took longer to achieve target serum levels [89].

Higher drug levels in older patients reflect the fact that vancomycin has a longer half-life, a larger volume of distribution and lower clearance in older patients, such that the same dosing regimen may result in higher drug levels [90–93]. Therefore, solely relying on creatinine-based eGFR calculations may not accurately reflect the true impact of underlying renal function on clearance in older patients [94]. The lack of relationship between age and drug levels in those on once-daily doses in my study likely reflects their poorer renal function, driving a once-daily regime, being the primary determinant of drug levels for these patients, rather than age. Although the OUH institutional guideline suggested initial TDM at 48 hours in all patients, patients with impaired renal function take longer to reach steady-state concentrations and obtaining trough levels at 72 hours in those on once-daily dosing with impaired renal function may be more accurate [95,96].

For subsequent dose adjustments, intriguingly, I found that drug levels were generally reduced to within the target range after reducing the maintenance dose, whilst increasing maintenance doses did not raise drug levels to the target within 72 hours. The current recommendation is to increase dosing by ~25% for those with sub-therapeutic levels (which was broadly followed, **Figure** 2.5**C**); however, this may be too conservative, particularly with concurrently improving renal function as individuals recover from acute infection or with augmented renal clearance of vancomycin [97].

Despite the modest and inconsistent effectiveness of $AUC_{24h}$/MIC in predicting clinical outcomes in other studies [98], the latest consensus guideline suggests transitioning to AUC-guided dosing due to concerns about the increased risk of nephrotoxicity, particularly if trough levels above those actually needed are targeted [72]. However, I found a low overall risk of AKI (5.7%, most of which was mild), which remained low (5.5%) in patients with trough levels of 15–20mg/L. This is lower than the range reported for vancomycin-induced nephrotoxicity (10–40%) [99–102], and may reflect in part the nature of the condition being treated; many of the cohort studied here were given vancomycin for orthopaedic device or neurosurgical infections rather than BSI. I found no evidence of increased nephrotoxicity after increasing the target trough level from 10–15mg/L to 15–20mg/L, suggesting concerns about nephrotoxicity from targeting 15–20mg/L trough levels may be smaller than previously reported [100,103,104]. However, the transition to AUC-based monitoring may still be beneficial, allowing for more flexible timing of blood sampling during TDM (e.g., using Bayesian methods, two-point estimates) [75,105,106], which may otherwise lead to misinterpretation of trough levels and consequent failure of dosing adjustments. Many studies have reported inappropriately timed sample collection [75,105–108], and the observations in my study also show this (**Figure** 2.8**D**).

Although the implementation of AUC-guided dosing and/or continuous infusions may further optimise vancomycin dosing, this requires significant training and logistics [88,109–112]. An alternative is to shift to other drugs, e.g. teicoplanin, another glycopeptide antimicrobial with comparable efficacy and better tolerability than vancomycin, and simpler dosing, though it is considerably more expensive [113].

The limitations of this study include the fact that it was performed in a single centre based on EHR, so there may have been unmeasured confounding factors and generalisability cannot be assumed. The guidelines in OUH were implemented prior to revised consensus guidelines, with recommendations remaining based on trough levels instead of AUC or $AUC_{24h}$/MIC. My new dosing recommendations have not been clinically validated, and this should be a focus of future work; however, pharmacokinetic estimates suggest that resulting drug levels are likely to be as intended. I also found that sex affected drug levels, and although I omitted this from my age, weight and renal function-specific dosing guideline for simplicity, this could be considered in future guidelines where computer-aided prescribing allows for more complex models to be used. I did not update loading dose recommendations, as my findings suggest that the effect of loading doses on steady-state levels is limited. I did not assess the effect of concomitant use of other nephrotoxic drugs on AKI, e.g., piperacillin-tazobactam [114,115]. Additionally, I focused on meeting an externally specified consensus trough target level. I, therefore, did not examine the clinical outcomes of patients given the heterogeneity in the indications for treatment ranging from localised orthopaedic device infection to suspected bacteraemia in profoundly immunosuppressed patients. However, this clearly a key aspect of setting optimal dosing targets that could be studied further using large-scale EHR data.

## 2.5 Conclusions

Good compliance with vancomycin guidelines was achieved with the assistance of a widely used web and phone app and EHR prompts containing a full suite of

antimicrobial guidelines and infection advice. New guidelines successfully achieved higher doses of vancomycin administration, but many patients still had sub-therapeutic drug levels. The risk of AKI in this study was relatively low at 5.7%. I propose that initial maintenance doses be adjusted for age, as well as weight and renal function. The narrow therapeutic window of vancomycin poses an ongoing challenge for dosing optimisation, and the impact of existing guidelines needs to be continuously monitored and adjusted to ensure therapeutic drug levels are achieved.

# Chapter 3 Estimating changes in routinely collected clinical parameters following negative or positive blood cultures.

The work presented in this Chapter was published in 2024 in the Journal of Infection [116]. Most of the tables and figures are the same as those published in the paper and its supplementary material.

## 3.1 Introduction

The widespread implementation of EHR offers the opportunity for a more nuanced approach to monitoring the trajectory of clinical parameters in infection management. This chapter aimed to characterise the response of inflammatory markers and physiological measurements over time following suspected BSI, and investigate how this may be influenced by factors such as causative pathogens, sources of infection, baseline antimicrobial treatment (antibiotics and antifungals) and patient characteristics.

Effective infection management begins with identifying the causative organism(s) and their antimicrobial susceptibilities to facilitate targeted therapy [4]. The overarching goal is to prescribe antimicrobials that are optimally tailored to combat the pathogen in question. However, this is complicated by the fact that, in many serious infections, blood cultures fail to identify a causative infectious agent [57,117], often compelling

clinicians to rely on empirical treatment strategies. This empiricism risks either inappropriately narrow or unnecessarily broad antimicrobial coverage, potentially exacerbating infection severity and increasing mortality rates on the one hand, or accelerating the rise of AMR on the other [1,118].

With unavailable/non-conclusive blood culture results, clinical parameters and scoring systems become instrumental in navigating the clinical course and potentially guiding treatment decisions. Routinely collected inflammatory markers such as CRP and WBC count, alongside physiological measurements like heart rate, respiratory rate, and temperature, can potentially help to monitor the response to infection and predict clinical outcomes [56,58,59,119]. Among these, the role of serial CRP measurements in monitoring treatment response has been previously studied most commonly [120–124]. CRP levels are indicative of the acute-phase response to infection and can be used to assess the ongoing inflammatory process [125]. Relative changes in CRP (i.e., CRP ratios vs baseline or previous measurements) were associated with clinical outcomes [120,123,126]. Likewise, the WBC count serves as a marker for the body's immune response [127]. Physiological measurements provide direct insight into the patient's systemic response to infection and inflammation [59]. Furthermore, scoring systems such as the SOFA score provide a more multifactorial view, facilitating the evaluation of organ dysfunction in response to sepsis [117].

However, the host response to infection and subsequent antimicrobial administration is nevertheless heterogeneous, both at presentation and throughout the course of infection [59,128], due to factors other than the infecting pathogens, such as sources of

infection, and individual patient characteristics. The associations between these variables and routine clinical parameters have not been well described. By examining the relationships between infection aetiology and the observed changes in these clinical response trajectories, clinicians and researchers can better understand the variance in individual patient responses and potentially guide more targeted treatment approaches.

In this context, EHR emerge as a valuable tool. They contain detailed patient data over time, affording the opportunity to discern different response trajectories to infection and the heterogeneity underpinning them. In this chapter, I, therefore, aimed to estimate changes in routinely collected clinical parameters following negative or positive blood cultures in adults with suspected BSI, stratified by different blood culture results, clinical syndrome, baseline antimicrobial susceptibility, and patient characteristics.

## 3.2 Methods

### 3.2.1 Research design and study population

The aim of this analysis was to use routinely collected electronic health records to estimate trajectories of routinely collected parameters (CRP, WBC and vital signs (heart rate, respiratory rate, tympanic temperature)) over the course of an infection episode, investigate underlying heterogeneity in responses and assess how this related to specific patient factors.

De-identified data from IORD was used. IORD contains information from all inpatient admissions (dates, times, specialties, and associated diagnostic codes) and patient demographics at OUH, UK, together with blood culture results (including organism and susceptibility results), laboratory tests (CRP, WBC), vital signs, antimicrobial prescriptions (date/time of administration and indication (free text)).

I defined a new suspected BSI episode when there was >14 days since the last collection of blood for culture using the culture dataset containing pseudonymised patient identifier, date and time of blood sample collection, and blood culture results (including antimicrobial susceptibilities). The index blood culture in each infection episode was determined by a hierarchy prioritising pathogen presence over contaminants and negative results, specifically, the first blood sample from which a microbial pathogen was cultured, otherwise the first blood sample from which a contaminant was identified, or otherwise the first blood sample (if all cultures were negative. I then merged demographic data, and excluded episodes in patients <16 years at the index blood culture and a small number of episodes with missing demographic information (**Figure** 3.1). After merging with information about inpatient admissions (including dates and diagnostic codes) I lastly excluded infection episodes with index blood cultures drawn 24 hours prior to inpatient admission or after discharge (**Figure** 3.1). Of 6,403 infection episodes excluded due to the timing of index blood cultures, 4,468 (70.0%) were culture-negative samples taken >24h before admission.

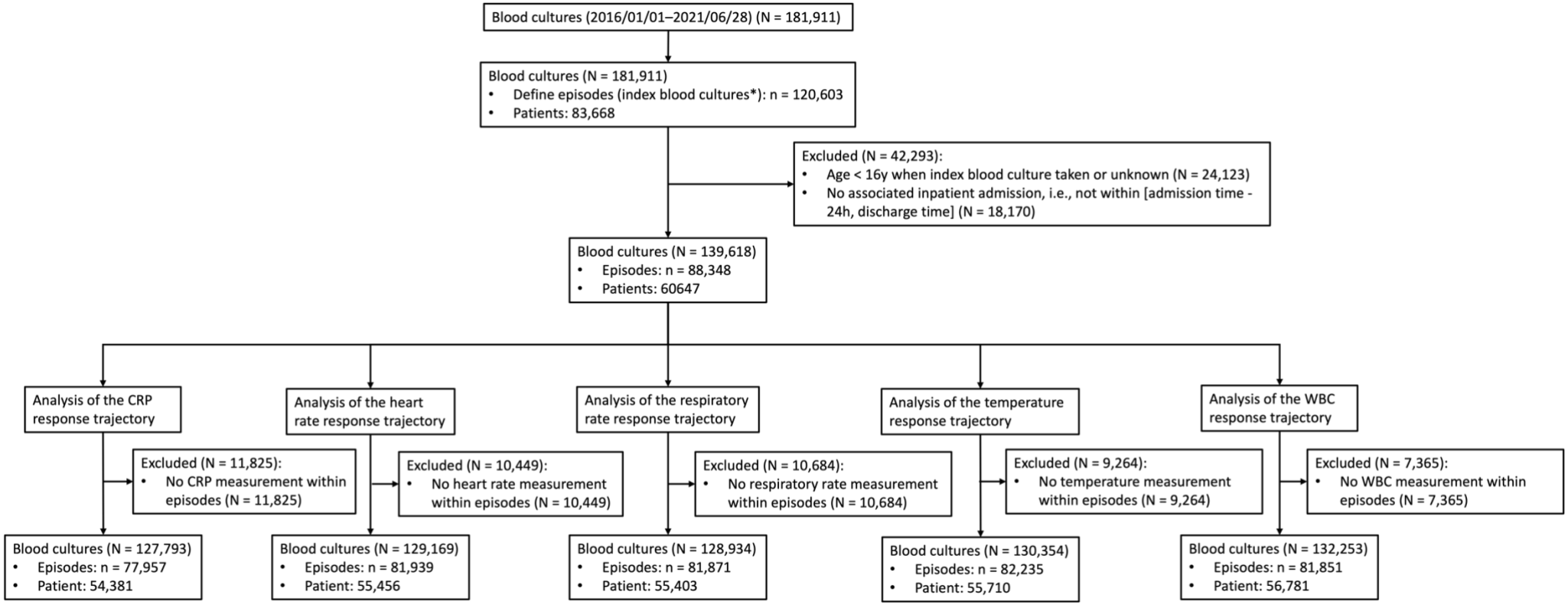


**Figure 3.1 Flowchart to identify study population.**

*Index blood culture: the first blood sample from which a microbial pathogen was cultured, otherwise the first blood sample from which a contaminant was identified, or otherwise the first blood sample (if all cultures were negative). Note: For those excluded due to the timing of index blood cultures, 70.0%[4,468/6,403] were culture-negative samples taken >24h before admission.

I chose to use the time of collection of blood for the index culture as time zero in analyses because this provided a consistent reference point across all episodes and for potential subsequent changes in management. This may be considered a proxy for the clinical recognition of a potential infection. However, it is later than the onset of symptoms and the initial infectious insult and does not account for variations in these versus blood collection. Assessing symptom onset is inevitably subjective, and this information is also not available in routine healthcare data, so it could not be used in this analysis.

### 3.2.2 Outcomes

All CRP, WBC and vital sign measurements within relevant time windows from the index blood culture (i.e., from -1 day (CRP, WBC) or -6 hours (vital signs) before to +8 days after) were extracted based on pseudonymised patient identifiers (total 213,632 CRP measurements, 232,021 WBC, 1,774,103 heart rate, 1,751,985 respiratory rate, 1,760,520 temperature). Episodes without CRP, WBC and vital sign measurements were excluded from the trajectory analysis, respectively (**Figure** 3.1).

### 3.2.3 Covariates

Variables in IORD include age, sex, date and time of admission, date and time of blood culture collection, blood culture results (negative or identified micro-organism(s) with antimicrobial susceptibility test results), prescribed antimicrobials and indications (free text), date and time of antibiotic administration, and ICD-10 diagnostic codes.

Several variables were defined or calculated based on these factors, including Charlson comorbidity and Elixhauser acuity scores, National Early Warning Score (NEWS) at baseline, immunosuppression status (yes/no), palliative care (yes/no), community-onset (yes/no), sources of infection, blood culture results and pathogen groups, and baseline antimicrobial susceptibility, as follows.

#### *3.2.3.1 Charlson and Elixhauser scores*

I calculated Charlson comorbidity and Elixhauser acuity scores using the "comorbidity" R package [129], which employs Quan et al.'s ICD-10 codes for 17 (Charlson) and 31 (Elixhauser) weighted comorbidities [130]. Both scores were calculated by incorporating all primary and secondary ICD-10 codes from completed episodes in the year prior to the inpatient episode containing the index blood culture and all secondary ICD-10 codes from the current inpatient episode corresponding to the index blood culture [131].

#### *3.2.3.2 Baseline NEWS*

The baseline NEWS was calculated using the closest set of vital signs within 1 day before to 1 day after the start of each episode. This calculation incorporates six physiological parameters: respiration rate, oxygen saturation, systolic blood pressure, heart rate, temperature, and level of consciousness or new confusion. Each parameter is assigned a score ranging from 0 to 3, based on predefined thresholds, with higher scores reflecting greater deviation from the norm and hence, increased risk of adverse clinical outcomes [132].

#### *3.2.3.3 Immunosuppression and palliative care*

Immunosuppression was determined by the presence of ICD-10 diagnostic codes for AIDS/HIV (B20–24), metastatic cancer and haematological malignancies (C77-96), primary immunodeficiencies (D80-84) and end-stage liver disease (K721, K729, K766, K767) using the same 1-year lookback period. Similarly, palliative care was determined by the presence of ICD-10 diagnostic codes (Z515) for palliative care using the same 1-year lookback period.

#### *3.2.3.4 Community-onset*

Community-onset was defined as the index blood sample being collected ≤48 hours from inpatient admission.

#### *3.2.3.5 Source of Infection*

Sources of infection were identified from antimicrobial prescribing indications using Natural Language Processing, based on a workflow developed in collaboration with my colleagues [133]. A pre-trained Bio+Clinical BERT model was used to infer potential sources of infection from free-text antibiotic indications. In training the model, we used a source dataset comprising of 940,887 free-text antibiotic indications from 302,568 hospital admissions at OUH where antibiotics were administered. From this dataset, we extracted the 4000 most common unique indications, accounting for 82% of records, which underwent independent labelling by two clinical researchers, with a third adjudicating any disagreements. This subset therefore represented the most frequently occurring reasons for antibiotic prescription and was identified with different ground-truth labels of working sources of infection such as respiratory, urinary, abdominal, skin

and soft tissue, orthopaedic, ear, nose and throat (ENT), central nervous system (CNS), other, multiple sources, and nonspecific, as well as labels indicating diagnostic uncertainty. We compared the distribution of sources of infection between ground-truth labels with that of ICD10 codes obtained from patient episodes (**Figure** 3.2). Using this high-frequency dataset, we trained and assessed three distinct models: an n-gram XGBoost, a baseline BERT, and the Bio+Clinical BERT. The Bio+Clinical BERT model was selected based on its superior performance following validation.

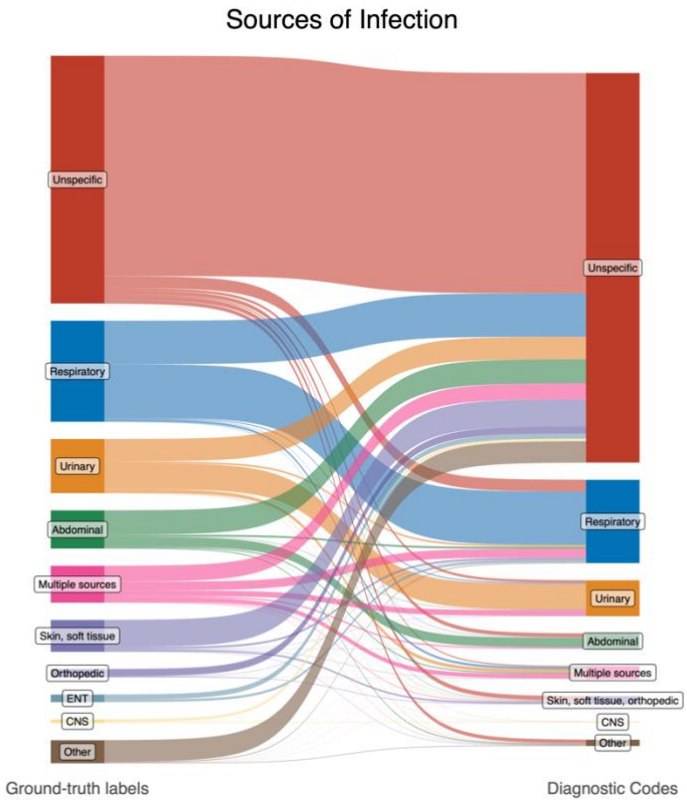


**Figure 3.2 Comparison of infection source distribution: clinician-reviewed ground-truth labels versus ICD10 codes.**

#### *3.2.3.6 Blood culture result and pathogen group*

Blood culture results were classified into 18 groups based on culture results (positive, potential contaminant, negative) as well as the genus and clinical significance of the positive microorganisms (**Table** 3.1).

**Table 3.1 Blood culture results**

| Gram-positive Pathogens | Gram-negative Pathogens | Other Pathogens | Potential Contaminant(s) and Culture-negative |
|---|---|---|---|
| *Staphylococcus aureus* | *Escherichia coli* | Other | Culture-negative |
| Beta-Hemolytic Streptococci | *Klebsiella* sp. | Polymicrobial | CoNS* (contaminant) |
| *Enterococcus* sp. | Other *Enterobacterales* | Anaerobes | Other Suspected Contaminants |
| *Streptococcus pneumoniae* | *Pseudomonas aeruginosa* | *Candida* sp. | Viridans and Other *Streptococcus* |
| Other Pathogenic *Streptococcus* | *Enterobacter* sp. | | |

*CoNS: Coagulase-negative staphylococci

#### *3.2.3.7 Baseline antimicrobial susceptibility*

Baseline antimicrobials (antibiotics and antifungals) were defined as those administered within 12h before to 24h after blood culture collection. Antivirals were not considered. The baseline antimicrobial susceptibility profile for each suspected BSI episode was evaluated based on the results of antimicrobial susceptibility testing as well as information on intrinsic resistance and antimicrobial activity in the Sanford Guide if susceptibility test results were not available for specific drugs (including both antibiotics and antifungals)[134]. Where results were not available and there was uncertainty about the expected susceptibility of an isolated organism then results were recorded as unknown. The susceptibility profile of rarer pathogens was defined as unknown where these were not tested and intrinsic susceptibility data were not available. Episodes where the patient was admitted directly to the intensive care unit, where baseline antimicrobial administration was recorded using a different EHR system from which data were not available (31 cases), were also defined as having unknown susceptibility. For monomicrobial infections, episodes were defined as susceptible if any antimicrobial received during the baseline window was susceptible to the pathogen isolated (including single dose gentamicin), otherwise resistant if the pathogen eventually isolated was resistant to all antimicrobials received in the baseline window. For polymicrobial infections, episodes were defined as resistant if any pathogen was resistant to all baseline antimicrobials, susceptible if all pathogens were susceptible to

any baseline antimicrobials, and unknown if any had unknown susceptibility to baseline antimicrobials. Using these definitions, *Candida* infections treated with only baseline antibiotics (79.0% [64/81]) were resistant to baseline antimicrobials.

### 3.2.4 Statistical analyses

Linear mixed models were used to estimate CRP, WBC and vital signs' trajectories throughout suspected BSI episodes, from -1 day (CRP, WBC) or -6 hours (vital signs) before to +8 days after the start of each episode, using box-cox transformed values as the outcome (to meet, at least approximately, the normality assumption). Modelling time was limited to 6 hours prior to the start of each episode for vital signs, as vital signs were not frequently measured before this point. Nonlinear trends were incorporated via natural cubic splines with four knots at the 20th, 40th, 60th and 80th percentiles of observed time values and included as fixed and random effects, as was the intercept (i.e. estimated vital sign/laboratory test value at the start of each episode). Fixed effects were included for baseline factors characterising each infection episode: source of infection, community-onset (blood sample collection ≤48 hours from admission), blood culture result (positive, potential contaminant, negative) and pathogen group (as in **Table** 3.1), age, sex, Charlson comorbidity and Elixhauser acuity scores, and immunosuppression. These covariates were selected based on clinical knowledge and prior literature, considering factors that may be associated with both the exposure (pathogen group or infection source) and the outcome (biomarker trajectories), and thus could potentially confound the observed associations. They were included regardless of statistical significance. Potential non-linear associations for age were considered via natural cubic splines with one knot at the 50th percentile (boundary

knots at 5th and 95th) if it improved model fit ($p<0.05$). Interactions between each covariate and the natural cubic splines for the time were assessed using likelihood ratio tests, comparing models with and without the interaction terms. A global p-value threshold of 0.05 was used to determine the inclusion of interaction terms in the final models, i.e. those with an impact on the trajectory as well as the baseline values (blood culture result and pathogen group, infection source, community-onset and immunosuppression). The final model had the form:

```
TimeSpline <- ns(df$time, knots = quantile(df$time, c(0.20, 0.40, 0.60, 0.80)),
Boundary.knots = quantile(df$time, c(0.01, 0.99)))
RE_CRP <- lmer(CRP ~ Elixhauser + Charlson + Sex + ns(df$Age, knots =
quantile(df$Age, c(0.50)), Boundary.knots = quantile(df$Age, c(0.05, 0.95)) +
TimeSpline * (BugGroup + Source + CommunityOnset + ImmunoSuppression) +
(TimeSpline | EpisodeID), data = df, REML = TRUE)
```

Separate adjusted models were fitted to examine the effects of the source of infection and baseline antimicrobial susceptibility. Models examining the effects of the source of infection were not adjusted for blood culture results because these would not be available for 24-48h but adjusted for other covariates above. Models examining baseline antimicrobial susceptibility were adjusted for blood culture results (i.e. pathogen group), source of infection and other covariates. These models included the main pathogen group covariate with categories as in **Table** 3.1 and then an additional covariate which reflected “Susceptible”, “Resistant”, “No Antimicrobial Recorded” and “Unknown” for the Gram-positive, Gram-negative and other pathogens in **Table** 3.1. Effectively, this was a partial interaction term, with no effect by definition for potential contaminants and culture-negative episodes, but for episodes with a pathogen, estimates that reflect the average effect of baseline antimicrobials being “Resistant”,

"No Antimicrobial Recorded" or "Unknown" vs "Susceptible" across pathogens. This allowed me to fit a model that was nested within the main model, preserving the random effects structure.

Analyses were performed using statistical software R, version 4.1.0 (R Project for Statistical Computing). Model fitting was performed using the 'lme4' package (version 1.1-27.1) (using restricted maximum likelihood estimation (REML) with the 't-tests using Satterthwaite's method' approach for approximating degrees of freedom, as implemented in the 'lmerModLmerTest' function). The R code for my analysis is available at github.com/guqingze/bsi_normal_response.

## 3.3 Results

From 1 January 2016 to 28 June 2021, 24.4% (95,928/392,443) inpatient admissions had blood cultures taken within them (39.5% [82,535/208,699] emergency and 4.4% [7,132/163,201] elective admissions; overall 122 blood cultures/1,000 patient-days). After deduplication of blood cultures taken within 14 days, there were 88,348 suspected BSI episodes in 60,647 patients (**Figure** 3.1). A single Gram-positive pathogen was identified in 1,914 (2.2%) episodes, a single Gram-negative pathogen in 3,736 (4.2%), 1,260 (1.4%) had other pathogens or were polymicrobial, 4,307 (4.9%) had only a potential contaminant isolated, and 77,131 (87.3%) were culture-negative (**Table** 3.2). The median age at the start of infection episodes was 67.3 (IQR 48.5–80.4) years. Patients had relatively few comorbidities (median Charlson 1 (IQR 0–2)), with only 12802 (14.5%) episodes in immunosuppressed patients; most episodes were

community-onset (71,258, 80.7%). Respiratory (22,818; 25.8%), multiple (11,012; 12.5%) or urinary (9,275; 10.5%) sources were most common.

**Table 3.2 Characteristics at the start of 88,348 BSI episodes between 01 January 2016 and 28 June 2021.**

| Characteristic | Gram-positive Pathogens N = 1,912 (2.2%)[1] | Gram-negative Pathogens N = 3,736 (4.2%)[1] | Other Pathogens N = 1,260 (1.4%)[1] | Potential Contaminant(s) N = 4,309 (4.9%)[1] | Culture-negative N = 77,131 (87.3%)[1] | Overall N = 88,348 (100%)[1] |
|---|---|---|---|---|---|---|
| Age at admission (years) | 70.6 (54.4, 82.1) | 74.9 (61.7, 84.1) | 65.3 (48.5, 78.9) | 69.0 (52.8, 81.2) | 66.6 (47.4, 80.1) | 67.3 (48.5, 80.4) |
| Sex (male) | 1,144 (59.8%) | 2,080 (55.7%) | 691 (54.8%) | 2,215 (51.4%) | 37,558 (48.7%) | 43,688 (49.4%) |
| Ethnicity | | | | | | |
| White | 1,589 (83.1%) | 3,044 (81.5%) | 980 (77.8%) | 3,449 (80.0%) | 61,647 (79.9%) | 70,709 (80.0%) |
| Other | 64 (3.3%) | 178 (4.8%) | 70 (5.6%) | 261 (6.1%) | 4,631 (6.0%) | 5,204 (5.9%) |
| Unknown | 259 (13.5%) | 514 (13.8%) | 210 (16.7%) | 599 (13.9%) | 10,853 (14.1%) | 12,435 (14.1%) |
| Charlson score | 1 (1, 2) | 2 (1, 3) | 1 (0, 2) | 1 (0, 3) | 1 (0, 2) | 1 (0, 2) |
| Elixhauser score | 3 (2, 5) | 3 (2, 5) | 3 (1, 4) | 3 (1, 4) | 2 (1, 4) | 2 (1, 4) |
| NEWS score (baseline) | 4 (2, 6) | 4 (2, 6) | 3 (2, 6) | 3 (1, 5) | 2 (1, 4) | 3 (1, 5) |
| Unknown | 131 (6.9%) | 210 (5.6%) | 117 (9.3%) | 442 (10.3%) | 6,684 (8.7%) | 7,584 (8.6%) |
| Immunosuppression | 310 (16.2%) | 719 (19.2%) | 306 (24.3%) | 662 (15.4%) | 10,805 (14.0%) | 12,802 (14.5%) |
| Diabetes mellitus | 490 (25.6%) | 972 (26.0%) | 254 (20.2%) | 971 (22.5%) | 14,415 (18.7%) | 17,102 (19.4%) |
| Palliative care | 179 (9.4%) | 359 (9.6%) | 144 (11.4%) | 308 (7.1%) | 3,986 (5.2%) | 4,976 (5.6%) |
| Community-onset | 1,505 (78.7%) | 2,852 (76.3%) | 863 (68.5%) | 3,074 (71.3%) | 62,964 (81.6%) | 71,258 (80.7%) |
| Source of infection | | | | | | |
| Respiratory | 431 (22.5%) | 378 (10.1%) | 185 (14.7%) | 1,180 (27.4%) | 20,644 (26.8%) | 22,818 (25.8%) |
| Multiple sources | 421 (22.0%) | 817 (21.9%) | 228 (18.1%) | 566 (13.1%) | 8,980 (11.6%) | 11,012 (12.5%) |
| Urinary | 132 (6.9%) | 1,044 (27.9%) | 116 (9.2%) | 427 (9.9%) | 7,556 (9.8%) | 9,275 (10.5%) |
| Abdominal | 101 (5.3%) | 590 (15.8%) | 169 (13.4%) | 254 (5.9%) | 5,798 (7.5%) | 6,912 (7.8%) |
| Skin, soft tissue, orthopaedic | 272 (14.2%) | 88 (2.4%) | 80 (6.3%) | 261 (6.1%) | 5,596 (7.3%) | 6,297 (7.1%) |
| CNS | 35 (1.8%) | 23 (0.6%) | 21 (1.7%) | 72 (1.7%) | 1,063 (1.4%) | 1,214 (1.4%) |
| Other | 117 (6.1%) | 60 (1.6%) | 87 (6.9%) | 160 (3.7%) | 2,432 (3.2%) | 2,856 (3.2%) |
| Unspecific | 403 (21.1%) | 736 (19.7%) | 374 (29.7%) | 1,389 (32.2%) | 25,062 (32.5%) | 27,964 (31.7%) |

[1]Median (IQR); n (%)

Note: CNS stands for central nervous system. Percentages in the header are of all episodes, and in the main body are column percentages within each group; continuous variables are summarised using median (IQR). The baseline NEWS score was calculated using the closest set of vital signs within 1 day before to 1 day after the start of each episode.

### 3.3.1 CRP response trajectories following negative/positive blood cultures

77,957 (88.2%) suspected BSI episodes in 54,381 (89.7%) patients had ≥1 CRP available (median 4 (IQR 2–6, range 1–20) measurements/episode); these were broadly similar to episodes without CRP measurements (standardised mean difference (SMD) ≤0.12, **Table** 3.3) with the exception of slightly fewer culture-negative results in those with CRP results (SMD=0.22). CRP increased sharply, generally peaking between day 1 and 2 post blood-culture collection, with varying rates of increase and peaks for different pathogen groups (interaction p<0.0001, **Figure** 3.3). Adjusted CRP response trajectories differed most substantially in Gram-positive infections (**Figure** 3.3**A**), rising much faster and earlier with *Streptococcus pneumoniae* infections than other Gram-positive (or Gram-negative) pathogens and peaking at day 1 (mean level ~290 mg/L), followed by rapid declines and near stability by day 6 (~65 mg/L). CRP also increased rapidly with beta-haemolytic Streptococci but peaked slightly later, reaching ~240 mg/L on day 1.3 and then decreasing rapidly (to ~50 mg/L by day 8). CRP response trajectories for Gram-negative infections were broadly similar to each other, peaking at 175–215 mg/L after day 1 before falling back to ~35mg/L (**Figure** 3.3**B**). For other pathogens, peak CRP levels were higher in episodes with anaerobic and polymicrobial infections (190–200 mg/L), and the latter had the slowest recovery rate, remaining at ~75 mg/L by day 8; recovery was also slower in *Candida* bloodstream infection episodes (~60 mg/L by day 8, **Figure** 3.3**C**). CRP responses were still seen in those with only potential contaminants or no organism identified, and were similar to each other, peaking at lower mean levels (95–115mg/L, at just after 24h) to those with pathogens identified (**Figure** 3.3**D**).

We considered infection sources in separate adjusted models, not including the pathogen group (since most blood cultures were negative, and clinical syndromes but not blood culture results were known at admission). Differences between most sources were smaller than between pathogen groups (**Figure** 3.3**E**). Episodes with abdominal or multiple source(s) elicited the strongest CRP responses, with mean levels reaching ~150 mg/L and ~130 mg/L, respectively, by day 1. CRP responses were lower for episodes with neurological and non-specific origin, with peaks of ~60 mg/L and ~80 mg/L. There was little difference between the remaining sources. In culture-positive infections, adjusting for pathogen group and infection source, episodes with pathogens susceptible to any baseline antimicrobial elicited higher CRP responses than those resistant to all baseline antimicrobials (~205 mg/L vs. ~170 mg/L on day 1.2, **Figure** 3.3**F**; **Figure** 3.4; **Table** 3.4).

**Table 3.3 Comparison of blood culture results for suspected BSI episodes with versus without ≥1 measurement of CRP within 1 day before to 8 days after the start of each episode.**

| **Blood Culture Results** | **CRP Measured at least once during the episode**, N = 77,957 (88.2%)[1] | **CRP Not Measured**, N = 10,391 (11.8%)[1] | **Standardised Difference**[2] |
|---|---|---|---|
| Gram-positive Pathogens | | | |
| *Staphylococcus aureus* | 697 (0.9%) | 19 (0.2%) | 0.10 |
| Beta-Hemolytic Streptococci | 388 (0.5%) | 31 (0.3%) | 0.03 |
| *Enterococcus* sp. | 329 (0.4%) | 14 (0.1%) | 0.05 |
| *Streptococcus pneumoniae* | 290 (0.4%) | 16 (0.2%) | 0.04 |
| Other Pathogenic *Streptococcus* | 124 (0.2%) | 4 (0.0%) | 0.04 |
| Gram-negative Pathogens | | | |
| *Escherichia coli* | 2,284 (2.9%) | 126 (1.2%) | 0.12 |
| *Klebsiella* sp. | 503 (0.6%) | 21 (0.2%) | 0.07 |
| Other *Enterobacterales* | 349 (0.4%) | 18 (0.2%) | 0.05 |
| *Pseudomonas aeruginosa* | 289 (0.4%) | 14 (0.1%) | 0.05 |
| *Enterobacter* sp. | 127 (0.2%) | 5 (0.0%) | 0.04 |
| Other Pathogens | | | |
| Other | 510 (0.7%) | 45 (0.4%) | 0.03 |
| Polymicrobial | 309 (0.4%) | 6 (0.1%) | 0.07 |
| Anaerobes | 284 (0.4%) | 23 (0.2%) | 0.03 |
| *Candida* sp. | 81 (0.1%) | 2 (0.0%) | 0.03 |
| Potential Contaminant(s) and Culture-negative | | | |
| Culture-negative | 67,464 (86.5%) | 9,667 (93.0%) | 0.22 |
| CoNS (contaminant) | 3,184 (4.1%) | 305 (2.9%) | 0.06 |
| Other Suspected Contaminants | 441 (0.6%) | 59 (0.6%) | 0.00 |
| Viridans and Other *Streptococcus* | 304 (0.4%) | 16 (0.1%) | 0.05 |

[1]n (%)

[2]Standardised Mean Difference

Note: Other Pathogenic *Streptococcus* include *Streptococcus anginosus*, *Streptococcus gallolyticus*, *Streptococcus constellatus*, *Streptococcus intermedius*, *Streptococcus lutetiensis*, *Streptococcus bovis*. CoNS (contaminant) refers to Coagulase negative staphylococci. Percentages in the header are of all episodes, and in the main body are column percentages within each group. The effect size was estimated using standardised mean difference (SMD), considering 0.2, 0.5, and 0.8 as small, medium, and large, respectively [135].

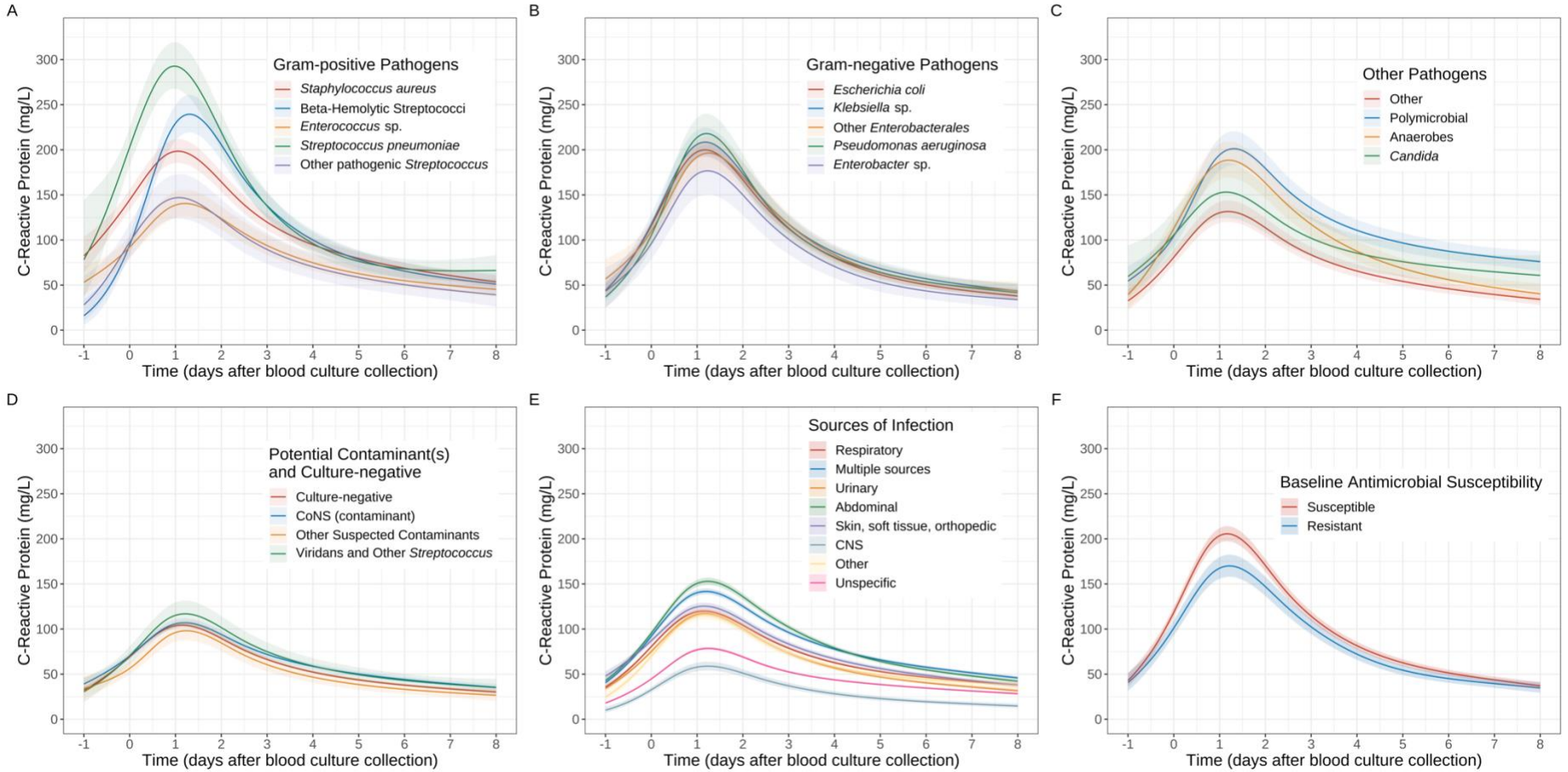


**Figure 3.3 CRP response trajectories following different blood culture results, sources of infection and baseline antimicrobial susceptibilities.**
CRP response trajectories following different blood culture results: Gram-positive pathogens (A), Gram-negative pathogens (B), other pathogens (C), and potential contaminants and culture-negative results (D) were adjusted for source of infection and other covariates; trajectories following different sources of infection (E) were not adjusted for blood culture results but adjusted for other covariates; and trajectories following different baseline antimicrobial susceptibilities (F) were adjusted for blood culture results, source of infection and other covariates. See **Figure** 3.4**A** for response trajectories where no baseline antimicrobial was recorded and for unknown baseline susceptibility. Predictions are plotted at the reference values of other adjusting variables: age = 64 years, male, Charlson score = 1, Elixhauser score = 3, community-onset, absence of immunosuppression, urinary source

(excluding panel E), and *E. coli* infection (panel F only). Nonlinear trends were incorporated via natural cubic splines with four knots at the 20th, 40th, 60th and 80th percentiles of observed time values (day 0, day 0.8, day 2.4, day 4.7).

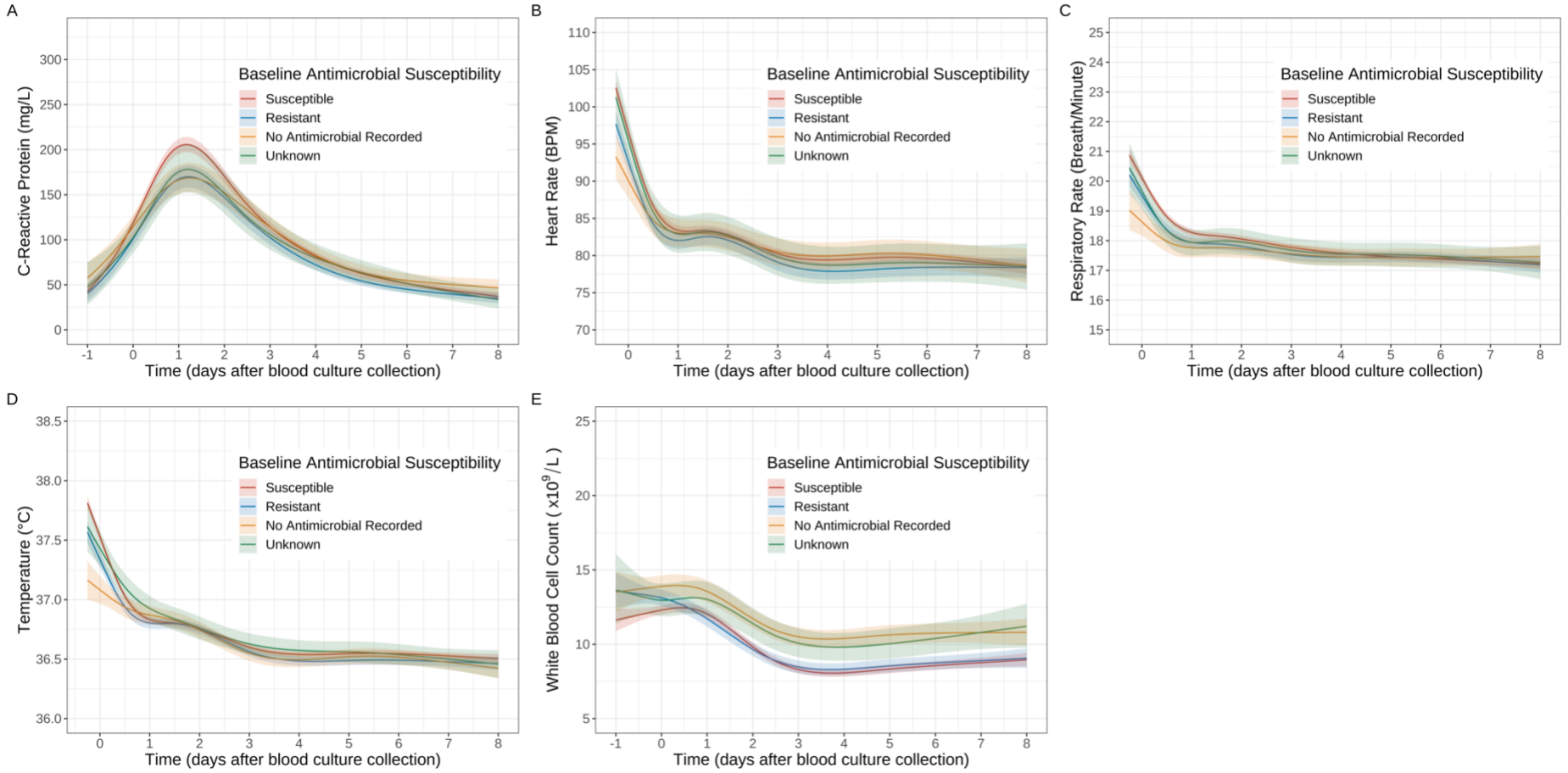


**Figure 3.4 Response trajectories for CRP (A), heart rate (B), respiratory rate (C), body temperature (D) and WBC count (E) for episodes with pathogens isolated with different baseline antimicrobial susceptibilities.**
Predictions are plotted at the reference values of other adjusting variables: age = 64 years, male, Charlson score = 1, Elixhauser score = 3, community-onset, absence of immunosuppression, urinary source, and *E. coli* infection.

**Table 3.4 Distribution of baseline antimicrobial susceptibility across pathogen groups for suspected BSI episodes with ≥1 measurement of CRP within 1 day before to 8 days after the start of each episode.**

| | Baseline Antimicrobial Susceptibility | | | | |
|---|---|---|---|---|---|
| | Susceptible | Resistant | No Antimicrobial Recorded | Unknown | Total |
| Gram-positive Pathogens | | | | | |
| *Staphylococcus aureus* | 601 (86%) | 26 (3.7%) | 67 (9.6%) | 3 (0.4%) | 697 (100%) |
| Beta-Hemolytic Streptococci | 372 (96%) | 0 (0%) | 14 (3.6%) | 2 (0.5%) | 388 (100%) |
| *Enterococcus* sp. | 224 (68%) | 53 (16%) | 49 (15%) | 3 (0.9%) | 329 (100%) |
| *Streptococcus pneumoniae* | 278 (96%) | 0 (0%) | 11 (3.8%) | 1 (0.3%) | 290 (100%) |
| Other Pathogenic *Streptococcus* | 101 (81%) | 2 (1.6%) | 20 (16%) | 1 (0.8%) | 124 (100%) |
| Gram-negative Pathogens | | | | | |
| *Escherichia coli* | 1,874 (82%) | 342 (15%) | 65 (2.8%) | 3 (0.1%) | 2,284 (100%) |
| *Klebsiella* sp. | 411 (82%) | 54 (11%) | 35 (7.0%) | 3 (0.6%) | 503 (100%) |
| Other *Enterobacterales* | 280 (80%) | 43 (12%) | 23 (6.6%) | 3 (0.9%) | 349 (100%) |
| *Pseudomonas aeruginosa* | 177 (61%) | 82 (28%) | 27 (9.3%) | 3 (1.0%) | 289 (100%) |
| *Enterobacter* sp. | 88 (69%) | 30 (24%) | 9 (7.1%) | 0 (0%) | 127 (100%) |
| Other Pathogens | | | | | |
| Other | 215 (42%) | 64 (13%) | 74 (15%) | 157 (31%) | 510 (100%) |
| Polymicrobial | 170 (55%) | 92 (30%) | 32 (10%) | 15 (4.9%) | 309 (100%) |
| Anaerobes | 222 (78%) | 32 (11%) | 27 (9.5%) | 3 (1.1%) | 284 (100%) |
| *Candida* sp. | 4 (4.9%) | 64 (79%) | 12 (15%) | 1 (1.2%) | 81 (100%) |
| Total | 5,017 (76%) | 884 (13%) | 465 (7.1%) | 198 (3.0%) | 6,564 (100%) |

Note: See section **3.2.3** for the definition of baseline antimicrobial susceptibility. Baseline antimicrobials include both antibiotics and antifungals. Culture-negative episodes and episodes with potential contaminants were excluded.

Additionally, after adjusting for infection source and pathogen group, CRP levels were independently higher in males (~20mg/L higher peak versus females, **Figure** 3.5**A**), in episodes with nosocomial onset (20–60mg/L higher during the episode versus community-onset, time-interaction p<0.0001, **Figure** 3.5**B**) and immunosuppressed patients after day-3 (time-interaction p<0.0001, **Figure** 3.5**C**), older patients up to 70 years (~9mg/L higher per 10 years older, **Figure** 3.5**D**) and those with lower Charlson comorbidity scores (**Figure** 3.5**E**).

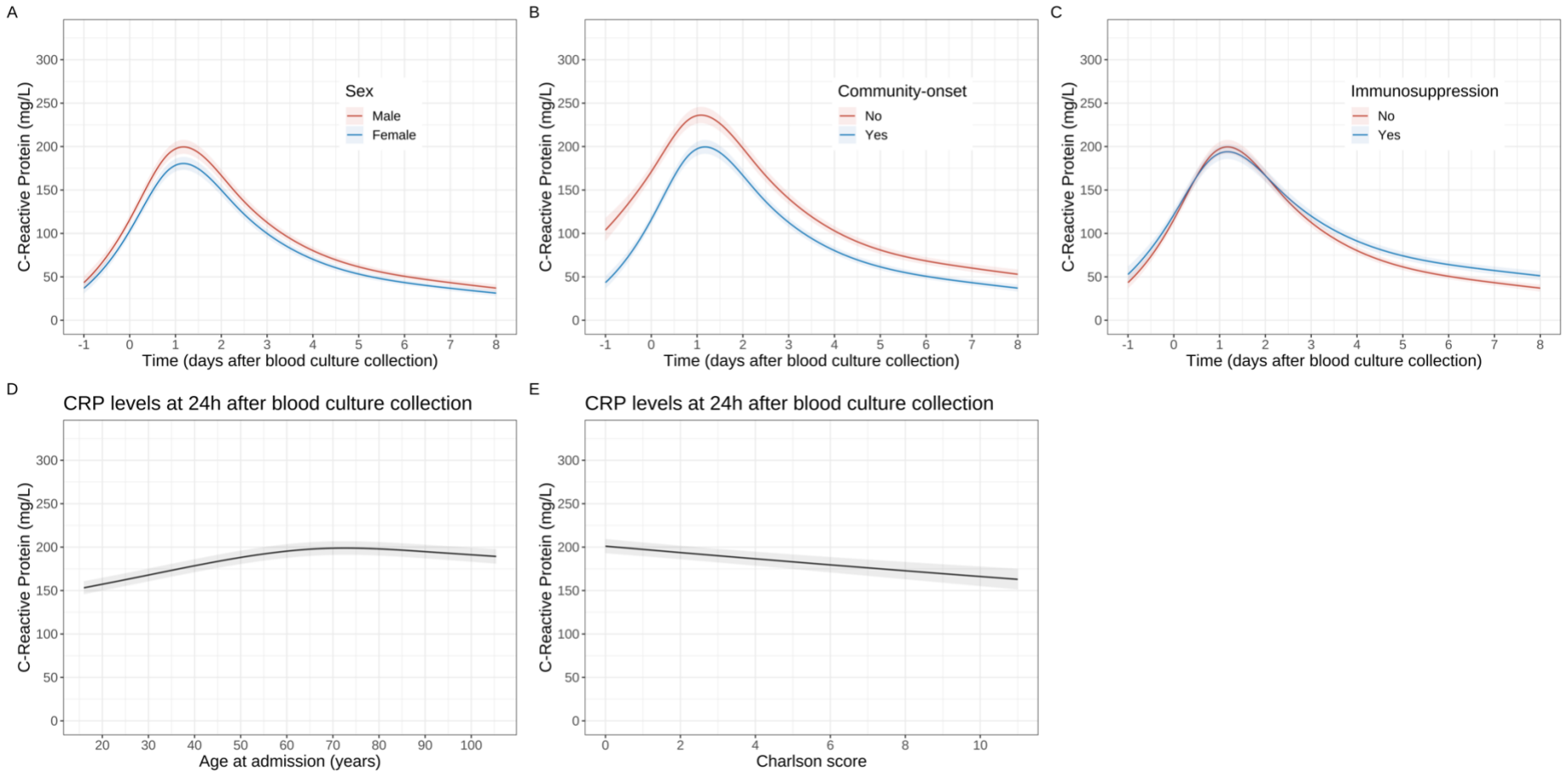


**Figure 3.5 The adjusted associations between CRP response and sex (A), community-onset (B), immunosuppression (C), age (D) and Charlson score (E).** Panels A–C present the relationships between CRP response trajectories from 1 days before to 8 days after the start of each episode. Panels D–E display CRP levels at 24 hours after the start of each episode to demonstrate the association between these continuous covariates and peak CRP levels (no evidence of interaction between these covariates and time; no evidence of association between Elixhauser and peak levels). Predictions are plotted at the reference values of other variables: age = 64 years, male, Charlson score = 1, Elixhauser score = 3, community-onset, absence of immunosuppression, urinary source, and *E. coli* infection. Nonlinear trends were incorporated via natural cubic splines with four knots at the 20th, 40th, 60th and 80th percentiles of observed time values (day 0, day 0.8, day 2.4, day 4.7).

### 3.3.2 Response trajectories for other physiological measurements

Similar adjusted associations were observed for other physiological measurements, although to a lesser extent than for CRP (**Figure** 3.6, **Figure** 3.7, **Figure** 3.8, **Figure** 3.9). WBC peaked earlier than CRP, whereas heart rate, respiratory rate and temperature all declined rapidly over the first day; however, differences associated with different pathogen groups were consistent. Specifically infections with *S. pneumoniae* and beta-haemolytic Streptococci had the highest initial heart rate, respiratory rate and temperature, at ~105 beats/minute, 22–23 breaths/minute and 37.9–38.2°C 6h before blood culture collection, respectively, dropping to ~83 beats/minute, ~18 breaths/minute and ~36.7°C by day 2, respectively (**Figure** 3.6**A**, **Figure** 3.7**A**, **Figure** 3.8**A**). They also had the highest WBC count, peaking around the time of blood culture collection at ~16x$10^9$/L (**Figure** 3.9**A**). Similar to CRP, recovery was slower in patients with *Candida* and polymicrobial infections (**Figure** 3.6**C**, **Figure** 3.7**C**, **Figure** 3.8**C**, **Figure** 3.9**C**), but response trajectories for other pathogen groups and sources of infection (**Figure** 3.6**E**, **Figure** 3.7**E**, **Figure** 3.8**E**, **Figure** 3.9**E**) were broadly similar to each other. There was little difference in response trajectories for other physiological measurements between susceptible and resistant baseline pathogens (**Figure** 3.6**F**, **Figure** 3.7**F**, **Figure** 3.8**F**, **Figure** 3.9**F**).

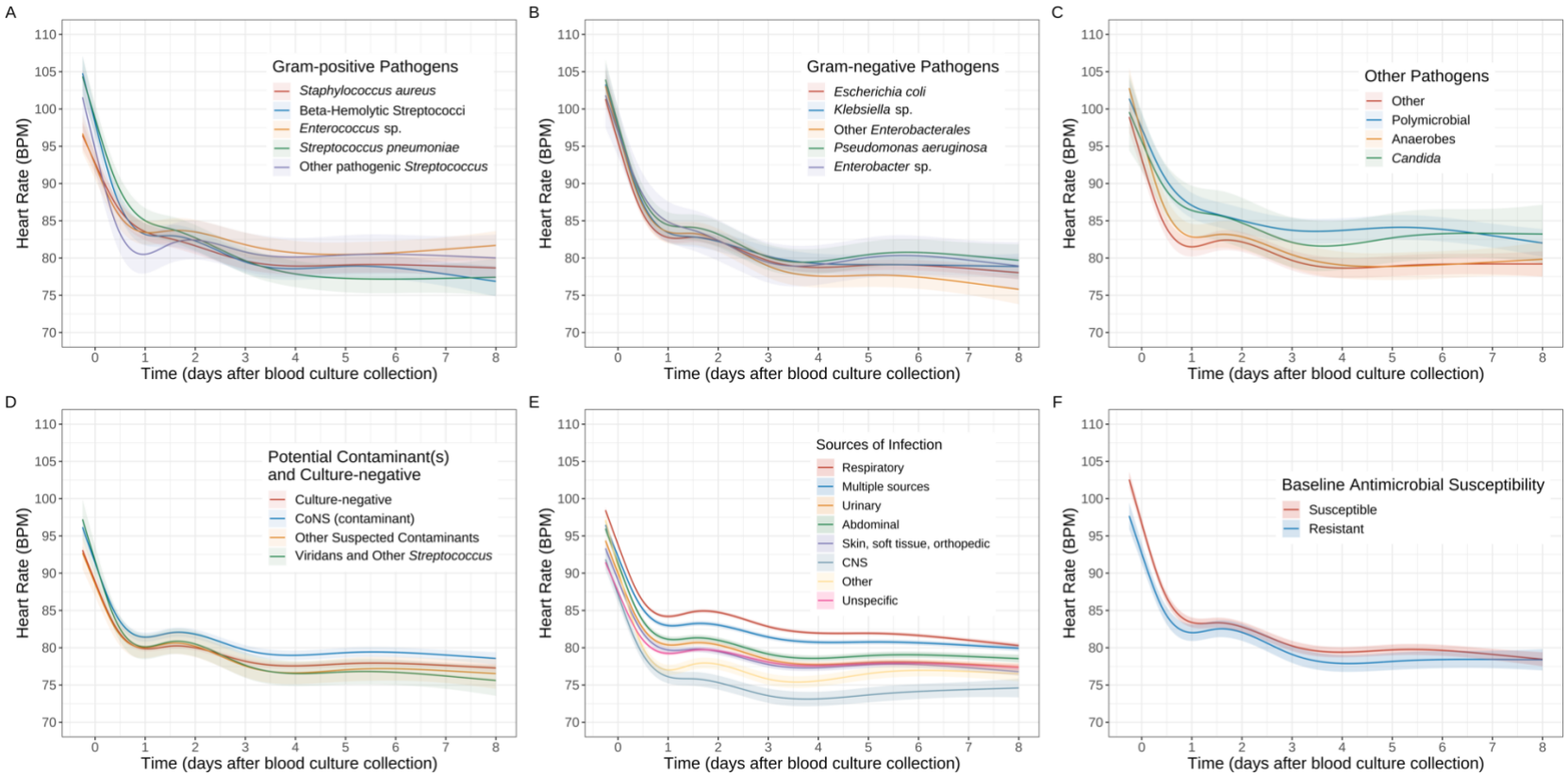


**Figure 3.6 Heart rate response trajectories following different blood culture results, sources of infection and baseline antimicrobial susceptibilities.** Heart rate response trajectories following different blood culture results: Gram-positive pathogens (A), Gram-negative pathogens (B), other pathogens (C), and potential contaminants and culture-negative results (D) were adjusted for source of infection and other covariates; trajectories following different sources of infection (E) were not adjusted for blood culture results but adjusted for other covariates; and trajectories following different baseline antimicrobial susceptibilities (F) were adjusted for blood culture results, source of infection and other covariates. See **Figure** 3.4**B** for response trajectories where no baseline antimicrobial was recorded and with unknown baseline susceptibility. Predictions are plotted at the reference values of other adjusting variables: age = 64 years, male, Charlson score = 1, Elixhauser score = 3, community-onset, absence of immunosuppression, urinary source (excluding panel E), and *E. coli* infection (panel F only). Nonlinear trends were incorporated via natural cubic splines with four knots at the 20th, 40th, 60th and 80th percentiles of observed time values (day 0.4, day 1.5, day 3.0, day 5.1).

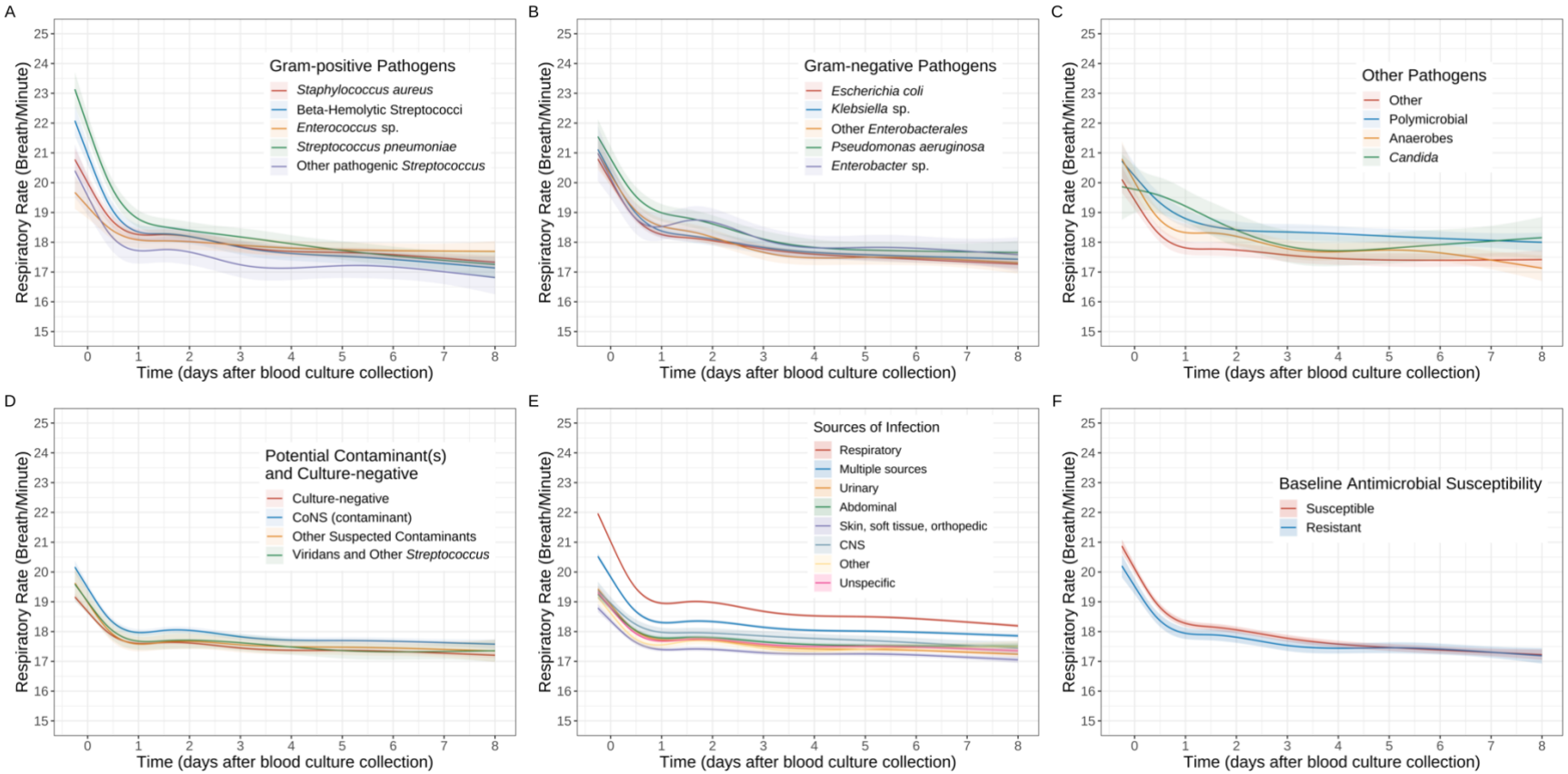


**Figure 3.7 Respiratory rate response trajectories following different blood culture results, sources of infection and baseline antimicrobial susceptibilities.** Respiratory rate response trajectories following different blood culture results: Gram-positive pathogens (A), Gram-negative pathogens (B), other pathogens (C), and potential contaminants and culture-negative results (D) were adjusted for source of infection and other covariates; trajectories following different sources of infection (E) were not adjusted for blood culture results but adjusted for other covariates; and trajectories following different baseline antimicrobial susceptibilities (F) were adjusted for blood culture results, source of infection and other covariates. See **Figure** 3.4**C** for response trajectories where no baseline antimicrobial was recorded and with unknown baseline susceptibility. Predictions are plotted at the reference values of other adjusting variables: age = 64 years, male, Charlson score = 1, Elixhauser score = 3, community-onset, absence of immunosuppression, urinary source (excluding panel E), and *E. coli* infection (panel F only).

Nonlinear trends were incorporated via natural cubic splines with four knots at the 20th, 40th, 60th and 80th percentiles of observed time values (day 0.4, day 1.5, day 3.0, day 5.1).

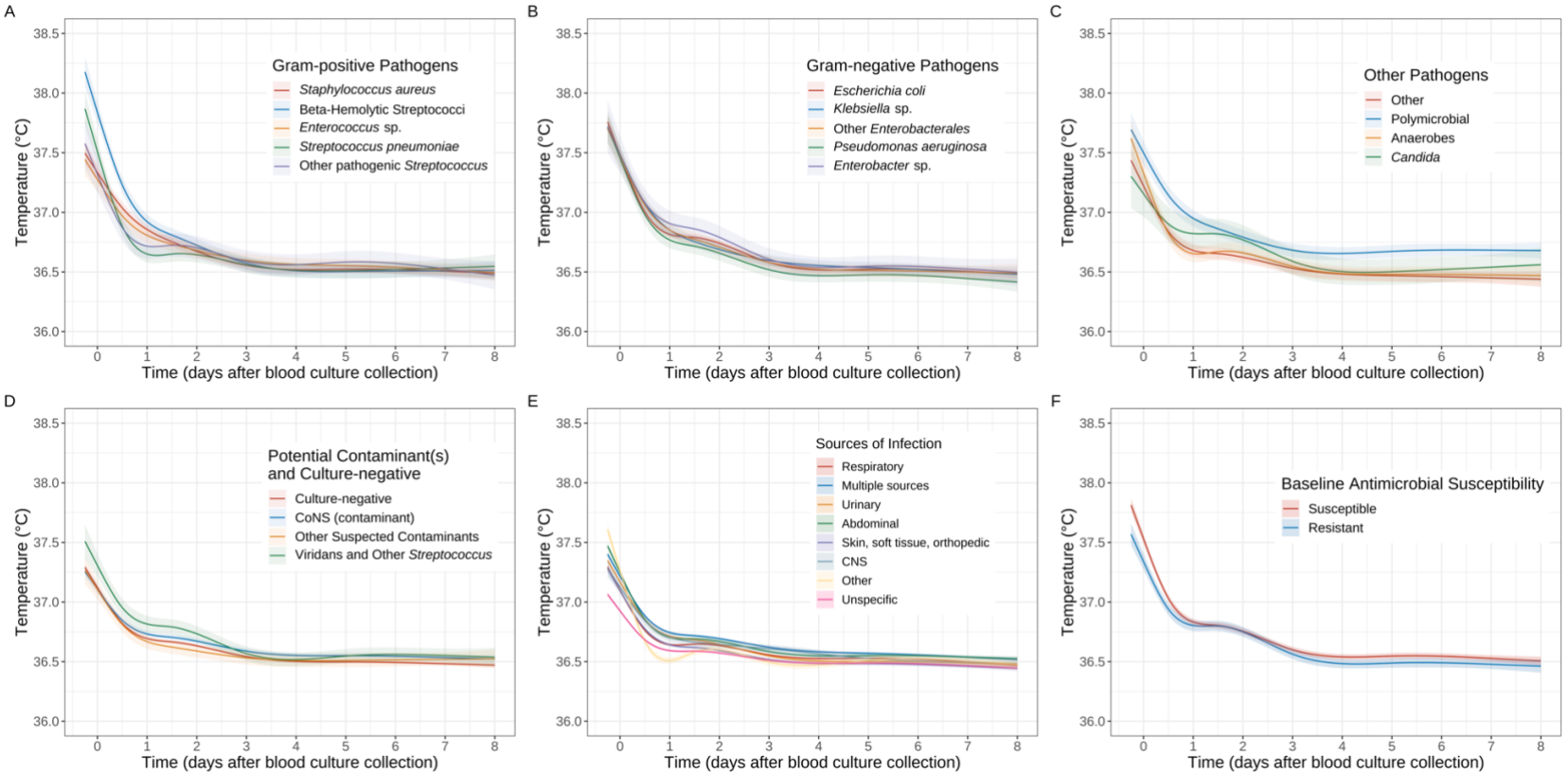


**Figure 3.8 Body temperature response trajectories following different blood culture results, sources of infection and baseline antimicrobial susceptibilities.**

Body temperature response trajectories following different blood culture results: Gram-positive pathogens (A), Gram-negative pathogens (B), other pathogens (C), and potential contaminants and culture-negative results (D) were adjusted for source of infection and other covariates, trajectories following different sources of infection (E) were not adjusted for blood culture results but adjusted for other covariates; and trajectories following different baseline antimicrobial susceptibilities (F) were adjusted for blood culture results, source of infection and other covariates. See **Figure** 3.4**D** for response trajectories where no baseline antimicrobial was recorded and with unknown baseline susceptibility. Predictions are plotted at the reference values of other adjusting variables: age = 64 years, male, Charlson score = 1, Elixhauser score = 3, community-onset, absence of immunosuppression, urinary source (excluding panel E), and *E. coli* infection (panel F only).

Nonlinear trends were incorporated via natural cubic splines with four knots at the 20th, 40th, 60th and 80th percentiles of observed time values (day 0.5, day 1.5, day 3.0, day 5.1).

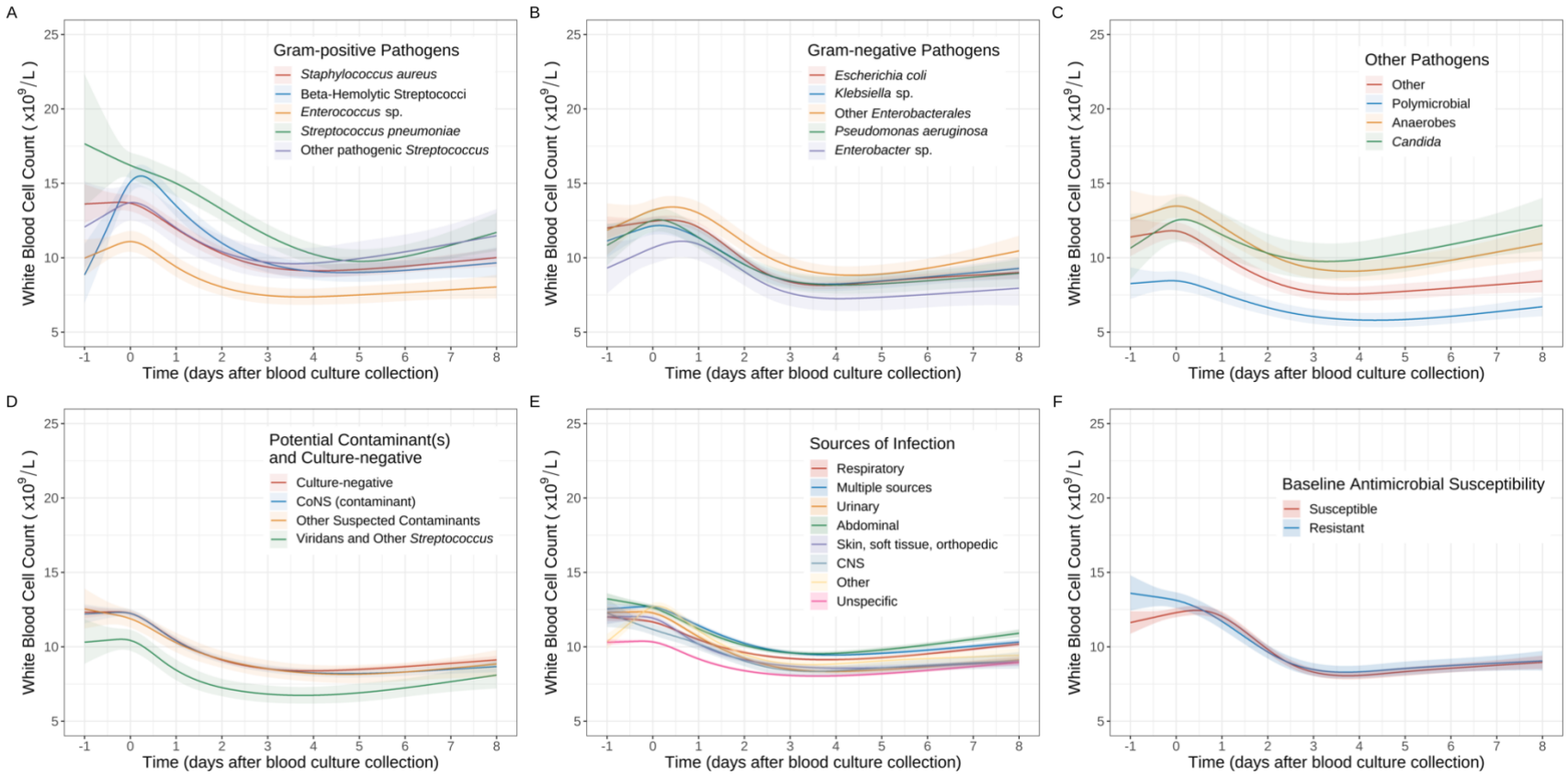


**Figure 3.9 WBC count response trajectories following different blood culture results, sources of infection and baseline antimicrobial susceptibilities.** WBC count response trajectories following different blood culture results: Gram-positive pathogens (A), Gram-negative pathogens (B), other pathogens (C), and potential contaminants and culture-negative results (D) were adjusted for source of infection and other covariates; trajectories following different sources of infection (E) were not adjusted for blood culture results but adjusted for other covariates; and trajectories following different baseline antimicrobial susceptibilities (F) were adjusted for blood culture results, source of infection and other covariates. See **Figure** 3.4**E** for response trajectories where no baseline antimicrobial was recorded and with unknown baseline susceptibility. Predictions are plotted at the reference values of other adjusting variables: age = 64 years, male, Charlson score = 1, Elixhauser score = 3, community-onset, absence of immunosuppression, urinary source (excluding panel E), and *E. coli* infection (panel F only). Nonlinear trends were incorporated via natural cubic splines with four knots at the 20th, 40th, 60th and 80th percentiles of observed time values (day 0, day 0.8, day 2.4, day 4.7).

## 3.4 Discussion

Using large-scale EHR data, the analyses in this chapter demonstrated that clinical response trajectories, as evidenced in laboratory tests and vital signs, are associated with both specific blood culture results and infection sources in individuals with suspected BSI. CRP typically rose sharply after blood culture collection and peaked within 1-2 days, with the rate of increase and peak values varying across pathogen groups. WBC count peaked earlier than CRP, between days 0 and 1, whereas heart rate, respiratory rate and temperature all declined rapidly over the first day following the collection of blood for culture. Nonetheless, there were consistent differences in these response patterns between different pathogen groups. Infections caused by *S. pneumoniae* and beta-haemolytic Streptococci had the most substantial initial clinical response relative to other Gram-positive (or Gram-negative) pathogens; recovery was generally slower in patients with *Candida* and polymicrobial infections.

Serial laboratory testing and vital signs monitoring have previously been investigated for their role in identifying infections [136,137], sub-phenotyping infections [59,138–142], assessing treatment response [120,121,124], and predicting clinical outcomes [120,122,123,126]. Yet, there seems to be a gap in the literature concerning the detailed differentiation of response trajectories by the specific causative organisms and infection sources. For example, several studies examined different CRP response trajectories and their associations with clinical outcomes [120,122,123,126]. However, these studies typically characterised response patterns solely in terms of changes in follow-up CRP relative to baseline without considering the underlying factors that contributed to host response heterogeneity. The findings reported in this chapter,

regarding the detailed temporal dynamics and peaks of several laboratory tests and vital signs across different pathogen groups, sources of infection, baseline treatment and patient characteristics, offer a better understanding of host responses to suspected BSI.

In response to an inflammatory stimulus, such as an infection, CRP levels usually begin to rise within 6-12 hours, peak around 36-50 hours, and then decline with a half-life of approximately 19 hours once the stimulus is removed [125,143,144]. The findings in this chapter are generally consistent with these known dynamics, as CRP levels peaked around day 1-2 post-blood culture collection in most subgroups. However, I have also shown that response trajectories were strongly associated with infection sources and culture results/pathogen groups, at least partly explaining heterogeneity in host responses to BSI. Higher and more prolonged inflammatory responses with abdominal and multiple sources of infection are consistent with earlier studies [145,146], and associations between these sources and higher mortality [145]. Respiratory and multiple infection sources were also consistently associated with higher clinical responses across different clinical parameters. The acute temperature and WBC count response with “other” source of infection was potentially driven by brisk immune responses in younger patients with ENT as well as obstetric infections (and/or potential overfitting in this relatively small group).

Previous evidence on associations between pathogen groups and biomarker responses is inconsistent. Several studies have reported stronger inflammatory responses (e.g., in PCT and CRP) in patients with Gram-negative infections [146–148], however, similar to my findings, others have found higher CRP levels in patients with Gram-positive infections, especially by *S. pneumoniae* [149,150]. This inconsistency may be caused by differences in the timing of single-point measurements or variability in patient cohorts with restricted sample sizes. Based on serial measurements from a larger population with suspected BSI, I found more pronounced CRP, WBC, heart rate, respiratory rate, and temperature responses to some Gram-positive bacteria (particularly *S. pneumoniae* and beta-haemolytic Streptococci) after adjusting for infection sources.

Infections susceptible to baseline antimicrobials were associated with higher CRP responses than resistant infections, possibly due to increased initial inflammatory responses from antimicrobial killing or reduced fitness costs from antimicrobial resistance. However, this difference was not apparent in other physiological measurements. Also, the group where no antimicrobial was recorded had relatively lower CRP and vital signs response – this group was likely enriched for people who were sufficiently well that they might not have received antimicrobials at baseline.

I also found different trajectories of CRP levels after suspected BSI according to different patient demographics and clinical conditions. Notably, males exhibited a higher peak CRP level compared to females (approximately 20 mg/L higher), which aligns with existing literature suggesting sex-based immunological differences. For

instance, studies have indicated that males generally mount a more robust acute-phase response compared to females, possibly due to the influence of sex hormones on immune modulation [151]. In contrast to community-onset infections, nosocomial infections were associated with substantially elevated CRP levels (20-60 mg/L higher) throughout the infection period. This finding is consistent with prior research indicating that hospital-acquired infections often involve more virulent pathogens, thus possibly prompting a more pronounced inflammatory response [152]. In immunosuppressed patients, CRP levels had slightly prolonged elevation, which may reflect a delayed but sustained inflammatory response due to the impaired immune system's inability to initially clear the infection. Other studies have also observed altered levels of CRP and other inflammatory markers in immunocompromised individuals, particularly those undergoing immunosuppressive therapy [153–155]. Higher CRP levels in older patients (~9 mg/L increase per decade, up to 70 years) may be attributed to "inflammaging", where the aging immune system exhibits altered cytokine production and inflammatory responses [156], thereby potentially leading to elevated CRP levels during infections. Little was known about CRP kinetics in elderly patients with infections during hospitalisation [157]. One study found lower CRP levels in older patients when measured on the day of blood culture collection and 2-3 days later, yet the effect was slight and did not adjust for potential confounding factors [158]. A lower Charlson comorbidity score was associated with higher CRP levels. This inverse relationship might be indicative of the fact that patients with fewer comorbidities are able to mount a more vigorous acute-phase response. Higher CRP levels have been observed elsewhere in subgroups of patients with higher Charlson scores, but the differences were modest [150].

Strengths of this study include the large sample size (77,957 suspected BSI episodes with CRP measurements) and longer follow-up (8 days) compared to previous studies, and its use of comprehensive clinical data over several years. The approach used in this chapter has several limitations. Given the complexity of the linear mixed models, I only adjusted for a pre-specified set of potential confounders: the effects of other potential confounders will have been captured within the episode-level random effects. Data were collected for clinical reasons, and CRP and other laboratory measurements are less likely to be (serially) repeated in those making a good recovery and will not be repeated post-discharge; measurements at later time points are therefore likely enriched for elevated values in patients doing less well. Hence true expected trajectories may fall more rapidly and more completely than currently estimated, particularly after day 3. Mitigating this entirely would require sampling irrespective of clinical progress and post-discharge, unlikely feasible at scale. Other limitations include the absence of CRP measurements in 10,391 (11.8%) suspected infection episodes, plausibly the less clinically severe ones. The relatively high culture-negative rate (87.3%) is partly due to my broad definition of suspected infection (any blood culture taken, regardless of physiology) and the historically high rate of taking blood cultures at OUH; nevertheless I have gone on to show in **Chapter 4** that 51.1% of culture-negative episodes still exhibited normal CRP responses, with peaks on days 1 and 2, suggesting that many of these culture-negative episodes likely represent true infections. Analyses only examined the association between baseline antimicrobial activity and CRP response, without adjusting for post-baseline antimicrobial changes due to the risk of time-dependent confounding. PCT can also help guide antimicrobial therapy duration, but this biomarker was not measured routinely at OUH, and therefore, I was

not able to analyse it. Furthermore, this analysis was limited to patient data available in one, albeit large, hospital group, which might influence generalisability.

## 3.5 Conclusions

In summary, I identified strong associations between clinical response trajectories and both infection sources and different pathogen groups in patients with suspected BSI. This chapter's findings highlight the complexity of the host response to BSI and the value of integrating comprehensive databases like EHR in clinical epidemiological research to identify distinct patterns of infection response. These patterns could be pivotal in developing algorithms for early identification and targeted management of infections, ultimately improving patient outcomes and optimising the use of healthcare resources.

# Chapter 4 Defining normal response to suspected bloodstream infections with positive and negative blood culture results

The work presented in this Chapter was published in 2024 in the Journal of Infection [116]. Most of the tables and figures are the same as those published in the paper and its supplementary material.

## 4.1 Introduction

As described in **Chapter 3**, the administration of empirical antimicrobials, while blood culture results are pending, is the standard initial approach to treating suspected BSI in clinical settings [4]. Typically, antimicrobials are promptly switched upon the identification of resistant pathogens. However, if culture results are negative, the identification of resistant infections is not feasible, leading to delayed or inappropriate treatment adjustment [57,117,159,160]. Key questions in this context would be: "How do I know my patient is on the right antibiotic?" and "How long do I have to wait to know that antibiotics are working?" These challenges underscore the need for additional strategies to inform treatment decisions, particularly those that allow timely adjustment of antimicrobial therapy.

Research has increasingly concentrated on the utility of biomarkers to predict clinical outcomes [120,123,126,128,137] and guide treatment plans [161–164,136,165,56,166–

169] in patients with infections. In this context, clinical parameters routinely collected in the EHR show promise in assessing individual-level observations against evidence-based references [170–173], potentially informing decisions on the escalation or de-escalation of antimicrobial therapy as well as its duration.

Several randomised trials have shown that biomarker-guided stewardship strategies were effective in reducing antibiotic usage without compromising patient safety (**Table** 4.1) [136,161,162,164,169,174]. Nonetheless, compliance with these protocols has been less than ideal [162,174,164–166,169,175] (**Table** 4.1), potentially due to their reliance on fixed absolute values and thresholds to determine actions, regardless of individual patient characteristics.

**Table 4.1 Characteristics of randomised trials exploring biomarker-guided stewardship strategies.**

| | Inclusion criteria | Biomarker | Protocol in Biomarker-guided Group | Protocol in Control Group | Primary Outcome | Results | Rate of Adherence |
|---|---|---|---|---|---|---|---|
| *Borges, et al. (2020) [168]* | Adult ICU patients (≥18 years) with suspected or confirmed infection and expected ICU stay >24h were considered for inclusion. | CRP | If CRP ≥100 mg/L, stop antibiotic(s) if CRP decreases ≥50% after 5 days. If CRP <100 mg/L, stop antibiotic(s) if CRP <35 mg/L after 3 days. | Rational clinical practice of antibiotic use (5-14 days based on infection type or focus). | Duration of antibiotic therapy. | Median antibiotic therapy duration for the index infection was 7.0 (5.0–8.8) days in the CRP group and 7.0 (7.0–11.3) days in the control group (p = 0.011). No significant difference was found in total antibiotic exposure or antibiotic-free days. | 92.2% (59/64) in CRP-guided group; 89.4% (59/66) in control group. |
| *von Dach, et al. (2020) [169]* | Adult patients (≥18 years) with gram-negative bacteria in blood culture(s) receiving effective antibiotics. | CRP | Stop antibiotic(s) if CRP decreases 75% from its peak and the patient had been afebrile for 48 hours. | A fixed 7-day duration, or a fixed 14-day duration. | Occurrence of clinical failure by day 30. | Median antibiotic duration: CRP group 7 (6–10) days. Primary outcome: CRP group 2.4% (4/164), 7-day group 6.6% (11/166), 14-day group 5.5% (9/163). Difference in CRP vs 14-day: -3.1% (CI, −∞ to 1.1; P < 0.001). Difference in 7-day vs 14-day: 1.1% (CI, −∞ to 6.3; P < 0.001). | 79% (135/169) in CRP-guided group; 85% (144/169) in 7-day group; 88% (145/165) in 14-day group. |
| *van der Does, et al. (2018) [166]* | Adult patients (≥18 years) in emergency department (ED) with fever (≥38.2 °C) | PCT | Bacterial infection deemed unlikely if PCT <0.5 µg/L; antibiotics discouraged. If PCT ≥0.5 µg/L, bacterial infection likely; antibiotics encouraged. | Standard care (usual diagnostic workup in accordance with international guidelines). | Efficacy: percentage of patients prescribed antibiotic. Safety: combined 30-day mortality, ICU admission, and ED return within 2 weeks. Accuracy: sensitivity, specificity, AUC of PCT for identifying bacterial infections. | PCT group 73% (200/275) prescribed antibiotics; control group 77% (212/276) (p=0.28). No significant difference in combined safety endpoint: PCT-guided 29 (11%) vs control 46 (16%) (p=0.16); non-inferiority margin 0.46% (n=526). AUC for bacterial infections: PCT 0.681 (95% CI 0.633–0.730). | 56% (150/267) in PCT-guided group (107 patients received antibiotic with PCT <0.5 µg/L, and 10 patients did not receive antibiotic with PCT ≥0.5 µg/L). |
| *Huang, et al. (2018) [165]* | Adult patients (≥18 years) in the ED with an initial diagnosis of acute lower respiratory tract infection (<28 days) and uncertain need for antibiotics. | PCT | Antibiotic(s) strongly discouraged for PCT levels <0.1 µg/L, discouraged for levels [0.1,0.25] µg/L, recommended for levels (0.25, 0.5] µg/L, and strongly recommended for levels >0.5 µg/L). | Usual care. | Total antibiotic exposure, defined as the total number of antibiotic days within 30 days after enrolment. | No significant difference in antibiotic-days (PCT group mean 4.2 vs usual-care group 4.3 (difference, −0.05; 95% CI, −0.6 to 0.5; P=0.87)) or adverse outcomes (PCT 11.7% vs usual-care 13.1% (difference, −1.5 percentage points; 95% CI, −4.6 to 1.7; P<0.001 for non-inferiority) within 30 days. | 64.8% (513/792) in PCT-guided group. |

| | Inclusion criteria | Biomarker | Protocol in Biomarker-guided Group | Protocol in Control Group | Primary Outcome | Results | Rate of Adherence |
|---|---|---|---|---|---|---|---|
| *de Jong, et al. (2016) [164]* | Adult ICU patients (≥18 years) who received antibiotics within 24h for suspected or confirmed infection. | PCT | Non-binding advice to discontinue antibiotics was given if procalcitonin decreased by ≥80% of its peak value or to ≤0.5 µg/L. | Patients were treated according to local antibiotic protocols. | Measured antibiotic consumption (in defined daily doses (DDD)) and treatment duration (in 24-hour periods). | Median antibiotic consumption: 7.5 DDD (IQR 4.0–12.7) in the PCT-guided group vs. 9.3 DDD (5.0–16.6) in control (difference 2.69 [95%CI 1.26–4.12], p<0.0001). Median treatment duration: 5 days (3–9) in the PCT-guided group vs. 7 days (4–11) in control (difference 1.22 [95%CI 0.65–1.78], p<0.0001). | 44% (243/557) in PCT-guided group. |
| *Branche, et al. (2015) [174]* | Adult patients (≥21 years) hospitalised with non-pneumonic lower respiratory tract illness. | PCT | Antibiotic initiation is strongly discouraged for PCT ≤0.1 ng/mL, discouraged for PCT 0.11–0.24 ng/mL, encouraged for PCT 0.25–0.49 ng/mL, and strongly encouraged for PCT ≥0.5 ng/mL. | Standard care. | Duration of antibiotic therapy. | No significant differences in antibiotic use or adverse events between intervention patients and control group. Shorter antibiotic durations among adherent intervention patients vs. control (2.0 vs 4.0 days; P = .004) | 64% (96/151) |
| *Oliveira, et al. (2013) [176]* | Adult patients (≥18 years) with suspected severe sepsis or septic shock. | CRP vs. PCT | CRP: <25 mg/L or decrease >50%. | PCT: <0.1 ng/mL or decrease >90%. | Duration of antibiotic therapy for the first episode of infection. | The median duration of antibiotic therapy for the first episode of infection was 7.0 (IQR 6.0–8.5) days in the PCT group and 6.0 (IQR 5.0–7.0) days in the CRP group (p = 0.13) | 87.8% (43/49) in PCT group; 85% (38/45) in CRP group. |
| *Bouadma, et al. (2010) [162]* | Adult ICU patients (≥18 years) with sepsis, or with suspected infections, either untreated or on antibiotics for less than 24h. | PCT | Start antibiotic(s): Strongly discouraged if <0.25 µg/L; discouraged if [0.25,0.5) µg/L; encouraged if [0.5,1) µg/L; Strongly encouraged if ≥1 µg/L. Stop or continue antibiotic(s): Strongly encouraged stop if <0.25 µg/L; encouraged stop if decrease ≥80% or [0.25,0.5) µg/L; encouraged continue if decrease <80% or ≥0.5 µg/L; strongly encouraged continue if increase from peak and ≥0.5 µg/L. | Recommendations derived from international and local guidelines. | Mortality at days 28 and 60 (non-inferiority analysis), and number of days without antibiotics by day 28 (superiority analysis). | Day 28 mortality: PCT 21.2% (65/307) vs control 20.4% (64/314); absolute difference 0.8% (90% CI –4.6 to 6.2). Day 60 mortality: PCT 30.0% (92/307) vs control 26.1% (82/314); 3.8% (–2.1 to 9.7). Antibiotic-free days: PCT 14.3 (SD 9.1) vs control 11.6 (SD 8.2); absolute difference 2.7 days (95% CI 1.4 to 4.1, p<0.0001). | 47.2% (145/307) in PCT group; 55.1% (173/314) in control group. |
| *Schuetz, at al. (2009) [161]* | Adult patients (≥18 years) admitted from the | PCT | Antibiotic(s) discouraged if <0.1 µg/L and ≤0.25 µg/L. Encouraged if >0.25 µg/L and | Recommendations from up-to-date guidelines. | Overall adverse outcomes occurring within 30 days | The rate of adverse outcomes was similar in PCT and control groups (15.4% [n=103] vs | 90.8% (609/671) in PCT group; 79.4% |

| | Inclusion criteria | Biomarker | Protocol in Biomarker-guided Group | Protocol in Control Group | Primary Outcome | Results | Rate of Adherence |
|---|---|---|---|---|---|---|---|
| | community or a nursing home with acute lower respiratory tract infections (<28 days' duration). | | strongly encouraged if >0.5 µg/L. Discontinuation of antibiotic(s) follows the same cutoffs. For initial PCT ≥10 µg/L, discontinue if decreases by 80%; strongly recommend discontinuation if decrease is 90%. | | following the ED admission. | 18.9% [n=130]; difference, −3.5%; 95% CI, −7.6% to 0.4%). Antibiotic duration was shorter in the PCT group (5.7 vs 8.7 days; relative change, −34.8%; 95% CI, −40.3% to −28.7%). | (546/688) in control group. |
| *Kristoffersen, et al. (2009) [175]* | Adult patients (≥18 years) with suspicion of pneumonia | PCT | Antibiotic(s) discouraged if <0.25 µg/L, encouraged if 0.25-0.50 µg/L, strongly encouraged if >0.5 µg/L. | Standard care. | Antibiotic use (defined as days of antibiotic treatment during hospitalization) and length of hospital stay. | Mean hospital stay: PCT group 5.9 days vs. control group 6.7 days (p = 0.22). Mean antibiotic treatment duration: PCT group 5.1 days vs. control group 6.8 days (p = 0.007). | 41% (42/103) in PCT group. |

The analyses in **Chapter 3** identified heterogeneity in inflammatory responses across different pathogen groups, sources of infection and other clinical covariates, with much of this variation was driven by differences around presentation. Theoretically, the CRP response can be summarised using a single centile-based reference chart, analogous to paediatric growth charts [177]. This centile reference chart, estimating typical recovery trajectories, potentially offer a more intuitive and individualised method that could aid in the identification of anomalous recovery patterns and enhance the uptake of biomarker-guided decision-making in clinical practice.

Identifying patterns of response to effective, as opposed to ineffective, antibiotic therapy is instrumental in defining such a "normal" response as a reference. Studies have examined sub-phenotypes using group-based trajectory models in patients with suspected sepsis based on various metrics, including vital signs, WBC counts, and SOFA scores [178,138,142,59,141,179,60,139,140]. Notably, such approaches have not been applied to serial CRP measurements, which is a more sensitive marker than vital signs and WBC counts based on the analyses in the previous chapter; nor have studies employed centile-based methods to estimate infection responses to my knowledge. Additionally, several studies defined 3 to 4 CRP ratio response patterns based on changes in follow-up CRP (e.g., on day 5 ) relative to baseline CRP values and explored their associations with clinical outcomes [120,122,123,126]. A trajectory model based on serial CRP measurements could provide a more nuanced analysis beyond simple CRP comparisons at two time points.

This chapter, therefore, aimed first to identify underlying CRP response patterns using latent class trajectory modelling to identify those responding standardly to (effective) antimicrobials. Furthermore, I then constructed centile reference charts for expected clinical response in standard responders, providing clinicians with a robust tool to potentially tailor treatment to individual patient responses and improve antibiotic stewardship practices.

## 4.2 Methods

### 4.2.1 Research design and study population

The same de-identified data from IORD was used as in Chapter 3 (see details in **3.2.1**). Patients ≥16y with ≥1 blood culture taken during an inpatient admission, and with at least one CRP measurement during the suspected infection episode from one day prior to eight days post- blood culture collection were included. See 3.2.1 for definitions of new suspected infection episodes and index blood cultures.

### 4.2.2 Variables

The same variables were used as in Chapter 3 (see details in section **3.2.2** and **3.2.3**).

### 4.2.3 Statistical analyses

Unadjusted latent class mixed models (LCMM) were used to identify underlying population-level heterogeneity in the response trajectories of routinely collected CRP measurements. I fitted LCMMs with between 1 and 6 classes, and the optimal number of classes was chosen based on the Bayesian Information Criterion (BIC) and percentage of class membership (requiring all to be ≥0.5% to prevent having a large

number of very small classes) (**Table** 4.2). This threshold was arbitrary but was chosen based on clinical judgment to balance model fit and the utility of the latent classes for understanding common CRP response patterns and guiding clinical decision-making. Patient characteristics and other covariates were not included in the models because I did not want to adjust for these potential causes of underlying heterogeneity but for the latent classes to reflect the underlying heterogeneity.

From the selected LCMM with 5 classes (**Table** 4.2), each episode was assigned to the class with the highest posterior probability. Classes exhibiting a rapid rise and prompt fall were assumed to represent patients responding standardly to (assumed effective) antibiotics and other treatments. I used this approach rather than trying to adjust for post-baseline changes in antimicrobials because of potential time-dependent confounding. It also allowed me to include culture-negative episodes; this is important because hospital-level empirical antibiotic recommendations are based on susceptibility data from recent previous infections, with treatment switched promptly if a resistant pathogen is identified in an individual patient. However, many infections are culture-negative, so resistant infections may be missed, and identifying culture-positive resistant infections may take several days.

I then compared characteristics between the latent class groups univariably. The SMD was used in the comparison given the large sample size, and to better account for differences in measurement scales. I did not employ the three-step approach [180] to test class membership predictors as the available package (lcmm 2.1.0) did not support this methodology [181]. I also used multivariable logistic regression to compare 30-day all-cause mortality between different latent classes.

**Table 4.2 Fit indices for latent class mixed models for CRP with different numbers of classes.**

| N classes | Log likelihood | AIC | BIC | SABIC | Entropy | Class 1 (%) | Class 2 (%) | Class 3 (%) | Class 4 (%) | Class 5 (%) | Class 6 (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | -522381.4 | 1044804.9 | 1044999.4 | 1044932.7 | 1.000 | 100.0 | | | | | |
| 2 | -505915.1 | 1011884.3 | 1012134.4 | 1012048.6 | 0.856 | 0.7 | 99.3 | | | | |
| 3 | -499823.5 | 999713.0 | 1000018.7 | 999913.8 | 0.598 | 5.5 | 61.2 | 33.2 | | | |
| 4 | -499309.0 | 998695.9 | 999057.2 | 998933.3 | 0.645 | 0.5 | 32.6 | 61.3 | 5.6 | | |
| 5 | -499012.2 | 998114.3 | 998531.2 | 998388.2 | 0.505 | 1.0 | 13.7 | 46.3 | 33.3 | 5.8 | |
| 6 | -498126.1 | 996354.2 | 996826.7 | 996664.6 | 0.542 | 0.4 | 7.1 | 37.7 | 25.9 | 25.9 | 3.0 |

Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; SABIC: Sample-size adjusted BIC.

Centile reference charts for expected CRP response in standard responders (i.e. those with peak response on day 1 and day 2) were then constructed using the lambda-mu-sigma (LMS) method [182], adopted by the World Health Organization (WHO) to generate the childhood growth standards [177,183], and implemented using the Generalised Additive Models for Location Scale and Shape (GAMLSS) library [184]. Three candidate distributions were considered: Box-Cox Cole Green (truncated standard normal distribution), Box-Cox power exponential (truncated exponential power distribution), and Box-Cox t (truncated t distribution), selected using the Generalised Akaike Information Criterion [185], with degrees of freedom for the penalised spline model smoothing parameters determined using the local Schwarz Bayesian Criterion [185]. With these parameters, z-scores and percentiles of CRP response can be generated for times after blood culture collection.

The LMS method assumes the measurements used for constructing centile charts are independent, whereas serial measurements of vital signs and laboratory tests are correlated within individuals [186]. This could potentially cause bias, especially if patients with abnormal responses get prolonged and more frequent measurements. The common solution of selecting one random observation for each patient can result in significant information loss. I addressed the problem of potentially informative numbers of measurements by first conducting sensitivity analyses by selecting one random observation per episode, and second by estimating centiles by constructing 100,000 bootstrap samples of the 40,620 episodes from standard responders and using a linear mixed model with only fixed and random effects for time (natural cubic spline) as above to simulate the CRP values of these patients at nine random time points up to 8 days after the start of each episode (incorporating fixed effects, correlated random effects per patient and additional measurement error in the prediction) then using these values (100,000 episodes, 900,000 observations) as outcomes for the LMS model.

Analyses were performed using statistical software R, version 4.1.0 (R Project for Statistical Computing). Model fitting was performed using the 'lcmm' package (version 2.1.0), and the 'gamlss' package (version 5.4-20). The R code for my analysis is available at github.com/guqingze/bsi_normal_response.

## 4.3 Results

### 4.3.1 Underlying heterogeneity in CRP response trajectories

A total of 77,957 suspected BSI episodes, each with ≥1 CRP measurement from one day prior to eight days post-onset, were included for LCMMs (see **Table** 3.3 for comparison

of pathogens isolated from included vs. excluded episodes). Five different underlying CRP response subgroups were identified (**Figure** 4.1**A**, **Table** 4.3; spaghetti plots in **Figure** 4.2), distinguished by having their peak on day 1 (36,091 [46.3%]) or day 2 (4,529 [5.8%]), slow recovery (10,666 [13.7%]), peak on day 6 (743 [1.0%]) and low values throughout (25,928 [33.3%]). Overall, 34,466 (51.1%) culture-negative and 1,916 (48.8%) contaminant-only episodes still had acute CRP responses (peaking day 1 or 2) followed by typical recovery vs. 4,238 (64.6%) pathogen-positive episodes (**Figure** 4.1**B**). For pathogen-positive episodes with susceptibility results, 67.8% (3,402/5,018) with susceptible baseline antimicrobials had peak CRP on day 1 or 2, vs. 59.8% (529/884) with resistant baseline antimicrobials (**Figure** 4.1**C,** see section 3.2.3 for the definition of baseline antimicrobial susceptibility). Interestingly, the biggest difference between susceptible and resistant episodes was in the percentage with low response (7.6% vs. 12.7%), whereas for slow recovery it was 24.3% vs. 26.6% (**Figure** 4.1**C**).

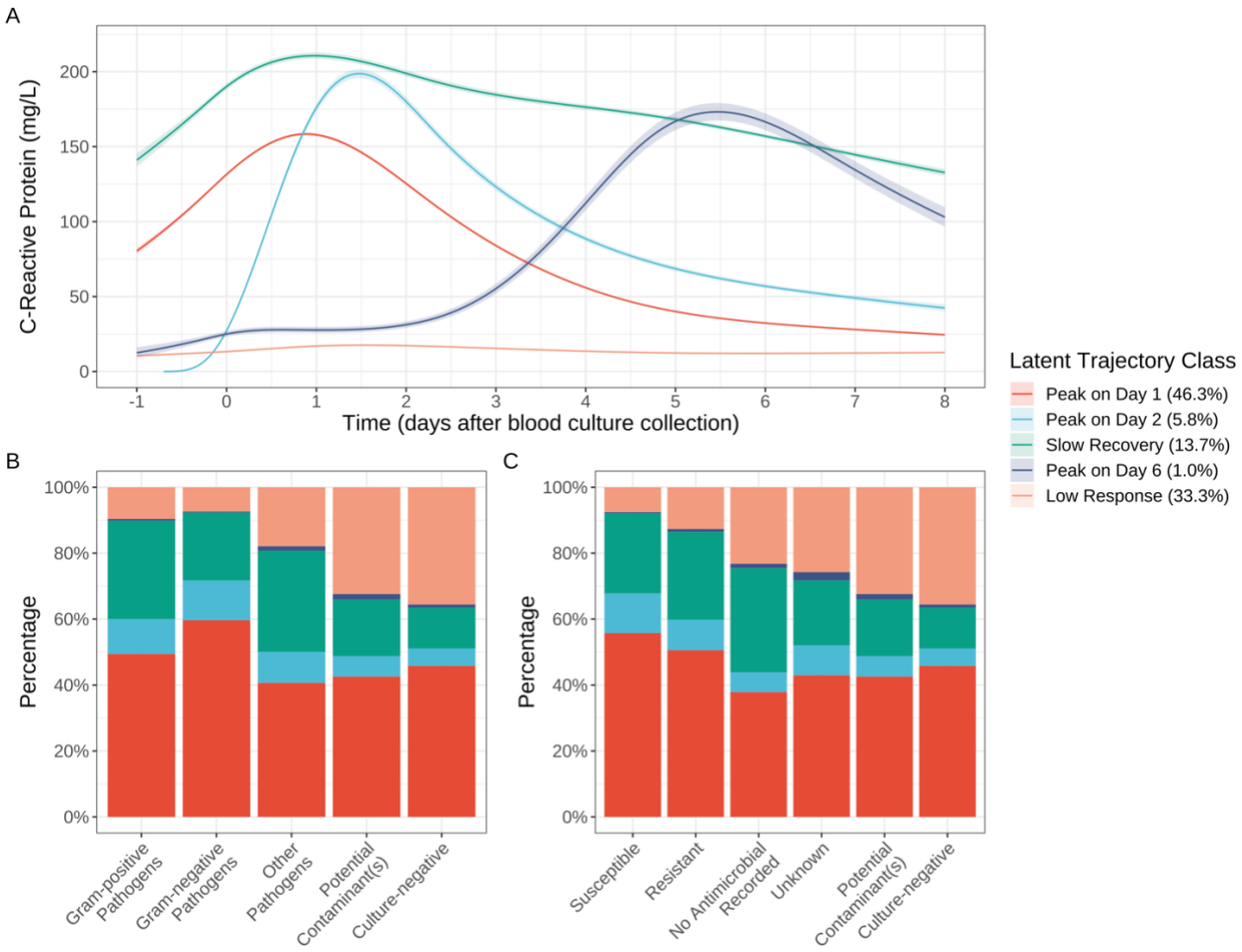


**Figure 4.1 Latent classes of CRP response trajectories (A) and their distribution across different blood culture results (B) and baseline antimicrobial susceptibility (C).**

Latent classes of CRP response trajectories were not adjusted for other covariates. See **Figure 4.3A** and **Figure 4.3B** for the distribution of blood culture results and baseline antimicrobial susceptibilities across each latent trajectory group.

**Table 4.3 Univariable comparison of episode characteristics between latent classes of CRP response trajectories.**

| Characteristic | Peak on Day 1 N = 36,091 (46.3%) | Comparisons with Peak on Day 1: Peak on Day 2 N = 4,529 (5.8%) | Difference[2] | Slow Recovery N = 10,666 (13.7%) | Difference[2] | Peak on Day 6 N = 743 (1.0%) | Difference[2] | Low Response N = 25,928 (33.3%) | Difference[2] | Overall N = 77,957 (100%) |
|---|---|---|---|---|---|---|---|---|---|---|
| Class-membership probability | 0·6 (0·5, 0·7) | 0·9 (0·6, 1·0) | – | 0·7 (0·5, 0·9) | – | 0·8 (0·6, 1·0) | – | 0·7 (0·6, 0·9) | – | 0·6 (0·5, 0·8) |
| Age at admission (years) | 69·2 (51·6, 81·1) | 68·4 (46·7, 81·7) | 0·06 | 70·3 (56·4, 81·0) | 0·13 | 70·1 (56·0, 81·6) | 0·11 | 63·6 (43·6, 79·3) | 0·19 | 67·8 (49·6, 80·6) |
| Sex (Male) | 18,865 (52·3%) | 2,240 (49·5%) | 0·06 | 6,178 (57·9%) | 0·11 | 415 (55·9%) | 0·07 | 11,363 (43·8%) | 0·17 | 39,061 (50·1%) |
| Charlson score | 1 (0, 2) | 1 (0, 2) | 0·01 | 1 (1, 3) | 0·16 | **2 (1, 3)** | **0·20** | 1 (0, 2) | 0·04 | 1 (0, 2) |
| Elixhauser score | 2 (1, 4) | 2 (1, 4) | 0·01 | **3 (2, 4)** | **0·20** | **3 (2, 4)** | **0·22** | 2 (1, 4) | 0·04 | 2 (1, 4) |
| Community-onset | 28,184 (78·1%) | **4,010 (88·5%)** | **0·28** | **7,162 (67·1%)** | **0·25** | 521 (70·1%) | 0·18 | **22,189 (85·6%)** | **0·20** | 62,066 (79·6%) |
| Immunosuppression | 4,909 (13·6%) | 533 (11·8%) | 0·06 | 2,222 (20·8%) | 0·19 | **164 (22·1%)** | **0·22** | 3,797 (14·6%) | 0·03 | 11,625 (14·9%) |
| Diabetes mellitus | 7,225 (20·0%) | 921 (20·3%) | 0·01 | 2,335 (21·9%) | 0·05 | 158 (21·3%) | 0·03 | 4,862 (18·8%) | 0·03 | 15,501 (19·9%) |
| Palliative care | 1,995 (5·5%) | 200 (4·4%) | 0·05 | **1,332 (12·5%)** | **0·24** | 79 (10·6%) | 0·19 | 892 (3·4%) | 0·10 | 4,498 (5·8%) |
| Pathogen(s) cultured | 3,503 (9.7%) | 734 (16.2%) | 0.19 | 1,641 | 0.17 | 36 (4.8%) | 0.19 | **650 (2.5%)** | **0.30** | 6,564 (8.4%) |
| >1 blood cultures in episode | 9,386 (26·0%) | **1,792 (39·6%)** | **0·29** | **6,096 (57·2%)** | **0·67** | **495 (66·6%)** | **0·89** | 4,688 (18·1%) | 0·19 | 22,457 (28·8%) |
| >1 positive blood cultures in episode | 706 (2·0%) | 136 (3·0%) | 0·07 | **663 (6·2%)** | **0·22** | 27 (3·6%) | 0·10 | 191 (0·7%) | 0·11 | 1,723 (2·2%) |
| Baseline antimicrobial susceptibility | | | **0·20** | | **0·20** | | **0·30** | | **0·32** | |
| Culture-negative | 30,916 (85.7%) | 3,550 (78.4%) | | 8,352 (78.3%) | | 642 (86.4%) | | 24,004 (92.6%) | | 67,464 (86.5%) |
| Potential contaminant(s) | 1,672 (4.6%) | 245 (5.4%) | | 673 (6.3%) | | 65 (8.7%) | | 1,274 (4.9%) | | 3,929 (5.0%) |
| Susceptible | 2,795 (7.7%) | 606 (13.4%) | | 1,220 (11.4%) | | 17 (2.3%) | | 379 (1.5%) | | 5,017 (6.4%) |
| Resistant | 447 (1.2%) | 82 (1.8%) | | 235 (2.2%) | | 8 (1.1%) | | 112 (0.4%) | | 884 (1.1%) |
| No antimicrobial recorded | 176 (0.5%) | 28 (0.6%) | | 147 (1.4%) | | 6 (0.8%) | | 108 (0.4%) | | 465 (0.6%) |
| Unknown | 85 (0.2%) | 18 (0.4%) | | 39 (0.4%) | | 5 (0.7%) | | 51 (0.2%) | | 198 (0.3%) |

[1]Median (IQR); n (%); [2]Standardised Mean Difference

Note: Peak on Day 1 was used as the reference group. The unadjusted effect size was estimated using standardised mean difference (SMD), considering 0.2, 0.5, and 0.8 as small, medium, and large, respectively (SMD>0.2 bolded and >0.5 also underlined for emphasis) [135].

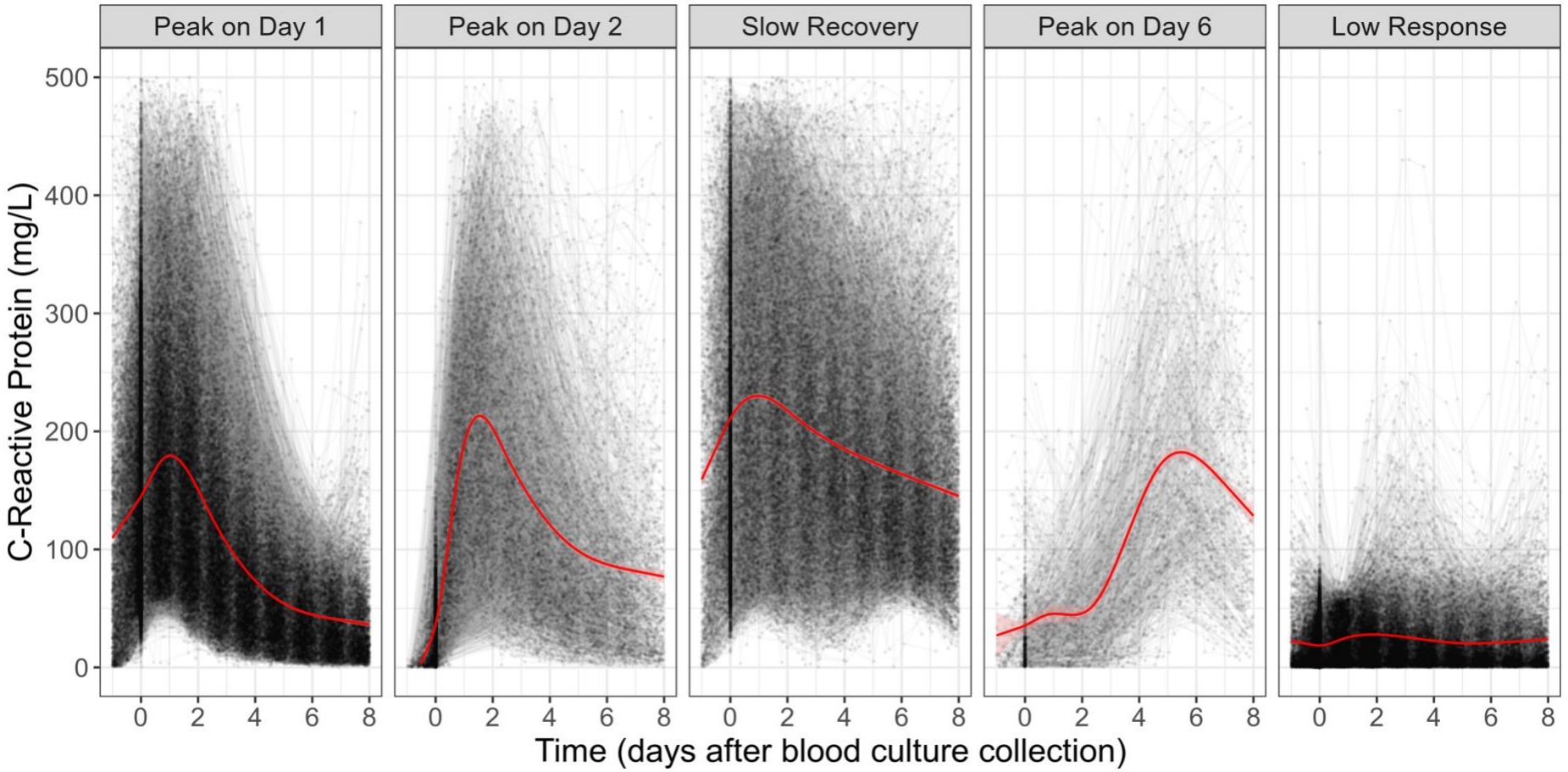


**Figure 4.2 Spaghetti plot illustrating raw data underpinning latent classes of CRP response trajectories.**
Black lines represent individual CRP response trajectories for suspected BSI episodes, while red lines show the mean response trajectory for each latent trajectory class.

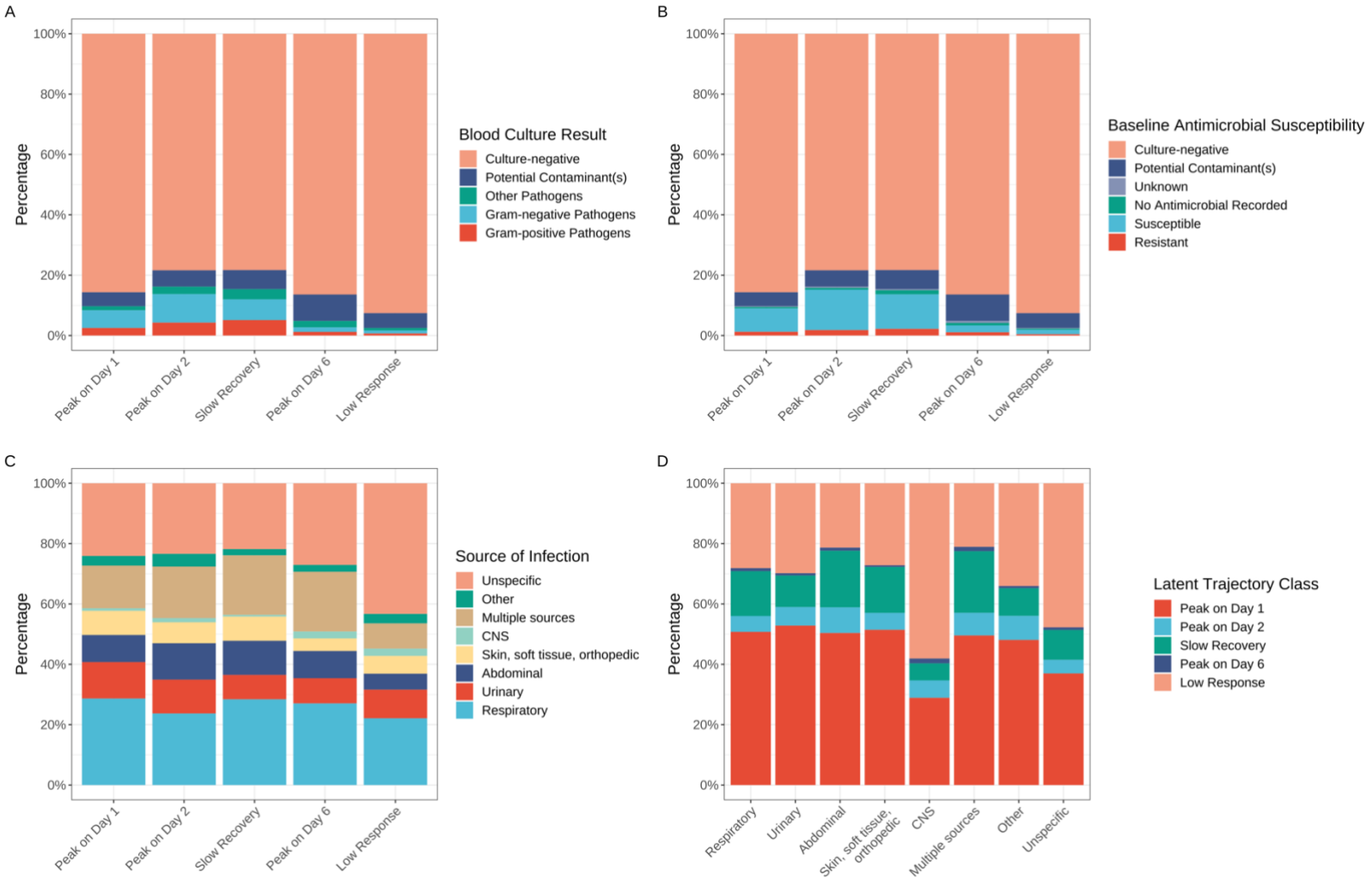


**Figure 4.3 Univariable associations between latent CRP trajectory classes and blood culture results (A), baseline antimicrobial susceptibility (B) and sources of infection (C, D).**

In subgroups with peaks on day 1 or 2 (total 52.1% of the study population), CRP levels initially rose dramatically, then dropped and stabilised by day 8 (**Figure** 4.1**A**). The subgroup peaking on day 2, however, had lower starting levels, potentially due to enrichment with community-onset infections (88.5% vs. 78.1%, SMD=0.28, **Table** 4.3). More of those peaking on day 2 also had >1 blood culture taken in their episode (39.6% vs. 26.0%, SMD=0.29), and more had pathogens cultured (16.2% vs. 9.7%, SMD=0.19) (**Table** 4.3, **Figure** 4.3**A**). The slow recovery subgroup (13.7% of the study population) had the highest peak yet recovered the slowest. Compared with those peaking on day 1, this subgroup were slightly older (median 70.3 vs. 69.2 years, SMD=0.13), had more comorbidities, immunosuppression (20.8% vs. 13.6%, SMD=0.19), nosocomial infections (32.9% vs. 21.9%, SMD=0.25), >1 positive blood cultures in the episode (6.2% vs. 2.0%, SMD=0.22) and more resistance to baseline antimicrobials (2.0% vs. 1.2%, SMD=0.2, **Table** 4.3). The very small subgroup that peaked at ~6 days (1.0% of the study population) had a similar profile to the slow recovery subgroup, with even more comorbidities and episodes with >1 blood culture (66.6% vs. 26.0% in those peaking on day 1, SMD=0.89, **Table** 4.3). Mean CRP in the low response subgroup (33.3% of the study population) remained <20mg/L throughout; this subgroup comprised younger patients (median 63.6 vs. 69.2 years, SMD=0.19) and had fewer repeat blood cultures (18.1% with >1 blood culture vs. 26.0% in those peaking on day 1, SMD=0.19), and fewer pathogens cultured (2.5% vs. 9.7%, SMD= 0.30) (**Table** 4.3). Additionally, there were more community-onset infections (85.6% vs. 78.1%, SMD=0.20) and more unspecific sources of infection (**Figure** 4.3**C**) in this group, which was over-represented in those with CNS infections (**Figure** 4.3**D**).

The 30-day all-cause mortality was 11.7%, occurring in 8,386/ 71,402 suspected BSI episodes, after excluding 6,555 episodes without baseline NEWS from a total of 77,957 episodes. After adjusting for potential confounders, compared with the day-1 peak subgroup, 30-day all-cause mortality was significantly higher in the slow recovery subgroup (OR=2.15 [95%CI 2.00,2.31], p<0.001) and the day 6 peak subgroup (OR=1.98 [1.56,2.50], p<0.001) (**Table** 4.4). Additionally, mortality was significantly lower in the low (CRP) response subgroup (OR=0.77 [0.71,0.83], p<0.001) and slightly lower in those peaking on day 2 (OR=0.84 [0.74,0.96], p=0.011).

**Table 4.4 Factors independently associated with 30-day all-cause mortality.**

| Characteristic | OR[1] | 95% CI[1] | p-value |
|---|---|---|---|
| Latent CRP trajectory class | | | |
| Peak on Day 1 | — | — | |
| Peak on Day 2 | 0.84 | 0.74, 0.96 | **0.011** |
| Slow Recovery | 2.15 | 2.00, 2.31 | **<0.001** |
| Peak on Day 6 | 1.98 | 1.56, 2.50 | **<0.001** |
| Low Response | 0.77 | 0.71, 0.83 | **<0.001** |
| Age at admission (10 years) | 1.57 | 1.53, 1.60 | **<0.001** |
| Sex (male vs female) | 1.09 | 1.03, 1.16 | **0.003** |
| Charlson score | 1.06 | 1.03, 1.09 | **<0.001** |
| Elixhauser score | 1.09 | 1.07, 1.11 | **<0.001** |
| NEWS score (baseline) | 1.22 | 1.21, 1.23 | **<0.001** |
| Immunosuppression | 1.61 | 1.49, 1.74 | **<0.001** |
| Palliative care | 11.2 | 10.4, 12.2 | **<0.001** |
| Community-onset | 0.79 | 0.74, 0.85 | **<0.001** |
| Blood culture result | | | |
| *E. coli* | — | — | |
| *Klebsiella* sp. | 1.24 | 0.89, 1.72 | 0.20 |
| Other *Enterobacterales* | 1.28 | 0.87, 1.86 | 0.19 |
| *Pseudomonas aeruginosa* | 1.41 | 0.95, 2.07 | 0.080 |
| *Enterobacter* sp. | 1.27 | 0.65, 2.35 | 0.47 |
| *Staphylococcus aureus* | 1.67 | 1.24, 2.22 | **<0.001** |
| Beta-Hemolytic Streptococci | 1.02 | 0.68, 1.50 | 0.94 |
| *Enterococcus* sp. | 1.41 | 0.96, 2.05 | 0.077 |
| *Streptococcus pneumoniae* | 0.77 | 0.49, 1.18 | 0.25 |
| Other Pathogenic *Streptococcus* | 0.90 | 0.44, 1.73 | 0.76 |
| Other pathogen | 1.71 | 1.21, 2.38 | **0.002** |
| Polymicrobial | 1.77 | 1.21, 2.56 | **0.003** |
| Anaerobes | 1.77 | 1.14, 2.70 | **0.010** |
| *Candida* sp. | 2.58 | 1.29, 4.91 | **0.005** |
| Culture-negative | 1.11 | 0.95, 1.29 | 0.19 |
| CoNS (contaminant) | 1.37 | 1.13, 1.67 | **0.002** |
| Other Suspected Contaminants | 1.10 | 0.70, 1.67 | 0.67 |
| Viridans and Other *Streptococcus* | 1.04 | 0.63, 1.65 | 0.89 |
| Source of infection | | | |
| Urinary | — | — | |
| Unspecific | 1.64 | 1.46, 1.85 | **<0.001** |
| Respiratory | 1.80 | 1.61, 2.02 | **<0.001** |
| Multiple sources | 1.51 | 1.34, 1.71 | **<0.001** |
| Abdominal | 1.46 | 1.26, 1.69 | **<0.001** |
| Skin, soft tissue, orthopaedic | 0.84 | 0.70, 1.01 | 0.070 |
| CNS | 2.73 | 1.96, 3.72 | **<0.001** |
| Other | 1.14 | 0.85, 1.51 | 0.37 |

[1]OR = Odds Ratio (multivariable), CI = Confidence Interval

Note: Baseline NEWS score was calculated using the closest set of vital signs within 1 day before to 1 day after the start of each episode.

Estimated response trajectories for heart rate, respiratory rate, temperature and WBC count fitted within each latent CRP trajectory class showed similar response patterns in terms of early/delayed/low response (**Figure** 4.4). For all groups, vital signs such as heart rate, respiratory rate, and temperature appeared to change more rapidly and show more immediate responses compared to CRP levels, which often have a delayed peak. Specifically, the low CRP response group still exhibited elevated baseline values for heart rate, respiratory rate, and temperature, which contrasts with their consistently low WBC counts throughout the observation period.

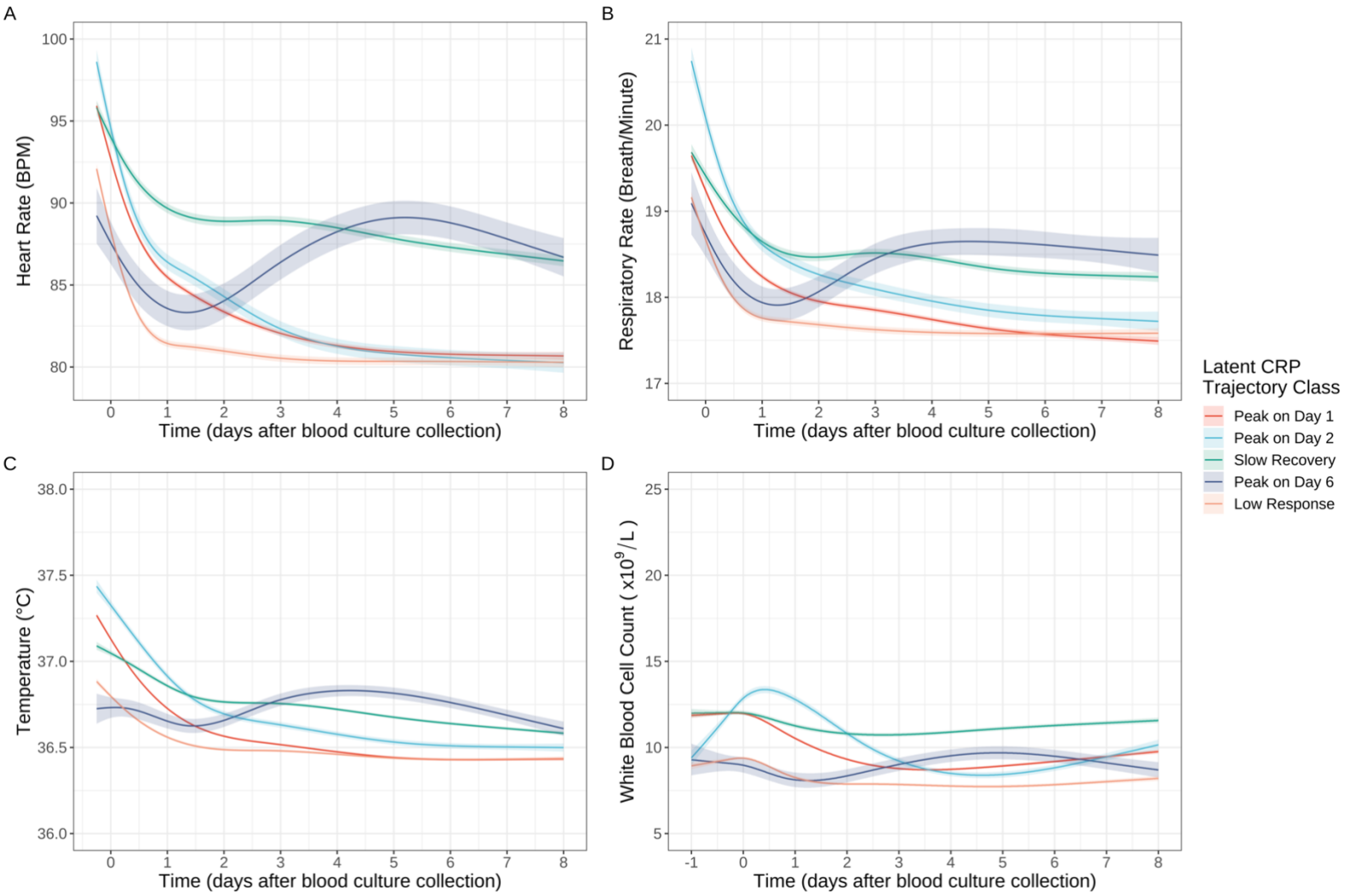


**Figure 4.4 Response trajectories for heart rate (A), respiratory rate (B), temperature (C) and WBC count (D), estimated separately within each latent CRP trajectory class.**

### 4.3.2 Expected CRP response

I included the 40,620 episodes in the subgroups with CRP peaking on day 1 or day 2, i.e., the response that would be clinically expected to an infectious insult followed by an uncomplicated recovery, in order to estimate the "normal" response to suspected BSI treated with effective antimicrobials (either empirically or through prompt switching), and expected underlying variation, regardless of whether a pathogen was identified. Estimated centile charts based on 100,000 bootstrap samples show 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles of a normal CRP response to suspected BSI, whether subsequently found to be culture-positive or not (**Figure** 4.5**A**). Estimates were similar to randomly sampling one measurement per patient, suggesting limited potential bias from multiple measurements per episode (**Figure** 4.6). Overall, median CRP peaked at ~165mg/L on day 1 (24h after blood culture collection), then decreased gradually to ~25mg/L by day 8. This chart clearly illustrates the challenges on relying on absolute CRP value to determine response or even change in CRP (**Figure** 4.5**B**), given individual-level heterogeneity. For example, a value of 150mg/L would be expected (50th percentile) 12h after blood culture collection for an average responder, but would still represent a standard (i.e. good) response at 2.7 days for a patient whose initial CRP was higher (75th percentile) and would still represent a standard response even later, at 3.7 and 4.2 days, for even higher initial CRP (90th and 95th percentile respectively). Expected CRP response centiles (10th, 50th, 90th) estimated separately for different infection sources showed little difference to the overall centiles (**Figure** 4.7).

Centile reference charts for heart rate, respiratory rate, temperature, and WBC count were constructed based on the same episodes from the two latent CRP trajectory classes peaking on days 1 and 2 (**Figure** 4.8).

To assess the extent to which individual patients' CRP trajectories follow the population-level centile charts within a BSI episode, I calculated the distribution of centile changes between consecutive days for all episodes with available CRP measurements, but excluding those from low CRP response group (**Figure** 4.9). Focusing on the recovery stage from day 2 onwards, I found that 90–96% of episodes had centile changes ≤25 between consecutive days, 84-93% episodes had centile changes ≤20 between consecutive days and 65-79% episodes had centile changes ≤10 between consecutive days. This finding suggests that most patients' response trajectories track along the centile curves, supporting using these charts to monitor individual patient progress and identify deviations from the expected recovery pattern.

To illustrate the application of the developed centile reference chart in a practical context, I plotted an individual's CRP values on the chart of expected CRP response against the patient's daily antibiotic usage (**Figure** 4.10). Subsequent microbiological test results confirmed the presence of extended-spectrum beta-lactamase-producing *E. coli*, resistant to penicillins and cephalosporins administered during the initial two days post blood culture collection. A switch to ertapenem on the third day resulted in a return to the patient's baseline CRP centile.

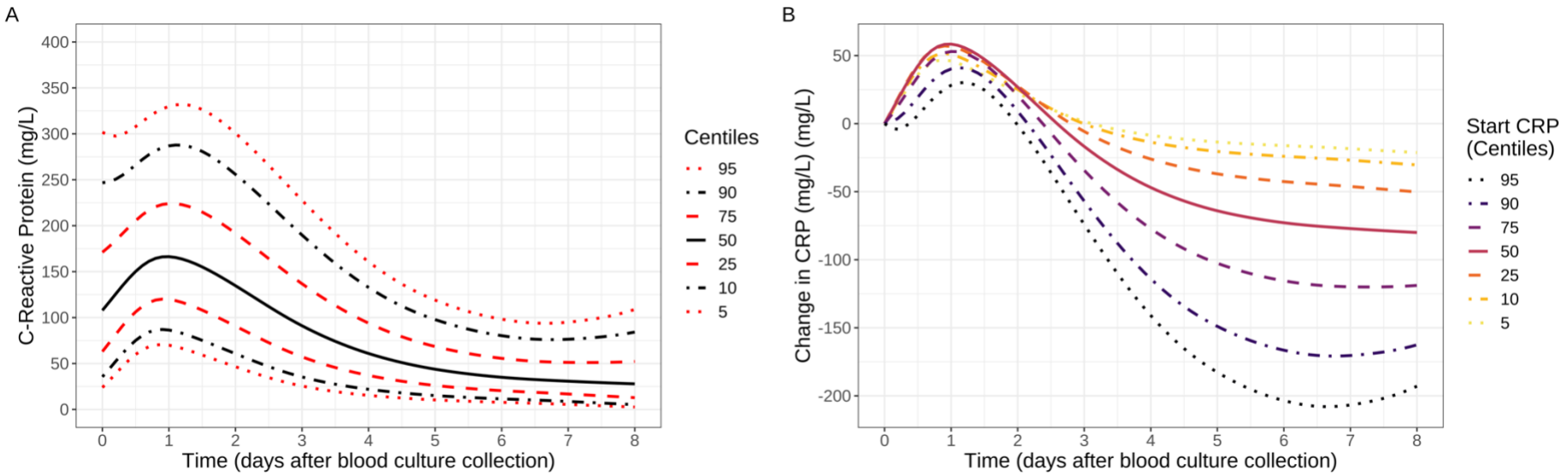


**Figure 4.5 Centile reference chart of expected CRP response in patients with culture-positive/negative suspected BSI responding standardly to antimicrobials (A) and change in CRP from initial value in centile (B).**

Change in CRP was calculated by subtracting the CRP value at time 0 (blood culture collection) from the estimated centiles in panel (A). Note: estimated from the two latent classes peaking on days 1 and 2 in **Figure** 4.1, regardless of the pathogen isolated.

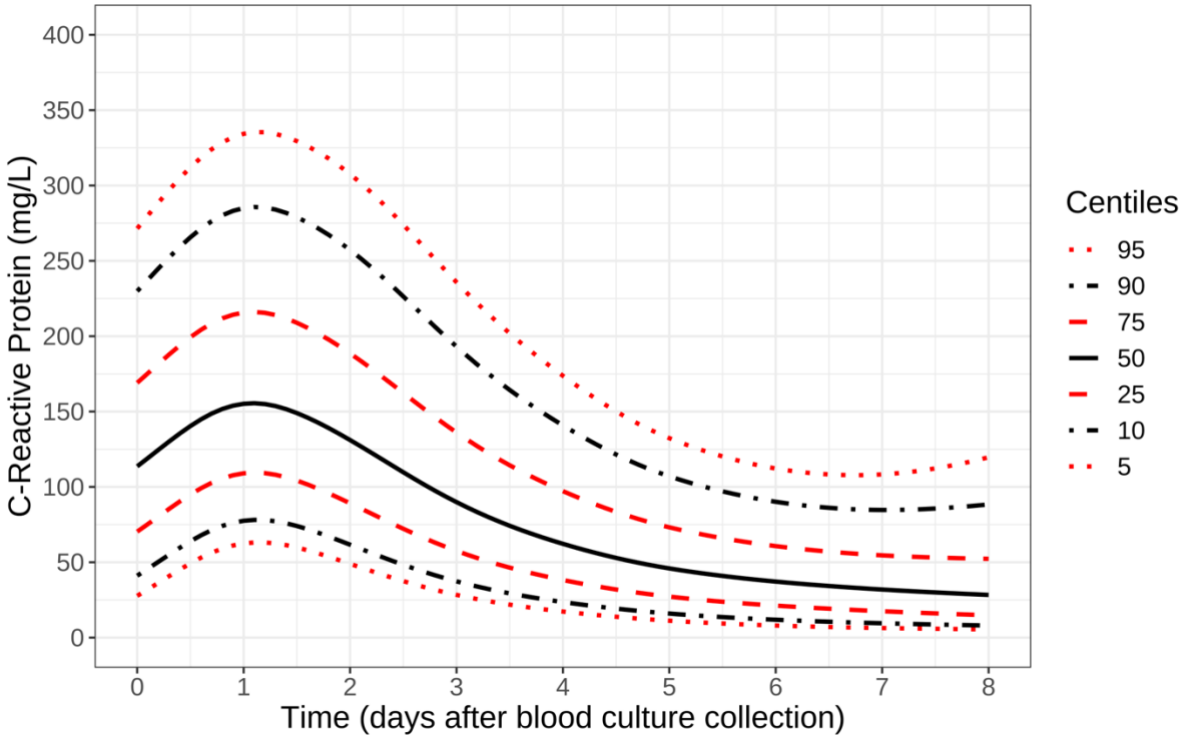


**Figure 4.6 Centile reference chart estimated by selecting one random observation for each episode from those peaking on days 1 and 2, regardless of the pathogen isolated.**

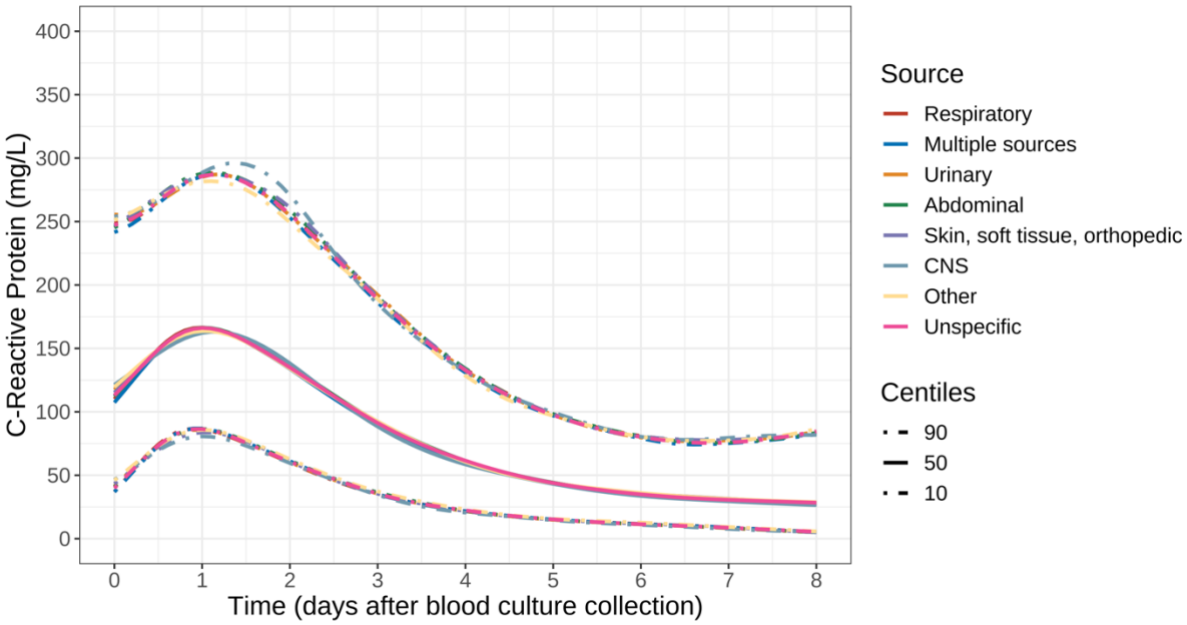


**Figure 4.7 10th, 50th and 90th centiles of expected CRP response in patients with culture-positive/negative suspected BSI following different sources of infection.**

Note: from the two latent classes peaking on days 1 and 2, centiles for different sources of infection were estimated separately based on relevant episode subgroups, regardless of pathogen isolated

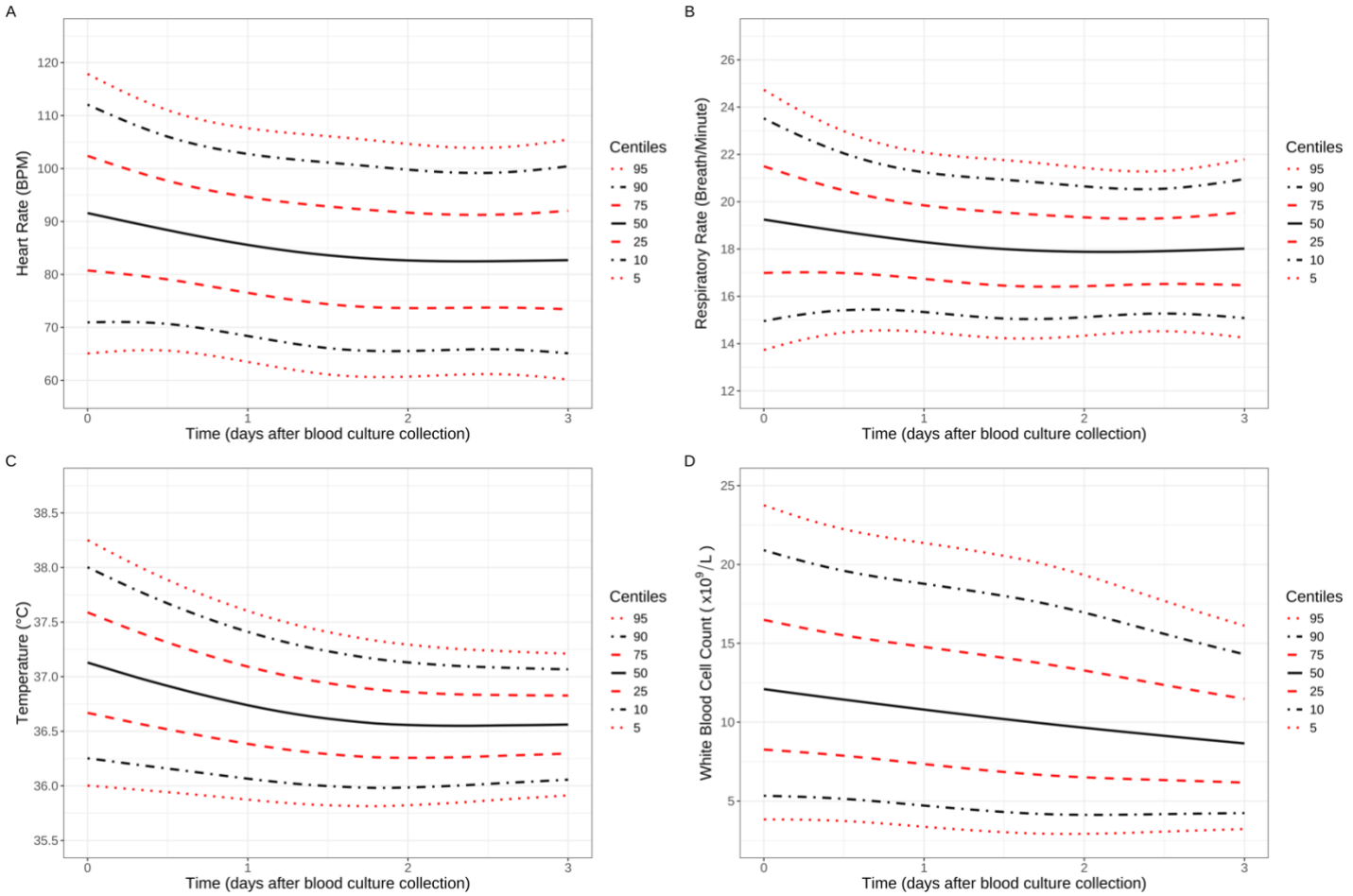


**Figure 4.8 Centile reference chart of expected responses for temperature, heart rate, respiratory rate and WBC count.**

Note: The same episodes from the two latent CRP trajectory classes peaking on day 1 and 2 (**Figure** 4.1) were used to estimate centile reference chart for heart rate, respiratory rate, temperature and WBC count.

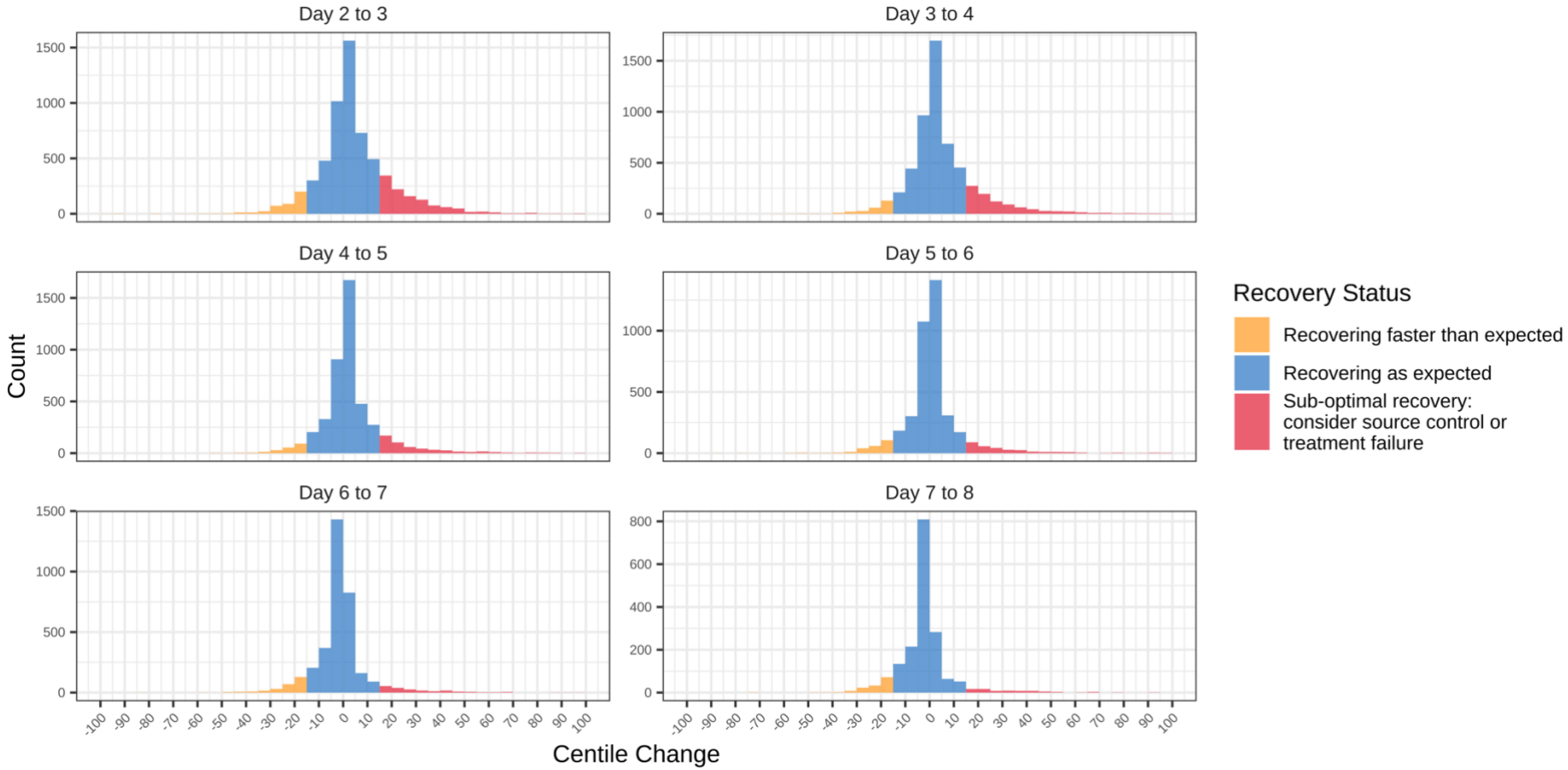


**Figure 4.9 Distribution of CRP centile changes between CRP measurements on two consecutive days.**
Centile changes < -15, -15–15 and >15 were considered as recovering faster than expected (orange), recovering as expected (blue) and sub-optimal recovery (red), respectively. Calculations were based on 13,011episodes (6,196 Peak on Day 1, 1,269 Peak on Day 2, 5,099 Slow Recovery, 447 Peak on Day 6 and excluding Low Response) that had CRP measurements on two consecutive days (25,645 pairs of CRP measurements) and focused on the recovery stage, starting from day 2 onwards, to allow for initial measurements to be influenced by time since presentation.

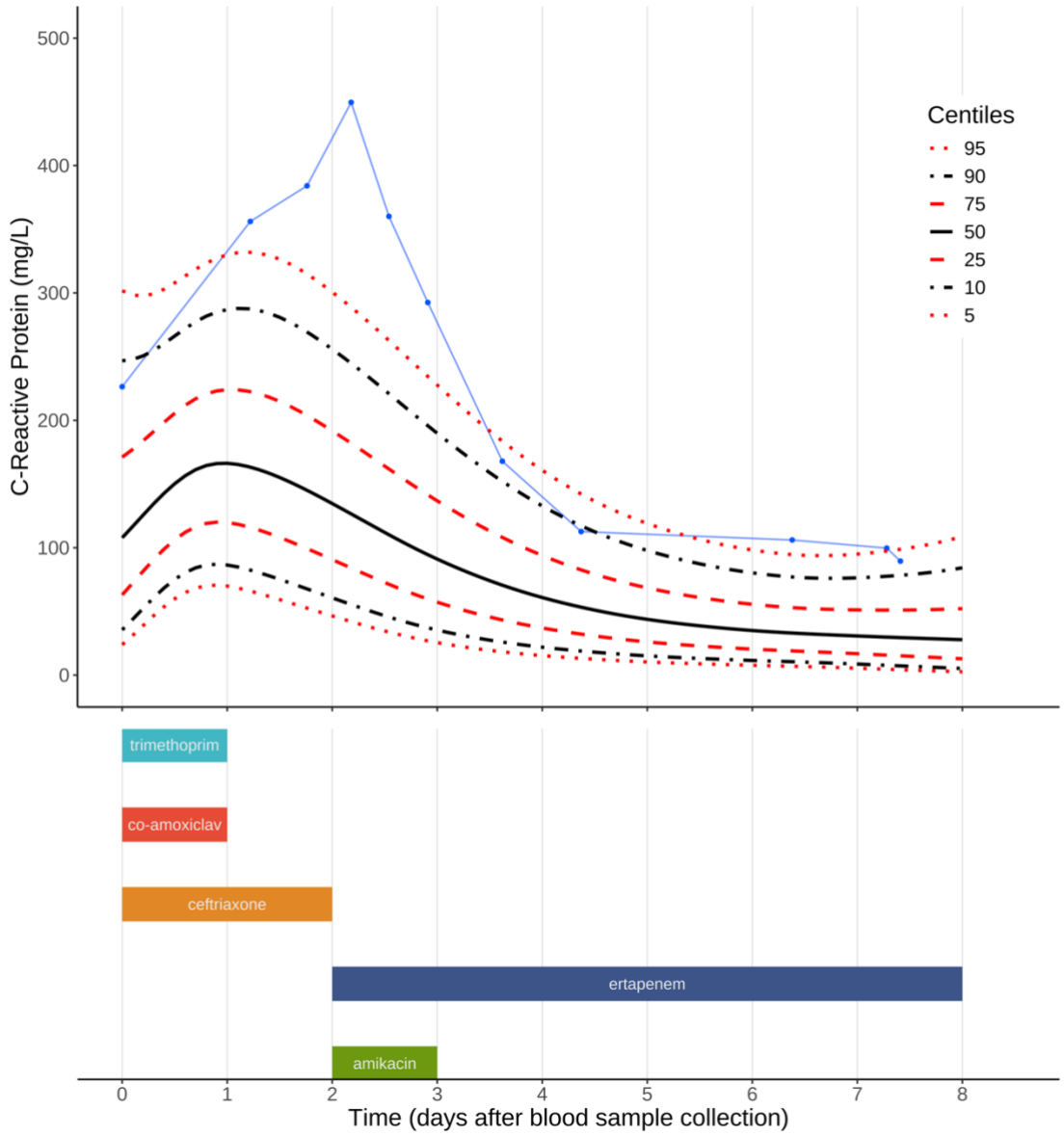


**Figure 4.10 Example of an individual patient's CRP response trajectory on the centile reference chart of expected CRP response against daily antibiotic use.**
Note: The blue line represents a patient infected with extended-spectrum beta-lactamase-producing *E. coli*.

## 4.4 Discussion

Five distinct patterns of CRP response trajectories were identified using latent class models, characterised by early peaks (day 1 or 2) followed by typical recovery (standard acute response), early peak followed by slow recovery, a delayed peak (day 6), or persistently low levels. Estimated response trajectories for heart rate, respiratory rate, temperature and WBC count within each predicted latent CRP trajectory class showed consistent response patterns, but vital signs appeared to change more rapidly and peak earlier than CRP. Notably, nearly 65% of culture-positive episodes with a pathogen, but also around half of culture-negative episodes, were associated with standard acute ("normal") responses. Centile reference charts were created based on these "normal" CRP responders to help standardise assessment of infection progression and treatment response in patients with suspected BSI; these could be used to guide management independent of microbiological test results.

The "normal" response demonstrated by the subgroups displaying peak CRP levels on either day 1 or day 2, accounting for 52.1% of all suspected infection episodes, also represent appropriate antimicrobial treatment in those with bacterial infection. The day-2 peak subgroup may represent either a slightly delayed response or detection of suspected BSI earlier in the illness, the latter consistent with a greater percentage of this subgroup being community-acquired infections. The slow recovery subgroup was characterised by stronger initial and more persistently elevated CRP. Like the small subgroup with a delayed peak on day 6, this group comprised more older patients with more comorbidities. It included a greater percentage of immunosuppressed patients and those on palliative care, and demonstrated higher 30-day all-cause mortality rates

compared with those peaking on day 1. The slow recovery subgroup also had more repeated positive blood cultures, suggesting a proportion could have persistent infection due to either lack of source control or treatment failure. A modestly higher proportion of episodes with inactive initial antimicrobial therapy in this subgroup may suggest that antimicrobial resistance could be a contributing factor to persistent infection in some cases. However, my study does not provide definitive evidence to differentiate between source control failure and treatment failure, as the underlying reasons for persistent infection were not systematically recorded. The subgroup with limited CRP response included younger patients with more negative blood cultures, with mean estimates likely reduced by the absence of bacterial infection or a systemic response in a substantial subset. Consistent with this, this subgroup was over-represented in those with CNS infections.

Whilst host response characteristics and clinical outcomes have previously been used to sub-phenotype patients with suspected BSI or sepsis, CRP response trajectories have not been described in this detail to my knowledge. Several studies defined 3 to 4 CRP ratio response patterns based on changes in follow-up CRP relative to baseline CRP values at specific timepoints, rather than across the entire response trajectory [120,122,123,126]. Specifically, Póvoa et al. identified four patterns of CRP ratio response in 44 ICU patients with confirmed BSI, namely fast response (CRP ratio at D4 was <0.4 relative to D0 CRP), slow response (a continuous and slow decrease in CRP ratio), non-response (CRP ratio remained ≥0.8), and biphasic response (an initial CRP ratio decrease to levels of <0.8, followed by a secondary rise to values of ≥0.8), with implications for patient outcomes [120,187]. Similarly, Moreno et al. examined CRP

trajectories in 64 ICU patients with nosocomial pneumonia, categorising responses into good and poor based on a CRP ratio threshold of 0.67 at day 10 [122]. These two groups were associated with mortality and the adequacy of antibiotic therapy. In 891 ICU patients with community-acquired sepsis (with confirmed pathogen or clinically suspected infection with antimicrobial therapy), Póvoa et al. established that patterns of CRP-ratio response could be classified into fast, slow, and non-response categories by day 5, with corresponding mortality rates of 23%, 30%, and 41%, respectively [123]. Relatively consistent response patterns were observed in serially measured body temperatures and SOFA scores, but not in WBC. Additionally, another study by Póvoa et al. evaluated CRP and albumin kinetics in 935 patients with community-acquired BSI (BSI occurring <3 days after hospital admission and without inpatient contact in the preceding 7 days), identifying patterns of CRP-ratio responses similar to their previous studies [126]. They again classified patients into fast response, slow response, non-response, and biphasic response categories, with mortality significantly higher in the non-response and biphasic response groups. Specifically, patients with non-response or biphasic response patterns had a 2.74 and 5.29 increased risk, respectively, of death within 30 days compared with fast responders.

My five response subgroups identified using CRP response trajectories map closely to these previously established categories and display consistent response patterns in heart rate, respiratory rate, body temperature, and white blood cell counts. The subgroups with peaks on day 1 or day 2 mirror the fast response patterns described above, likely representing patients with a robust initial immune response to infection, and with better outcomes due to effective early treatment, as discussed earlier. The

slow recovery subgroup in my study, where CRP levels gradually decrease over time, corresponds to the slow response and potentially the non-response patterns noted in earlier studies. The non-response patterns in previous research were identified by comparing CRP levels on days 4/5 to those on day 1, effectively comparing CRP levels during the recovery stage with their peak values. Minimal differences in CRP levels between these time points defined non-response, which appeared to be a mixture of the slow recovery group and the low response group identified in my study. However, it is likely that there were fewer low responders in the earlier studies due to their stricter definitions of BSI. Also, the slow recovery group in my study had a significantly higher 30-day all-cause mortality, which aligns with the poorer outcomes associated with the slow response and the non-response patterns noted by Póvoa et al. Additionally, the group with the late peak on day 6 in my study potentially aligns with the biphasic response group identified by Póvoa et al. Both groups exhibited elevated CRP levels at a later stage and significantly higher 30-day all-cause mortality.

Others have applied group-based trajectory models to longitudinal vital signs, WBC, or SOFA score [59,60,138–142,179]. Broadly mirroring my observations, three studies identified four temperature trajectory groups using measurements within the first 72h: "hyperthermic, slow resolvers", "hyperthermic, fast resolvers", "normothermic", and "hypothermic" [138,139,178]. In my study, subgroups with CRP peaking on day 1 or 2 had temperature responses corresponding to the "hyperthermic, fast resolvers"; the late CRP response subgroup likely corresponded to the "hypothermic" group, both comprising older patients with more comorbidities. However, although the slow recovery CRP subgroup in my study had a similar temperature trajectory to the

"hyperthermic, slow resolvers", my subgroup consisted mainly of relatively old rather than young patients as found in previous studies. WBC response trajectories estimated by the predicted latent CRP subgroups were also broadly consistent with a previous study identifying seven WBC trajectories from 917 ICU patients [141].

Despite the heterogeneity in CRP responses by pathogens and clinical syndromes, for a given initial CRP value, responses were relatively consistent, meaning they could be summarised using a single centile reference chart. This heterogeneity in CRP response trajectories according to initial values illustrates the limitations of a "one-size-fits-all" approach to using absolute CRP values, or even change in CRP, to determine escalation, de-escalation or duration of antimicrobial therapy in patients with suspected BSI. This is because my findings show that absolute value/change means something different depending on initial CRP values; the centile chart provides a potentially useful alternative. Spotting unexpected deterioration and biomarker-guided antibiotic stewardship are key potential applications [56,167]. Although some previous biomarker-guided stewardship interventions reduced antibiotic prescription and duration while demonstrating non-inferior or lower mortality (**Table** 4.1), compliance remained suboptimal [161,162,164,169]. The centile reference chart potentially provides a more visually intuitive means of assessing response, potentially aiding clinical decisions by incorporating individual-level observations alongside evidence-based references for expected recovery in patients treated with effective treatment. Its implementation could be supported by embedding it within EHR systems.

The strengths of this study include the large sample size (77,957 suspected BSI episodes, of which 40,620 episodes showed "normal" responses) and longer follow-up for CRP (8 days) compared to previous studies, and inclusion of comprehensive clinical data over several years. However, the limitations previously noted in Chapter 3 regarding the use of EHR data to estimate changes in clinical parameters apply equally to the methodology employed in this Chapter. That is, measurements of CRP and other laboratory markers are less frequently performed consecutively in patients who are recovering well. As a result, data obtained at subsequent time points may disproportionately represent elevated values. This may lead to centile reference charts with overestimated values at later timepoints, whereas the true reference response may decline more rapidly and completely than my estimates. Mitigating this entirely would require sampling irrespective of clinical progress and post-discharge, unlikely feasible at scale. Nevertheless, one could also argue that the charts likely show centiles of response in those still having CRP measured at day 5-8, and may therefore be more useful for those remaining in the hospital and still having values measured than including the population who already well enough to have been discharged home.

Similarly, due to the lack of data on the timing of blood culture collection relative to the onset of symptoms in EHR, biomarker trajectories were estimated relative to the first blood culture collection. This may differ from onset of symptoms, potentially explaining the two "normal" response subgroups with CRP peaking on day 1 or 2. However, the relationship between the onset of symptoms and the initial inflammatory insult is also unknown, and symptom onset may be subjectively reported. Future studies could aim to collect more detailed information on symptom onset and duration to better

characterise the temporal dynamics of host response in suspected BSI. Additionally, the use of alternative statistical methods, such as alignment algorithms or time-warping techniques [188], could be explored to account for variations in the timing of clinical measurements relative to disease onset.

It is also possible that some patients within the "normal" response group had elevated CRP measurements for other reasons in the absence of infections, including trauma, recent surgery, and inflammatory conditions such as pancreatitis; although these are likely to account for a minority of episodes. It is also an intriguing possibility that similar CRP centile charts could be used to determine normal post-operative recovery patterns, with deviations potentially indicative of surgical site infection. The low CRP response class had elevated baseline heart rate, respiratory rate, and temperature, despite maintaining a low WBC count throughout the observation period, potentially caused by viral infections. Viral infections are known to elicit varied immune responses, often characterised by less pronounced elevations in CRP levels but significant alterations in vital signs [189]. This aligns with the observed elevated baseline heart rate, respiratory rate, and temperature in the low CRP group. However, the current analysis did not stratify patients based on the presence or absence of viral infections. Future studies should aim to differentiate the low CRP response group into subcategories based on viral infection status to determine if the vitals differ significantly between those with and without viral infections.

I used multivariable logistic regression to compare 30-day all-cause mortality between different latent classes, instead of using survival analysis, which is preferable for time-

to-event data. While survival analysis would enable the appropriate handling of censored data and avoid making assumptions about individuals lost to follow-up, I opted for logistic regression for simplicity, given the minimal proportion of individuals without information 30 days after index blood culture collection (2.1% [1,494/71,402]). The small proportion of incomplete follow-ups suggests that this choice is unlikely to have significantly impacted our findings.

Furthermore, my analysis showed that the derived response trajectories for key indicators such as heart rate, respiratory rate, temperature, and WBC count demonstrated consistent response patterns when estimated according to the predicted latent CRP trajectory class. Notably, vital signs appeared to change more rapidly and show more immediate responses without a delayed peak as seen in CRP, suggesting that these metrics might be more effective markers for early antibiotic decision-making. However, due to time constraints and the size of the vital sign measurement dataset, I did not conduct latent class analysis to discern their response patterns because of the substantial computational demands this would have necessitated. Future work should focus on repeating the analysis for each vital sign to provide a more detailed understanding of their response patterns.

## 4.5 Conclusions

In summary, distinct CRP response patterns were found in patients with suspected BSI, reflecting normal, slow, and delayed or limited responses. Considering the dynamic nature of BSI and sepsis and heterogeneity in individual CRP response trajectories, the centile reference charts developed here may provide a valuable tool for guiding

individualised infection management. Building on these findings, Chapter 5 further explores associations between CRP levels/centiles and changes in antimicrobial therapy, both to assess if there is evidence that sub-optimal CRP responses lead to changes in antimicrobials and if switching from inactive to active therapy changes CRP trajectories. Future research could also aim to evaluate the practical application of centile reference charts in clinical settings.

# Chapter 5 Antibiotic prescribing patterns for suspected bloodstream infections and their association with clinical response

## 5.1 Introduction

BSI remain a critical challenge in clinical practice due to their high morbidity and mortality rates [190]. Effective management often necessitates the prompt initiation of empirical antibiotic therapy before definitive microbiological diagnoses are available [4]; further, no pathogen is ever cultured in the majority (see **Chapter 3**). While essential, this approach carries inherent risks, including the possible lack of efficacy of inappropriate narrow-spectrum coverage or the potential for fostering antimicrobial resistance through the overuse of broad-spectrum antibiotics [15]. Given these concerns, optimising antibiotic prescribing practices is of paramount importance.

A crucial aspect of BSI management involves the timely adjustment of antibiotic therapy based on patient-specific indicators. Empirically, broad-spectrum antibiotics are often employed due to the high consequences of under-treatment in the early stages of suspected infection [191]. However, this practice must be balanced with the need to de-escalate to narrower-spectrum agents as soon as pathogen-specific susceptibilities are identified or clinical markers suggest a favourable response [15,160,192,193]. Strategic de-escalation not only mitigates resistance development

but also minimises unwanted side effects, supporting the overall goals of antibiotic stewardship [193,194].

Recent advancements in biomarker research, particularly CRP, have shown promise in guiding more tailored treatment strategies in infections, thus reducing the reliance on broad-spectrum empiricism [56,195]. As discussed in **Chapter 4**, previous studies have demonstrated the utility of repeated CRP measurements in assessing disease progression and response to therapy [120,124,121–123]. Specifically, changes in CRP levels at specific timepoints can provide actionable insights into whether patients are responding adequately to treatment or modifications are required [121,124]. This assessment typically involves considering the percentage drop from the observed peak [169,176], whether absolute levels fall below a specified threshold [176], or the ratio of CRP measurements on days 4 or 5 relative to baseline levels [120,123,126].

Considering the dynamics of CRP centile changes provide an opportunity to further refine antibiotic therapy. Studies have demonstrated that decreasing CRP levels generally indicate effective control of infection, while non-decreasing or increasing levels may signal treatment failure or complications [120,121,124]. Thus, linking CRP trajectories with antibiotic prescribing decisions may enhance the precision of infection management.

My previous work established centile reference charts for CRP and vital signs trajectories during suspected BSI episodes, providing clinicians with a potentially valuable tool to monitor patients' recovery, taking into account heterogeneity in these

parameters at initial presentation, arising from multiple sources but potentially confounding responses [116]. Building on this foundational research, the current chapter investigates antibiotic prescribing patterns in suspected BSI and examines their association with CRP dynamics. I aim to elucidate whether, and how changes in CRP percentiles influence prescribing behaviours and evaluate the impact of antibiotic adjustments on subsequent CRP centile shifts.

## 5.2 Methods

### 5.2.1 Study population

The same de-identified data from IORD was used as in **Chapter 3** (see details in section **3.2.1**). Patients ≥16y with ≥1 blood culture taken during an inpatient admission, and with at least one CRP measurement during the suspected infection episode were included. See section **3.2.1** for definitions of new suspected infection episodes and index blood cultures. I included suspected BSI episodes occurring in adults (≥16 years old) with CRP measurements and antibiotic administrations. Episodes were excluded from this current analysis if patients were admitted to the ICU (where antimicrobial prescriptions were unknown because these were recorded on different systems), had fungi detected in blood cultures (because the current analysis focus on bacterial infection and antibiotic treatments), lacked baseline NEWS data, or had no CRP measurements and antibiotic administration records (**Figure** 5.1).

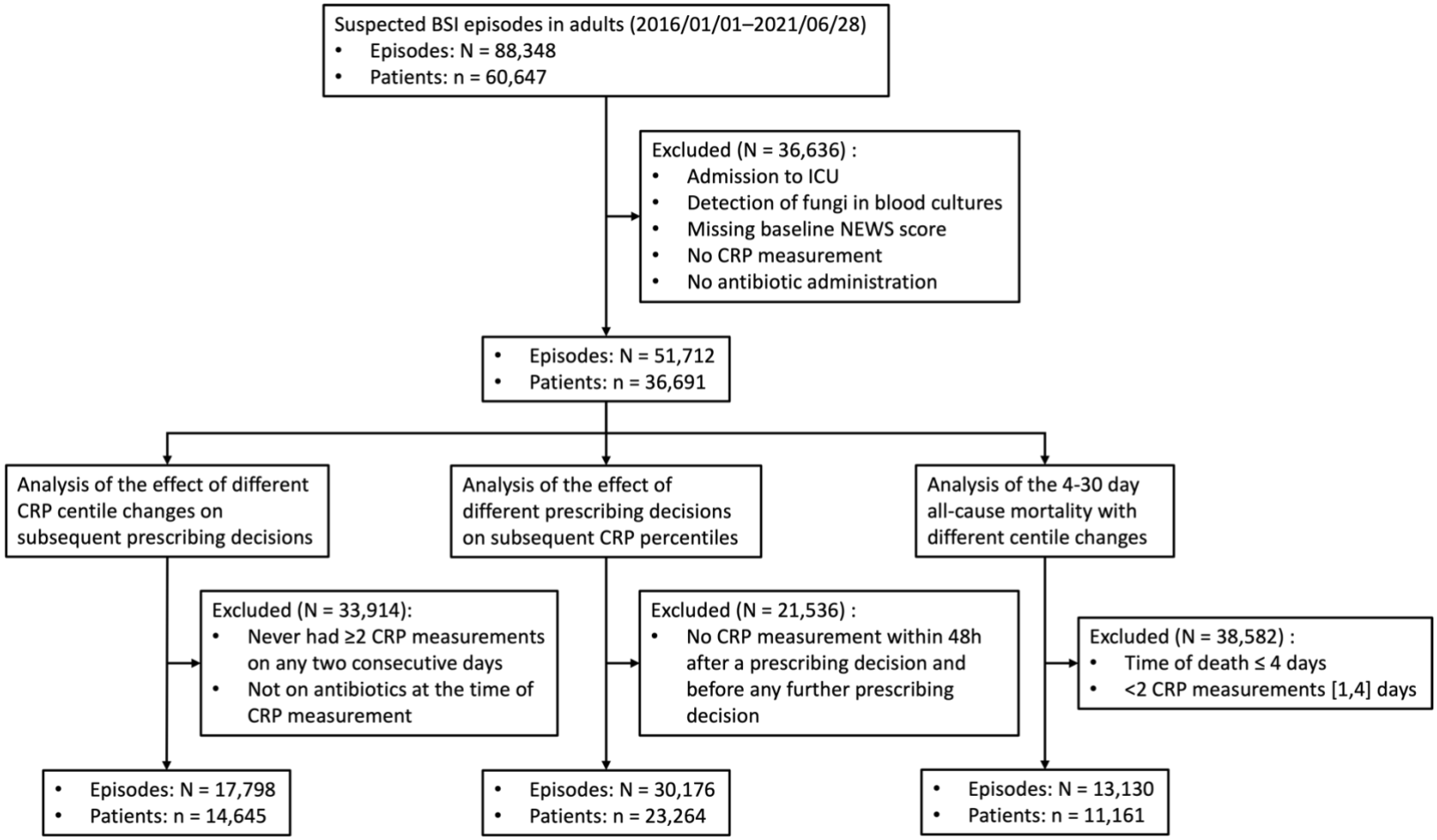


**Figure 5.1 Flowchart to identify study population for different analyses.**

### 5.2.2 Research design and statistical analyses

#### *5.2.2.1 Antibiotic hierarchy and escalation/de-escalation*

Antibiotic treatment records (both in-hospital and discharge prescriptions) within 14 days following index blood culture collection were analysed to characterise prescribing patterns for suspected BSI. The antibiotics were grouped and ranked according to their spectrum of activity against bacterial pathogens, their clinical importance, and with reference to existing research (**Table** 5.1) [196]. This resulted in 5 groups, from 1, the most narrow spectrum, to 5, the most broad spectrum antibiotic.

Antibiotic differences between two timepoints were defined as escalation, unchanged, de-escalation, and stop, based on differences in the pre-defined antibiotic ranking, number of different antibiotics administered, and route of administration. Specifically, an upgrade or downgrade in the antibiotic ranking was considered escalation or de-escalation, respectively. A decrease in the number of antibiotics prescribed or a change in the route of administration from intravenous to oral administration was considered a de-escalation if there was no change in antibiotic ranking, and vice versa for escalation. When multiple antibiotics were used at a given point in time, the highest-ranked antibiotic determined the antibiotic ranking; intravenous was dominant if both intravenous and oral were used. Stopping was defined by ≥48 hours between successive doses of antibiotics or after the last recorded dose was administered; if the patient died within 14 days of the last dose, it was defined as “stopped and died within 14d”.

CRP measurements and antibiotic treatment records within 8 days after taking index blood cultures were included in analyses. Absolute CRP levels were converted to centiles based on my pre-defined centile chart (**Chapter 4**).

| 1 | | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| Narrow Spectrum | Additions to any (or "narrow spectrum" if used as monotherapy) | Broad spectrum | Extended spectrum | Antipseudomonal | Protected |
| First/Second generation cephalosporins[1] | Aminoglycosides[2] | Fluoroquinolones[3] | Third generation cephalosporins[4] | Antipseudomonal penicillin[5] | Antipseudomonal carbapenem[6] |
| Amoxicillin | Clarithromycin | Co-amoxiclav | | Ceftazidime | Linezolid |
| Metronidazole | Clindamycin | Co-trimoxazole | | Aztreonam | Daptomycin |
| Flucloxacillin | Azithromycin | | | | Colistin |
| Doxycycline | Erythromycin | | | | Tigecycline |
| Nitrofurantoin | Rifampicin | | | | Ceftazidime/avibactam |
| Benzylpenicillin | Vancomycin | | | | Ceftolozane/tazobactam |
| Phenoxymethylpenicillin | Teicoplanin | | | | Ertapenem |
| Trimethoprim | | | | | |
| Fosfomycin | | | | | |
| Pivmecillinam | | | | | |

[1] First/Second generation cephalosporins: cefalexin, cefazolin, cefradine, cefuroxime

[2] Aminoglycosides: amikacin, gentamicin, streptomycin, tobramycin

[3] Fluoroquinolones: ciprofloxacin, ofloxacin, levofloxacin, moxifloxacin

[4] Third generation cephalosporins: cefixime, cefotaxime, cefoxitin, ceftriaxone

[5] Antipseudomonal penicillin: piperacillin/tazobactam, temocillin, piperacillin

[6] Antipseudomonal carbapenem: imipenem, meropenem, imipenem/cilastatin

**Table 5.1 Ranking list of antibiotics.**

Antibiotic agents used for suspected BSI were ranked on a five-tiered scale, which considered the agents' spectrum of activity against bacterial pathogens as well as the priority for stewardship.

#### *5.2.2.2 The impact of CRP changes on antibiotic prescribing*

Multinomial logistic regression was used to investigate the association between subsequent prescribing decisions (classified as escalation, unchanged (including no change in prescription or a change but with the same ranking, number of drugs and route), de-escalation, or stop according to the predefined criteria in **Table** 5.1) and prior CRP centile changes. To define the subsequent prescribing decisions, the analysis compared antibiotics given in the 24 hours after the second of two consecutive daily CRP measurements with those given at the time of the second CRP measurement (**Figure** 5.2**;** See **Figure** 5.1 for exclusion criteria). CRP centile change was truncated at ±30 centiles, and potential non-linearity in its effect on antibiotics received was modelled using natural cubic splines with three knots at -15, 0, and 15 (based on **Figure** 4.9 from **Chapter 4**), and boundary knots at -25 and 25, interacting with the day of the second CRP measurement relative to blood culture collection (interaction $p<0.0001$). The timing of the second CRP measurement was also modelled with natural cubic splines using three knots at days 3, 5, and 7, and boundary knots at days 2.2 and 8.1 (95% percentiles).

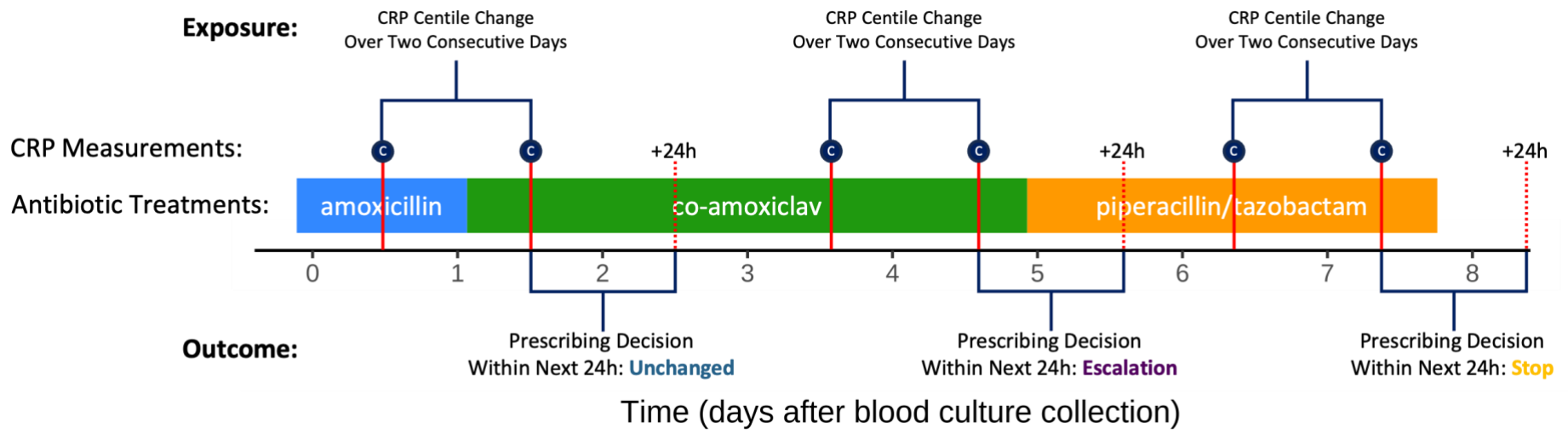


**Figure 5.2 Illustrative diagram of analysis of impact of changes in CRP centiles on prescribing decisions.**

#### *5.2.2.3 The impact of antibiotic prescribing changes on CRP*

Linear mixed models were used to estimate subsequent CRP centile changes over time following different prescribing decisions, including all CRP measurements from the initiation of a new prescribing decision up to 48 hours after or until the next prescribing change, whichever occurred first, and excluding any CRP measurements before the new prescribing decision (**Figure** 5.3; See **Figure** 5.1 for exclusion criteria). Those with only one CRP measurement were also included in this analysis, as they can still contribute population-level information about the average CRP centile values in the study population [197]. The possibility that centile trajectories varied non-linearly over time from the most recent prescribing decision was incorporated using natural cubic splines (as fixed and random (prescription-specific) effects) with one knot at 24h, and boundary knots at 0.7h and 44.2h (95% percentiles). Models were adjusted (as fixed effects) for the type of prescribing decisions (escalation, unchanged, de-escalation, stop as above) and the day of prescribing relative to blood culture collection (as a natural cubic spline using three knots at days 1, 3, and 5, and boundary knots at days 0.1 and 6.5 (95% percentiles)). Two-way interactions between the type of prescribing decision, time following the prescribing decision, and the day of prescribing after blood culture collection were included (interaction $p<0.0001$).

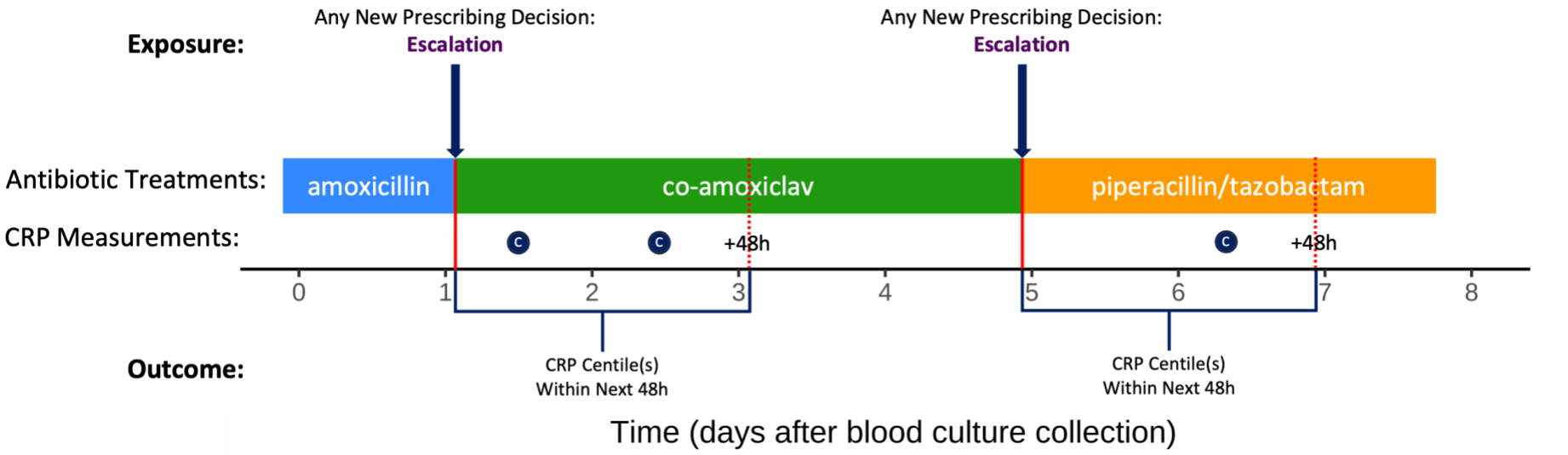


**Figure 5.3 Illustrative diagram of analysis of impact of prescribing decision on CRP centile changes.**

#### *5.2.2.4 The impact of early centile changes on 4-30 day all-cause mortality*

Logistic regression was used to examine the association between 4-30 day all-cause mortality with mean centile change per day between days 1-4 (the post-peak recovery period based on findings in Chapter 3), excluding patients who died or were lost to follow-up before day 4. Receiver operating characteristic (ROC) curves and area under the curve (AUROC) were calculated to assess the predictive power of models including other covariates only (see below), centile changes only, or both. Centile change per day was calculated using linear regression within episodes across days 1-4. Associations between this mean change per day (per episode) and mortality were then estimated using natural cubic splines using five knots at -15, -7.5, 0, 7.5, and 15 and boundary knots at -25 and 25.

All models for the three analyses described above were adjusted for infection source (identified from antimicrobial prescribing indications [133]), community-onset (≤48h after admission), blood culture result (positive, potential contaminant, negative) and pathogen group (based on genus and clinical significance), age, sex, Charlson and Elixhauser scores, renal dialysis, diabetes mellitus, baseline NEWS (calculated using the closest set of vital signs within 1 day before to 1 day after the start of each episode), immunosuppression and palliative care. Definitions of these covariates were as described in **Chapter 3** (details in section **3.2.3**). Diabetes mellitus with/without complications (E100-149) and end-stage renal disease requiring dialysis (Z992, Z49, N186, T824) were determined by the presence of ICD-10 diagnostic codes within the same 1-year lookback period used to calculate other comorbidity-related covariates.

## 5.3 Results

There were 88,348 suspected BSI episodes in adults based on definitions in Chapter 3 (**Figure** 5.1). After exclusion, there were 51,712 suspected BSI episodes in 36,691 patients with CRP measurements who received antibiotic treatment within 14 days following index blood culture collection (**Table** 5.2). The subset studied were similar to the overall group without exclusions in **Chapter 3** (**Table** 3.2). A single Gram-positive pathogen was identified in 1,457 (2.8%), a single Gram-negative pathogen in 2,925 (5.7%), 776 (1.5%) had other pathogens or were polymicrobial, 2,649 (5.1%) had only a potential contaminant, and 43,905 (84.9%) were culture-negative. The median age was 71.0 (IQR 54.6–82.4) years. Among these episodes, 1,001 (1.9%) patients died ≤4 days after the index blood culture collection and were excluded from analyses of mortality between 4-30 days, while 4,230 (8.2%) died between 4 and 30 days.

**Table 5.2 Characteristics at the start of 51,712 suspected BSI episodes receiving antimicrobial treatment between 01 January 2016 and 28 June 2021.**

| Characteristic | **Gram-positive Pathogens**, N = 1457 (2.8%)[1] | **Gram-negative Pathogens**, N = 2925 (5.7%)[1] | **Other Pathogens**, N = 776 (1.5%)[1] | **Potential Contaminant(s)**, N = 2649 (5.1%)[1] | **Culture-negative**, N = 43905 (84.9%)[1] | **Overall**, N = 51712 (100%)[1] |
|---|---|---|---|---|---|---|
| Age at admission (years) | 72.6 (55.8, 83.4) | 75.8 (63.4, 84.8) | 66.4 (49.6, 80.2) | 71.9 (56.7, 83.1) | 70.6 (53.9, 82.2) | 71.0 (54.6, 82.4) |
| Sex (male) | 874 (60.0%) | 1,637 (56.0%) | 435 (56.1%) | 1,347 (50.8%) | 22,603 (51.5%) | 26,896 (52.0%) |
| Charlson score | 1 (1, 3) | 2 (1, 3) | 1 (1, 3) | 2 (1, 3) | 1 (0, 2) | 1 (0, 2) |
| Elixhauser score | 3 (2, 5) | 3 (2, 5) | 3 (1, 4) | 3 (2, 5) | 3 (1, 4) | 3 (1, 4) |
| Renal dialysis | 46 (3.2%) | 62 (2.1%) | 15 (1.9%) | 40 (1.5%) | 866 (2.0%) | 1,029 (2.0%) |
| Diabetes mellitus | 393 (27.0%) | 779 (26.6%) | 148 (19.1%) | 620 (23.4%) | 9,253 (21.1%) | 11,193 (21.6%) |
| NEWS score (baseline) | 3 (2, 6) | 4 (2, 6) | 3 (1, 5) | 3 (1, 5) | 3 (1, 5) | 3 (1, 5) |
| Immunosuppression | 245 (16.8%) | 573 (19.6%) | 212 (27.3%) | 466 (17.6%) | 7,178 (16.3%) | 8,674 (16.8%) |
| Palliative care | 135 (9.3%) | 273 (9.3%) | 97 (12.5%) | 200 (7.6%) | 2,745 (6.3%) | 3,450 (6.7%) |
| Community-onset | 1,161 (79.7%) | 2,293 (78.4%) | 567 (73.1%) | 1,931 (72.9%) | 35,759 (81.4%) | 41,711 (80.7%) |
| Death time | | | | | | |
| Died ≤ 4 days | 42 (2.9%) | 91 (3.1%) | 21 (2.7%) | 68 (2.6%) | 779 (1.8%) | 1,001 (1.9%) |
| Died 4-30 days | 153 (10.5%) | 272 (9.3%) | 93 (12.0%) | 230 (8.7%) | 3,482 (7.9%) | 4,230 (8.2%) |
| Survived > 30 days | 1,262 (86.6%) | 2,562 (87.6%) | 662 (85.3%) | 2,351 (88.8%) | 39,644 (90.3%) | 46,481 (89.9%) |
| Source of infection | | | | | | |
| Respiratory | 347 (23.8%) | 287 (9.8%) | 117 (15.1%) | 865 (32.7%) | 14,997 (34.2%) | 16,613 (32.1%) |
| Multiple sources | 336 (23.1%) | 689 (23.6%) | 156 (20.1%) | 454 (17.1%) | 7,138 (16.3%) | 8,773 (17.0%) |
| Urinary | 119 (8.2%) | 872 (29.8%) | 75 (9.7%) | 331 (12.5%) | 5,623 (12.8%) | 7,020 (13.6%) |
| Abdominal | 77 (5.3%) | 477 (16.3%) | 114 (14.7%) | 200 (7.6%) | 4,412 (10.0%) | 5,280 (10.2%) |
| Skin, soft tissue, orthopedic | 235 (16.1%) | 65 (2.2%) | 61 (7.9%) | 198 (7.5%) | 4,156 (9.5%) | 4,715 (9.1%) |
| CNS | 15 (1.0%) | 15 (0.5%) | 13 (1.7%) | 32 (1.2%) | 514 (1.2%) | 589 (1.1%) |
| Other | 89 (6.1%) | 44 (1.5%) | 64 (8.2%) | 120 (4.5%) | 1,059 (2.4%) | 1,376 (2.7%) |
| Unspecific | 239 (16.4%) | 476 (16.3%) | 176 (22.7%) | 449 (16.9%) | 6,006 (13.7%) | 7,346 (14.2%) |

[1]Median (IQR); n (%)

Note: Percentages in the header are of all episodes, and in the main body are column percentages within each group; continuous variables are summarised using the median (IQR). The baseline NEWS was calculated using the closest set of vital signs within 1 day before to 1 day after the start of each episode.

### 5.3.1 Antibiotic prescribing patterns

Examining inpatient and post-discharge antibiotic use for suspected BSI episodes from the index blood culture up to 14 days after showed notable de-escalation from broad-spectrum to narrow-spectrum antibiotics within the first four days in Gram-positive bacterial infections (28.0% (408/1,457); **Figure** 5.4**A, Figure** 5.5**A**). However, for Gram-negative infections, the most broad spectrum antibiotics (including extended-spectrum antibiotics, anti-pseudomonal agents, and protected antibiotics) were used in 30.8-47.6% of cases in the first three days, and the use of broad-spectrum antibiotics did not decline as rapidly as in Gram-positive infections (**Figure** 5.4**B, Figure** 5.5**B**). Similarly, for episodes with polymicrobial infections, 66.3% (128/193) episodes received advanced antibiotics by day 3, and 72.0% (139/193) were still on antibiotics after 2 weeks (**Figure** 5.4**C, Figure** 5.5**C**). Broad-spectrum antibiotics remained widely used in episodes with negative blood cultures and potential contaminants, accounting for 48.8-50.8% in the first three days. However, in most cases, treatment was stopped somewhat earlier, with 28.2% (13,131/46,554) stopping after a week (**Figure** 5.4**D, Figure** 5.5**D**).

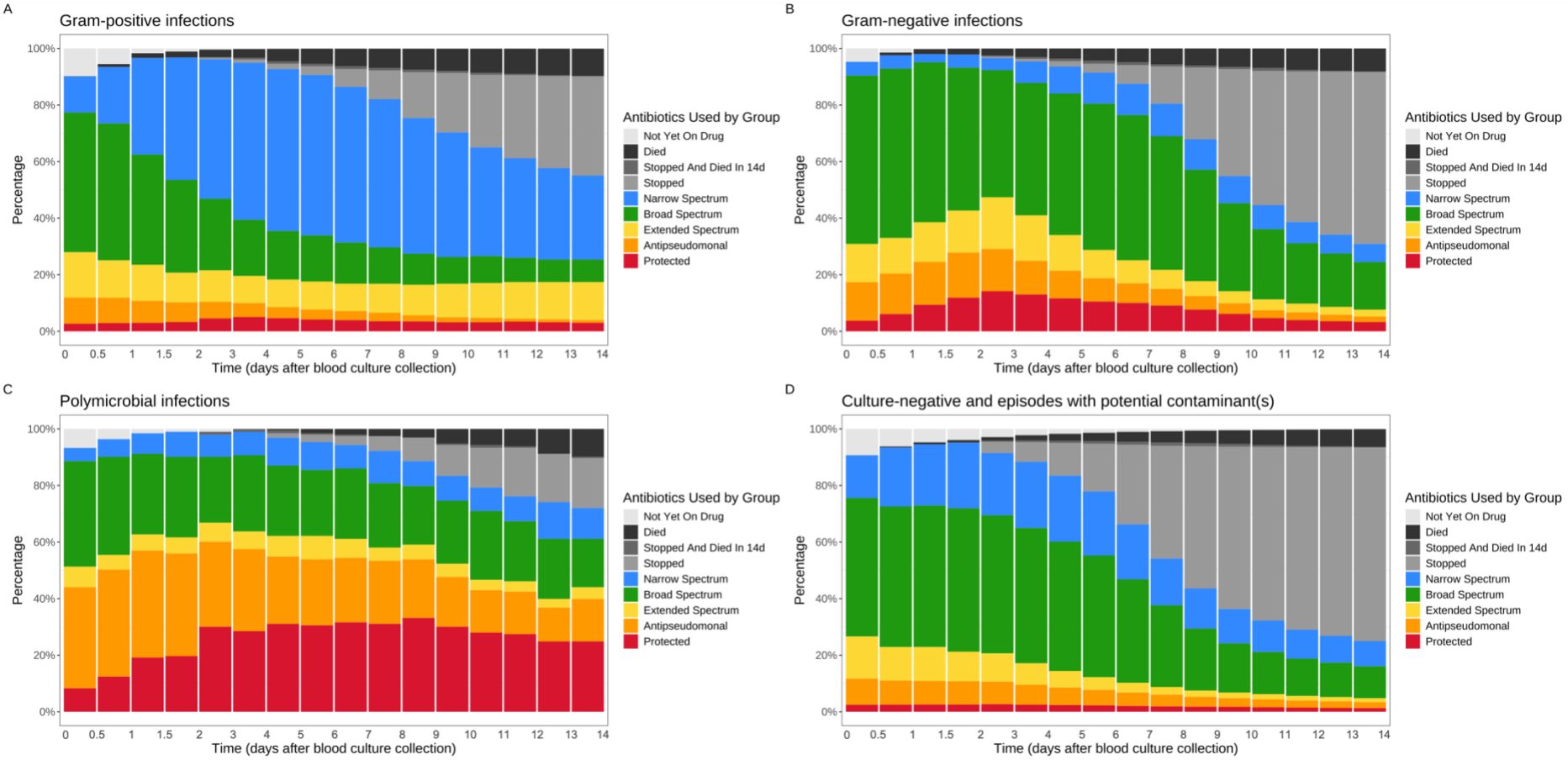


**Figure 5.4 Trends in inpatient and discharge antibiotic use for suspected BSI episodes within 14 days following index blood culture collection.** 1,743 episodes were infected with Gram-positive pathogens (A), 3,361 episodes with Gram-negative pathogens (B), 289 episodes with polymicrobial infections (C), and 57,155 episodes with potential contaminants and culture-negative results (D)).

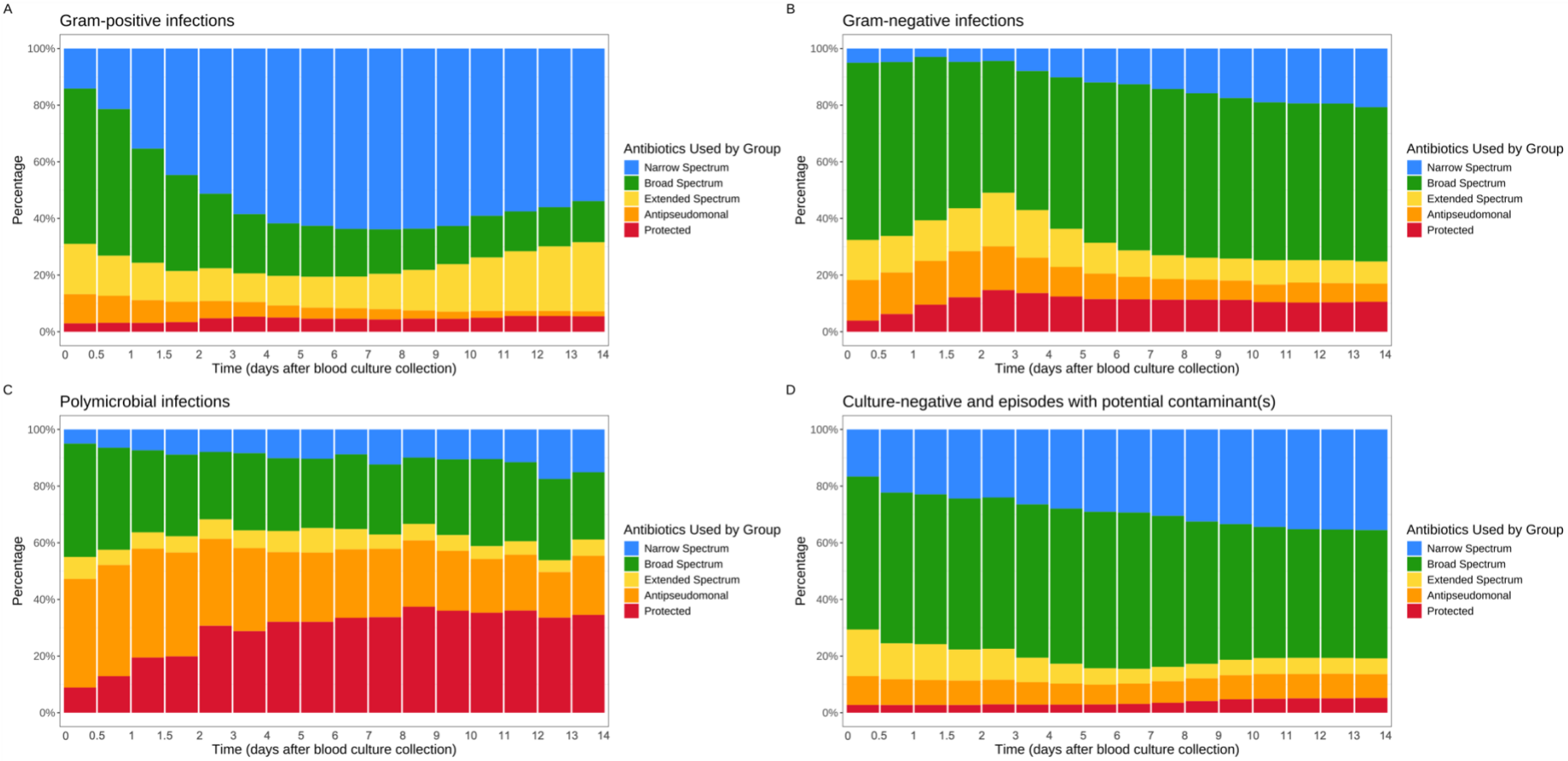


**Figure 5.5 Trends in inpatient and discharge antibiotic use for suspected BSI episodes still on antibiotics within 14 days following index blood culture collection.**

Gram-positive infections in panel A, Gram-negative infections in panel B, polymicrobial infections in panel C, and potential contaminants and culture-negative results in panel D.

### 5.3.2 Prescribing decisions following different CRP centile changes

A total of 30,601 pairs of CRP measurements were taken on consecutive days during days 0-8 across 17,798 episodes (**Figure** 5.1, **Table** 5.3). A CRP centile change of less than 15 in absolute magnitude was observed in 70.0% of cases (21,406/30,601; **Figure** 5.6, **Table** 5.3), suggesting a normal recovery trajectory and arbitrarily defined as recovering as expected (based on **Figure** 4.9 in **Chapter 4**). In 13.9% of cases (4,246/30,601), the CRP centile decreased by more than 15, suggesting a faster-than-expected recovery. Conversely, 16.2% of cases (4,949/30,601) exhibited a sub-optimal recovery with a CRP centile increase of more than 15. Overall, most antibiotics were unchanged in the 24h following the second CRP measurement (63.9% [19,551/30,601]). More escalation occurred following sub-optimal recovery compared to cases recovering faster than expected (16.9% [834/4,949] vs. 9.2% [390/4,246], $p<0.001$). Conversely, there was more de-escalation in cases recovering faster than expected (24.0% [1,018/4,246] vs. 16.3% [806/4,949] of those recovering more slowly than expected, $p<0.001$). Changes in antibiotic ranking following different CRP centile changes also revealed a higher frequency of de-escalation and stopping of antibiotics, particularly after day 4, in patients recovering faster than expected or as expected, although some patients still receiving antibiotics escalated despite improving CRP values and vice versa (see **Supplementary Figures** at the end of this Chapter).

**Table 5.3 Prescribing decisions in the 24h following different categories of CRP centile changes over the preceding two days.**

| Characteristic | **Recovering faster than expected**, N = 4,246[1] | **Recovering as expected**, N = 21,406[1] | **Sub-optimal recovery**, N = 4,949[1] | **Overall**, N = 30,601[1] | **p-value**[2] |
|---|---|---|---|---|---|
| Prescribing Decision | | | | | **<0.001** |
| Escalation | 390 (9.2%) | 2,375 (11.1%) | 834 (16.9%) | 3,599 (11.8%) | |
| Unchanged | 2,606 (61.4%) | 13,846 (64.7%) | 3,099 (62.6%) | 19,551 (63.9%) | |
| De-escalation | 1,018 (24.0%) | 3,816 (17.8%) | 806 (16.3%) | 5,640 (18.4%) | |
| Stop | 232 (5.5%) | 1,369 (6.4%) | 210 (4.2%) | 1,811 (5.9%) | |

[1]n (%)

[2]Pearson's Chi-squared test

Note: Centile changes were calculated from CRP measurements over two consecutive days and compared with prescribing decisions made in the 24h following the second CRP measurement. Centile changes of <−15, −15 to 15 and >15 were considered as recovering faster than expected, recovering as expected and sub-optimal recovery, respectively.

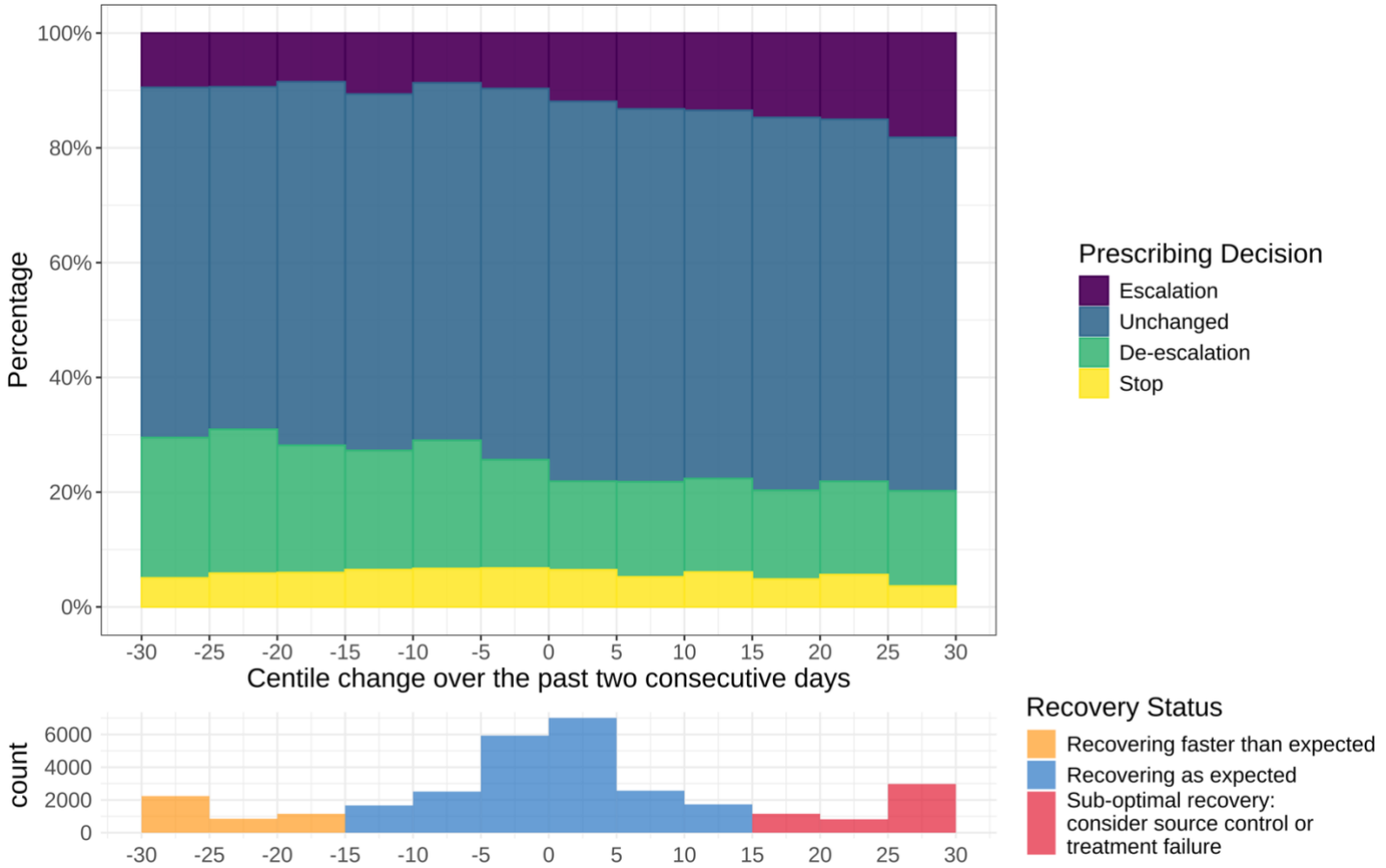


**Figure 5.6 The percentage of different prescribing decisions made on days 2-8 following different ranges of centile change over the past two consecutive days.**

Centile change <−15, −15 to 15 and >15 were considered as recovering faster than expected (orange), recovering as expected (blue) and sub-optimal recovery (red), respectively.

After adjusting for baseline patient characteristics, the probability of antibiotics remaining unchanged was consistently high at 55–60% as changes in CRP centiles over the past two days varied and over 2 to 8 days from the initial blood culture collection (**Figure** 5.7; **Table** 5.4). Conversely, the probability of stopping antibiotics was initially low, regardless of centile changes, but gradually increased to approximately 5% by day 8. Greater decreases in CRP centiles were associated with an increased likelihood of de-escalation, reaching ~35% if centiles decreased by 15-30; while greater increases in CRP centiles were associated with a gradually increased likelihood of escalation, from 10% to 20%. The probability of de-escalation peaked at 29% during days 3-4 before decreasing, while the probability of escalation dropped to 10% by day 4 before increasing again subsequently.

Furthermore, patients on renal dialysis had a lower probability of de-escalation (RRR=0.79 [96%CI 0.67,0.94]) and stopping (RRR=0.54 [0.40,0.72]). Immunosuppressed patients were also less likely to stop antibiotics (RRR=0.69 [0.60,0.79]). Patients receiving palliative care were less likely to de-escalate (RRR=0.62 [0.54,0.71]). For community-onset infections, the probability of either type of antibiotic adjustments was independently higher (RRR=1.28 [1.18,1.39] for escalation; RRR=1.78 [1.65,1.92] for de-escalation). Infections with *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and polymicrobial infections were associated with a lower likelihood of stopping antibiotics compared to *E. coli* infections, while potential contaminants and culture-negative results were associated with a higher likelihood of stopping antibiotics (**Table** 5.4). Regarding infection sources, respiratory, multiple, and abdominal sources were linked with a higher probability of escalation (**Table** 5.4).

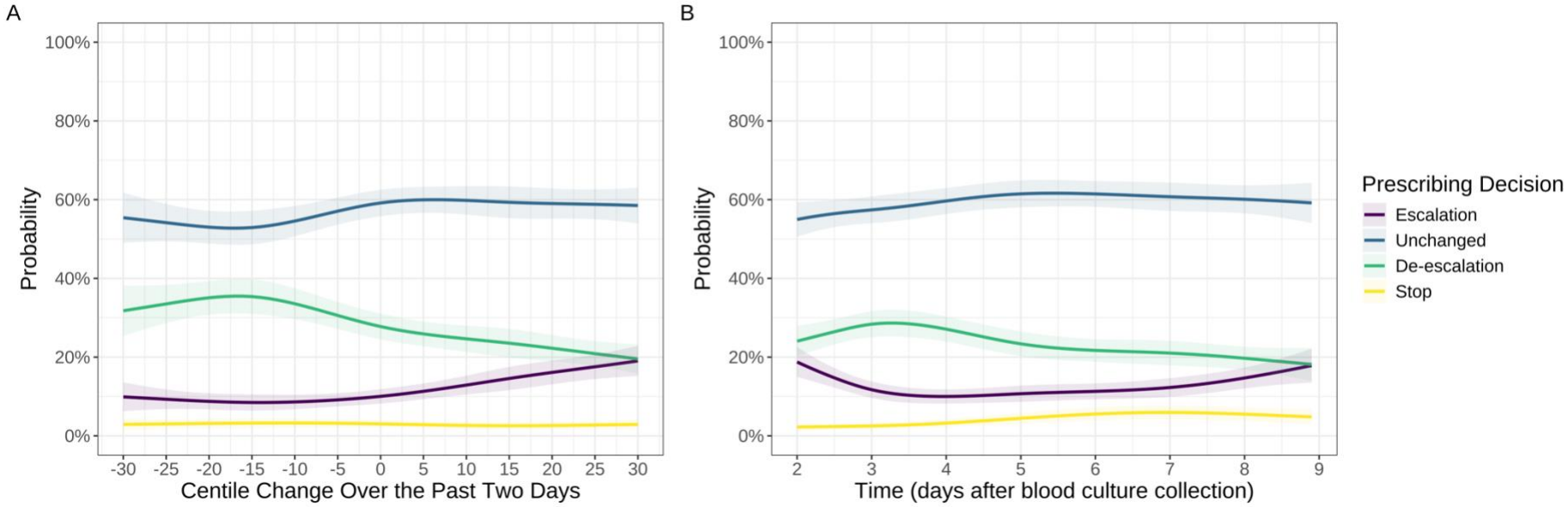


**Figure 5.7 Predicted probability of various prescribing decisions as CRP centile changes (A) and over time since index blood culture collection (B).** Predictions are plotted using the reference values for other adjusting variables (median for continuous variables): prescribing day = 2 (Panel A), Centile change = 0 (Panel B), age = 67 years, male, Charlson score = 2, Elixhauser score = 3, no renal dialysis, no diabetes, baseline NEWS = 3, absence of immunosuppression, no palliative care, community-onset, urinary source, and *E. coli* infection.

**Table 5.4 Factors independently associated with different prescribing decisions following CRP centile changes.**

| | Escalation | | | De-escalation | | | Stop | | |
|---|---|---|---|---|---|---|---|---|---|
| **Characteristic** | **RRR[1]** | **95% CI[1]** | **p-value** | **RRR[1]** | **95% CI[1]** | **p-value** | **RRR[1]** | **95% CI[1]** | **p-value** |
| Centile change | See **Figure** 5.7 | — | | See **Figure** 5.7 | — | | See **Figure** 5.7 | — | |
| Prescribing day | See **Figure** 5.7 | — | | See **Figure** 5.7 | — | | See **Figure** 5.7 | — | |
| Age at admission (10 years) | 0.98 | 0.96, 1.00 | 0.056 | 0.99 | 0.97, 1.00 | 0.155 | **1.03** | **1.00, 1.07** | **0.031** |
| Sex (male vs female) | 1.03 | 0.96, 1.11 | 0.404 | 1.05 | 0.99, 1.12 | 0.105 | **0.88** | **0.80, 0.98** | **0.014** |
| Charlson score | 1.03 | 0.99, 1.08 | 0.142 | 1.02 | 0.99, 1.06 | 0.242 | 1.04 | 0.98, 1.11 | 0.185 |
| Elixhauser score | **0.96** | **0.93, 0.98** | **0.001** | **0.94** | **0.92, 0.97** | **<0.001** | 0.98 | 0.94, 1.01 | 0.198 |
| Renal dialysis | 0.90 | 0.74, 1.09 | 0.262 | **0.79** | **0.67, 0.94** | **0.008** | **0.54** | **0.40, 0.72** | **<0.001** |
| Diabetes mellitus | 0.95 | 0.86, 1.05 | 0.322 | 0.97 | 0.89, 1.06 | 0.503 | 0.98 | 0.86, 1.13 | 0.799 |
| NEWS score (baseline) | 1.01 | 0.99, 1.02 | 0.340 | 1.01 | 1.00, 1.02 | 0.128 | **0.98** | **0.96, 1.00** | **0.031** |
| Immunosuppression | 1.03 | 0.94, 1.14 | 0.534 | **1.09** | **1.01, 1.18** | **0.036** | **0.69** | **0.60, 0.79** | **<0.001** |
| Palliative care | 1.07 | 0.93, 1.22 | 0.332 | **0.62** | **0.54, 0.71** | **<0.001** | 0.89 | 0.73, 1.09 | 0.266 |
| Community-onset | **1.28** | **1.18, 1.39** | **<0.001** | **1.78** | **1.65, 1.92** | **<0.001** | 1.06 | 0.95, 1.18 | 0.282 |
| Blood culture results | | | | | | | | | |
| *Escherichia coli* | — | — | | — | — | | — | — | |
| *Klebsiella* sp. | 0.97 | 0.72, 1.32 | 0.862 | **1.32** | **1.02, 1.72** | **0.033** | 0.63 | 0.32, 1.25 | 0.189 |
| Other Enterobacterales | 0.96 | 0.66, 1.38 | 0.805 | 1.00 | 0.72, 1.39 | 0.998 | 0.48 | 0.19, 1.22 | 0.124 |
| *Pseudomonas aeruginosa* | 1.01 | 0.70, 1.45 | 0.965 | **0.64** | **0.43, 0.94** | **0.022** | **0.25** | **0.08, 0.81** | **0.020** |
| *Enterobacter* sp. | 0.72 | 0.39, 1.33 | 0.295 | 0.82 | 0.48, 1.38 | 0.448 | 0.50 | 0.15, 1.64 | 0.253 |
| *Staphylococcus aureus* | **0.70** | **0.53, 0.93** | **0.015** | 0.83 | 0.65, 1.05 | 0.124 | **0.28** | **0.13, 0.61** | **0.002** |
| Beta-Hemolytic Streptococci | **0.61** | **0.38, 0.95** | **0.031** | **1.46** | **1.07, 2.00** | **0.018** | 0.72 | 0.26, 2.03 | 0.535 |
| *Enterococcus* sp. | **1.46** | **1.04, 2.06** | **0.030** | 1.28 | 0.92, 1.79 | 0.146 | 0.98 | 0.50, 1.90 | 0.946 |
| *Streptococcus pneumoniae* | 0.68 | 0.42, 1.11 | 0.126 | 1.38 | 0.98, 1.96 | 0.068 | 0.42 | 0.10, 1.75 | 0.234 |
| Other Pathogenic *Streptococcus* | **0.37** | **0.17, 0.82** | **0.014** | 0.76 | 0.42, 1.39 | 0.379 | 0.27 | 0.04, 2.00 | 0.201 |
| Other | 1.23 | 0.89, 1.72 | 0.214 | 1.09 | 0.80, 1.50 | 0.578 | 0.68 | 0.32, 1.46 | 0.326 |
| Polymicrobial | **1.45** | **1.06, 1.98** | **0.020** | 1.11 | 0.81, 1.53 | 0.501 | **0.41** | **0.17, 0.96** | **0.040** |
| Anaerobes | 0.77 | 0.48, 1.23 | 0.271 | 1.23 | 0.85, 1.78 | 0.266 | 0.88 | 0.37, 2.10 | 0.777 |
| Culture-negative | **0.66** | **0.57, 0.76** | **<0.001** | 0.88 | 0.78, 1.00 | 0.058 | **2.06** | **1.57, 2.68** | **<0.001** |
| CoNS (contaminant) | 0.92 | 0.74, 1.13 | 0.410 | 0.89 | 0.74, 1.09 | 0.260 | **2.32** | **1.67, 3.23** | **<0.001** |
| Other Suspected Contaminants | 1.08 | 0.67, 1.75 | 0.741 | 1.08 | 0.69, 1.67 | 0.745 | **2.14** | **1.05, 4.35** | **0.035** |
| Viridans and Other Streptococcus | 0.90 | 0.57, 1.43 | 0.661 | 1.38 | 0.96, 1.99 | 0.080 | 0.83 | 0.35, 1.97 | 0.676 |
| Source of infection | | | | | | | | | |
| Urinary | — | — | | — | — | | — | — | |
| Unspecific | **0.65** | **0.55, 0.77** | **<0.001** | **0.73** | **0.65, 0.82** | **<0.001** | **1.26** | **1.04, 1.51** | **0.016** |
| Respiratory | **1.25** | **1.09, 1.43** | **0.002** | **0.83** | **0.75, 0.92** | **<0.001** | 0.90 | 0.76, 1.07 | 0.245 |
| Multiple sources | **1.85** | **1.62, 2.11** | **<0.001** | 1.05 | 0.95, 1.17 | 0.327 | **0.72** | **0.60, 0.87** | **<0.001** |
| Abdominal | **1.37** | **1.18, 1.59** | **<0.001** | **0.79** | **0.70, 0.90** | **<0.001** | 1.13 | 0.93, 1.36 | 0.215 |
| Skin, soft tissue, orthopaedic | 1.06 | 0.88, 1.27 | 0.553 | 0.88 | 0.77, 1.01 | 0.071 | **0.51** | **0.39, 0.67** | **<0.001** |
| CNS | 0.86 | 0.59, 1.28 | 0.465 | **0.54** | **0.38, 0.76** | **<0.001** | 1.12 | 0.74, 1.69 | 0.602 |
| Other | 1.01 | 0.78, 1.31 | 0.941 | 0.83 | 0.67, 1.02 | 0.079 | 0.76 | 0.52, 1.13 | 0.177 |

[1]RRR = Relative-Risk Ratio vs. Unchanged, CI = Confidence Interval

### 5.3.3 CRP centile changes following different prescribing decisions

A total of 48,332 prescription changes were followed by ≥1 CRP measurement within the subsequent 48 hours or until the next prescription change, whichever occurred first (Median 1 (IQR 1–1, range 1–7)). Among these, 15,015 (31.1%) new prescriptions represented escalation decisions, 13,652 (28.2%) had no change in the spectrum of activity, 13,426 (27.8%) were de-escalation decisions, and 6,239 (12.9%) stopped antibiotics.

CRP centile changes following different prescribing decisions were relatively small and within the ±15 percentiles threshold previously defined in Chapter 4, consistent with standard response. In general, CRP centile levels were higher at the time of the prescribing decision for episodes with treatment escalation and lower for those who stopped antibiotics. CRP centiles at the population level increased slightly over the 48h following all prescribing decisions made within the first four days of blood culture collection (if a patient is recovering as expected and is receiving the "correct" antibiotic management, one would expect the centile line to be flat), but they remained stable or decreased after escalated, unchanged or de-escalated antibiotic treatment later on day 5 (interaction $p<0.0001$, **Figure** 5.8). CRP centiles increased by ~4 percentiles over 48h following escalation or no change in antibiotic therapy on day 1 after blood culture collection. In cases where antibiotics were de-escalated or stopped, the centile approximately flatted in the first 24h but increased again over the next 24h. On days 2 and 3, CRP centiles increased by 4-9 units after all prescribing decisions, with the highest increase observed after antibiotic cessation (~9 percentiles) and the lowest increase after de-escalation (~4 percentiles). Following escalation on day 3, CRP

centiles increased by ~6 percentiles in the first 24h after escalation but stabilised over the subsequent 24h. On day 5, CRP centiles decreased by ~3 percentiles after de-escalation and by ~1 percentile after escalation, stabilised after no change, and increased slightly by ~2 percentiles over 24-48h following antibiotic cessation.

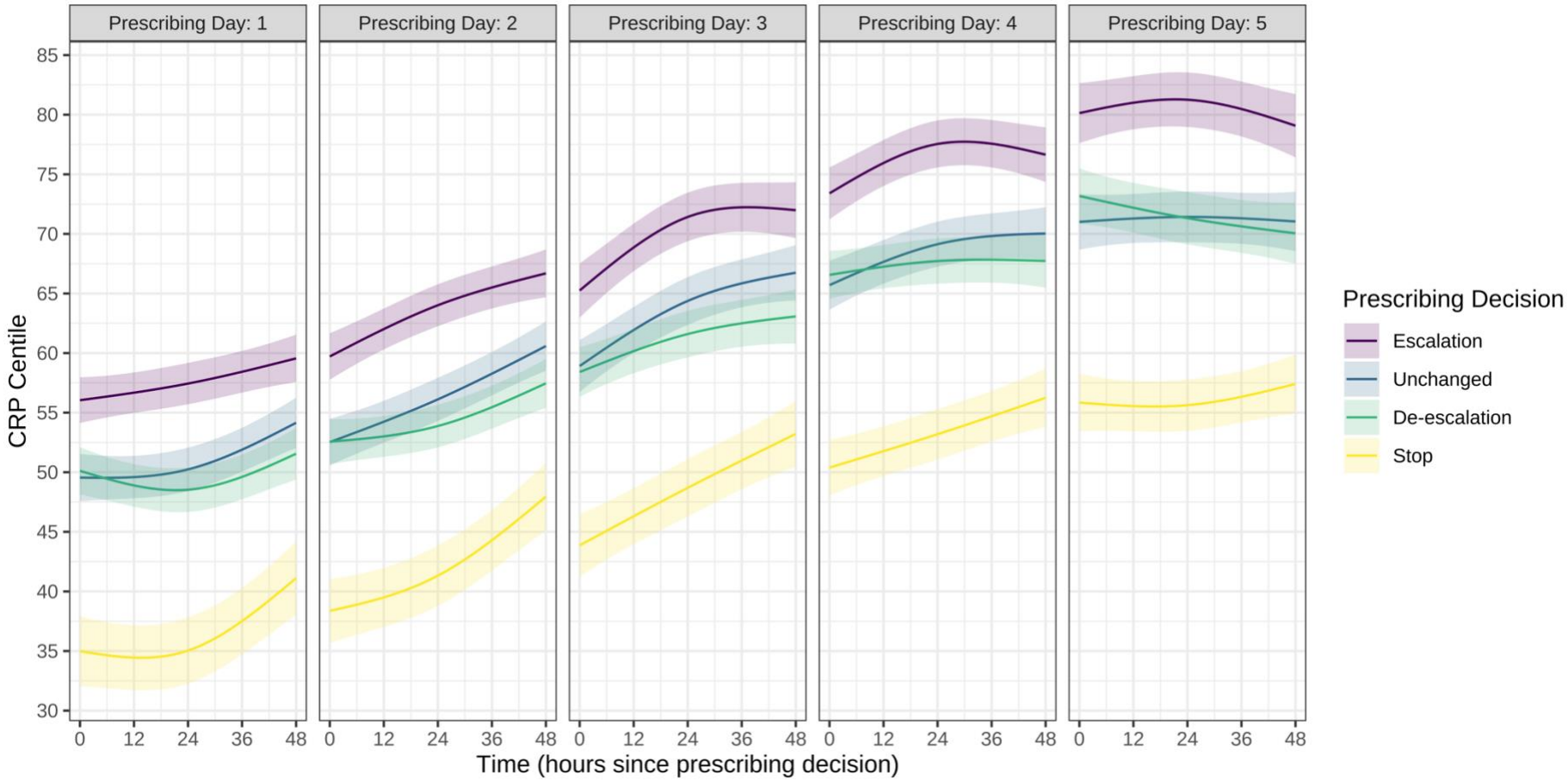


**Figure 5.8 Predicted CRP centile trajectories over the next 48 hours following different prescribing decisions on days 1, 2, 3, 4 and 5 since blood culture collection (prescribing day).**

Predictions are plotted using the reference values for other adjusting variables: age = 67 years, male, Charlson score = 2, Elixhauser score = 3, no renal dialysis, no diabetes, baseline NEWS = 3, absence of immunosuppression, no palliative care, community-onset, urinary source, and *E. coli* infection.

### 5.3.4 Mortality after different early changes in CRP centile

After adjusting for potential confounders, the probability of 4-30 day all-cause mortality increased non-linearly with higher daily CRP centile changes during days 1-4 (**Figure** 5.9). The predicted probability of mortality was ~4% for a mean centile change of <-5/day, increased to ~6.5% for a mean centile change of 0-10/day, and further increased to ~12% for a mean centile change of 20-30/day. Other significant factors included age (OR per 10 years older=1.55 [95%CI 1.46,1.65], p<0.001), Charlson score (OR=1.17 per unit higher [1.08,1.27], p<0.001), diabetes mellitus (OR= 0.71 [0.58,0.86], p<0.001), baseline NEWS score (OR=1.11 per unit higher [1.08,1.13], p<0.001), immunosuppression (OR=1.24 [1.02,1.50], p=0.027), and palliative care (OR=13.3 [11.0,16.1], p<0.001) (**Table** 5.5). Blood culture results and source also had strong associations with mortality risk. Factors such as polymicrobial infections (OR= 2.92 vs. *E. coli* [1.35,6.09], p=0.005), CNS infections (OR=2.63 vs. urinary source [1.15,5.44], p=0.014), and respiratory source (OR= 2.23 [1.70,2.94], p<0.001) showed the most substantial impacts on mortality risk.

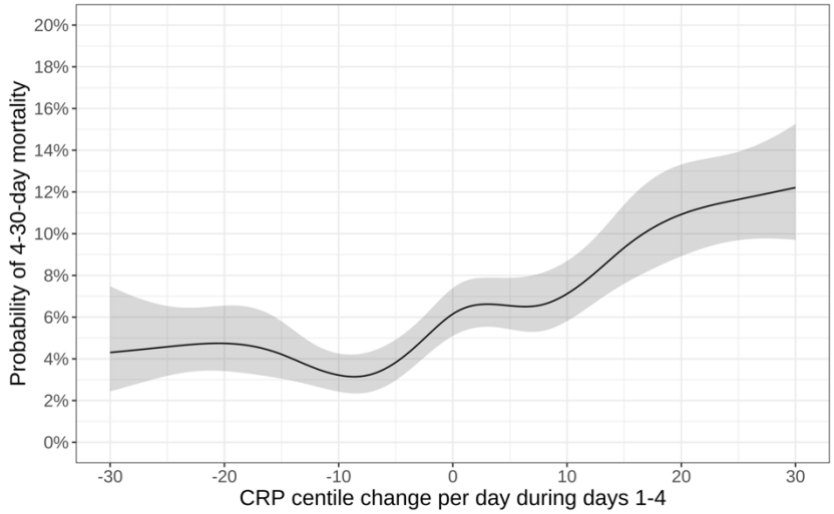


**Figure 5.9 Predicted probability of 4-30 day all-cause mortality by mean CRP centile change per day during days 1-4.**
Note: See **Table 5.5** for further details on the covariates included in the adjustment.

**Table 5.5 Factors independently associated with 4-30 days of all-cause mortality.**

| Characteristic | OR[1] | 95% CI[1] | p-value |
|---|---|---|---|
| CRP centile change | See **Figure** 5.9 | – | |
| Age at admission (10 years) | 1.55 | 1.46, 1.65 | **<0.001** |
| Sex (male vs female) | 1.17 | 1.01, 1.36 | **0.036** |
| Charlson score | 1.17 | 1.08, 1.27 | **<0.001** |
| Elixhauser score | 1.06 | 1.01, 1.12 | **0.019** |
| Renal dialysis | 0.75 | 0.43, 1.22 | 0.27 |
| Diabetes mellitus | 0.71 | 0.58, 0.86 | **<0.001** |
| NEWS score (baseline) | 1.11 | 1.08, 1.13 | **<0.001** |
| Immunosuppression | 1.24 | 1.02, 1.50 | **0.027** |
| Palliative care | 13.3 | 11.0, 16.1 | **<0.001** |
| Community-onset | 0.98 | 0.83, 1.16 | 0.82 |
| Blood culture result | | | |
| *E. coli* | — | — | |
| *Klebsiella* sp. | 1.08 | 0.46, 2.34 | 0.85 |
| Other *Enterobacterales* | 2.14 | 0.98, 4.49 | **0.048** |
| *Pseudomonas aeruginosa* | 0.89 | 0.33, 2.12 | 0.80 |
| *Enterobacter* sp. | 1.88 | 0.41, 6.26 | 0.35 |
| *Staphylococcus aureus* | 1.62 | 0.85, 3.03 | 0.13 |
| Beta-Hemolytic Streptococci | 0.77 | 0.22, 2.10 | 0.65 |
| *Enterococcus* sp. | 1.41 | 0.57, 3.18 | 0.43 |
| *Streptococcus pneumoniae* | 0.80 | 0.25, 2.09 | 0.67 |
| Other Pathogenic *Streptococcus* | 1.32 | 0.38, 4.09 | 0.64 |
| Other | 2.47 | 1.14, 5.07 | **0.017** |
| Polymicrobial | 2.92 | 1.35, 6.09 | **0.005** |
| Anaerobes | 1.04 | 0.25, 3.44 | 0.96 |
| Culture-negative | 1.24 | 0.88, 1.80 | 0.24 |
| CoNS (contaminant) | 1.15 | 0.71, 1.88 | 0.57 |
| Other Suspected Contaminants | 0.74 | 0.11, 2.95 | 0.71 |
| Viridans and Other *Streptococcus* | 0.77 | 0.19, 2.33 | 0.67 |
| Source of infection | | | |
| Urinary | — | — | |
| Unspecific | 1.09 | 0.79, 1.50 | 0.61 |
| Respiratory | 2.23 | 1.70, 2.94 | **<0.001** |
| Multiple sources | 1.53 | 1.16, 2.04 | **0.003** |
| Abdominal | 1.03 | 0.72, 1.45 | 0.88 |
| Skin, soft tissue, orthopaedic | 0.66 | 0.40, 1.06 | 0.10 |
| CNS | 2.63 | 1.15, 5.44 | **0.014** |
| Other | 1.07 | 0.53, 2.01 | 0.85 |

[1]OR = Odds Ratio, CI = Confidence Interval

Note: CRP centile change was calculated from day 1 to day 4.

The ROC curves illustrated the predictive performance of various models: adjusted and unadjusted CRP centile models, a covariates-only model (**Figure** 5.10), and adjusted and unadjusted models for both absolute and log CRP change (**Figure** 5.11**A** and **Figure** 5.11**B**, respectively). The CRP centile change over days 1-4 was only modestly predictive (AUC=0.62 [0.59,0.66]), outperforming absolute CRP change (AUC=0.58 [0.55, 0.60]) and comparable to log CRP change (AUC=0.62 [0.60, 0.65]). The covariates-only model achieved an AUC of 0.85 [0.83,0.88]. The adjusted model achieved an AUC of 0.86 [0.84,0.89], showing a small but statistically significant improvement over the covariates-only model (p=0.0008).

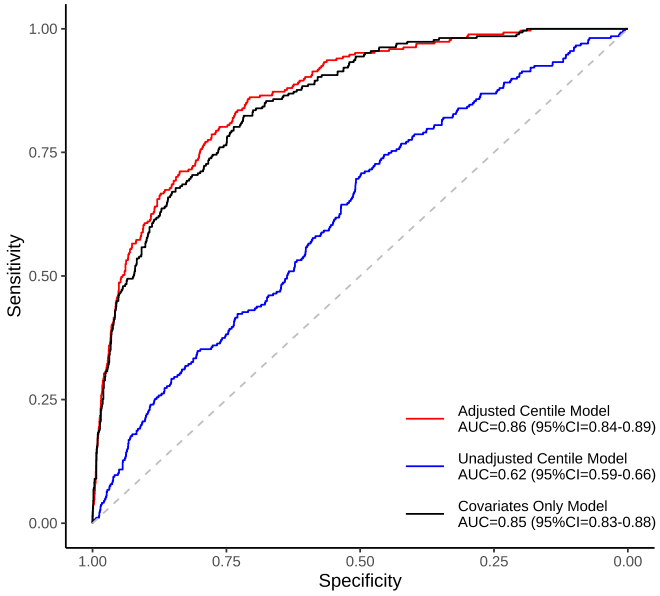


**Figure 5.10 ROC curves for covariates only model, unadjusted CRP centile model and adjusted CRP centile model.**

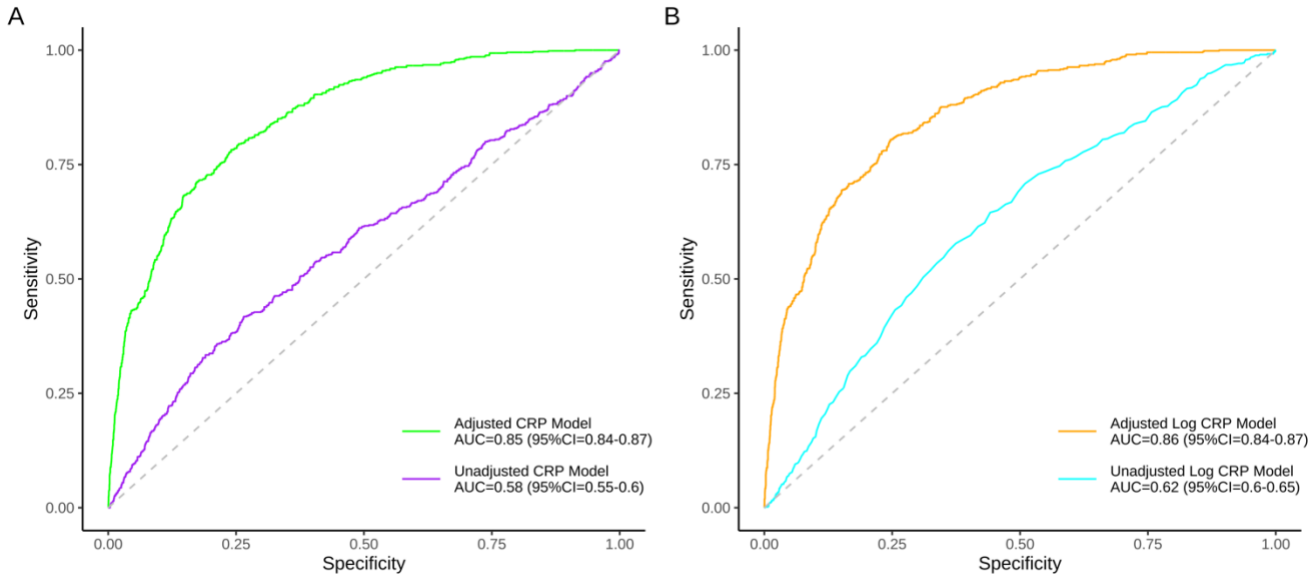


**Figure 5.11 ROC curves for adjusted/unadjusted model for absolute CRP value (A), and adjusted/unadjusted model for log CRP value (B).**

Kaplan-Meier survival curves for mortality during 4-30 days after blood culture collection, stratified by CRP centile change per day over days 1-4, showed that individuals in the groups with centile change <-5 and [-5, 0) consistently had the highest survival probabilities, ~94% by day 30 (**Figure** 5.12). These groups remained separated from those groups with higher centile change (i.e., centile change [0, 10), [10, 20) and ≥20). Conversely, the centile change ≥20 group had the lowest survival probabilities throughout, ~80% by day 30.

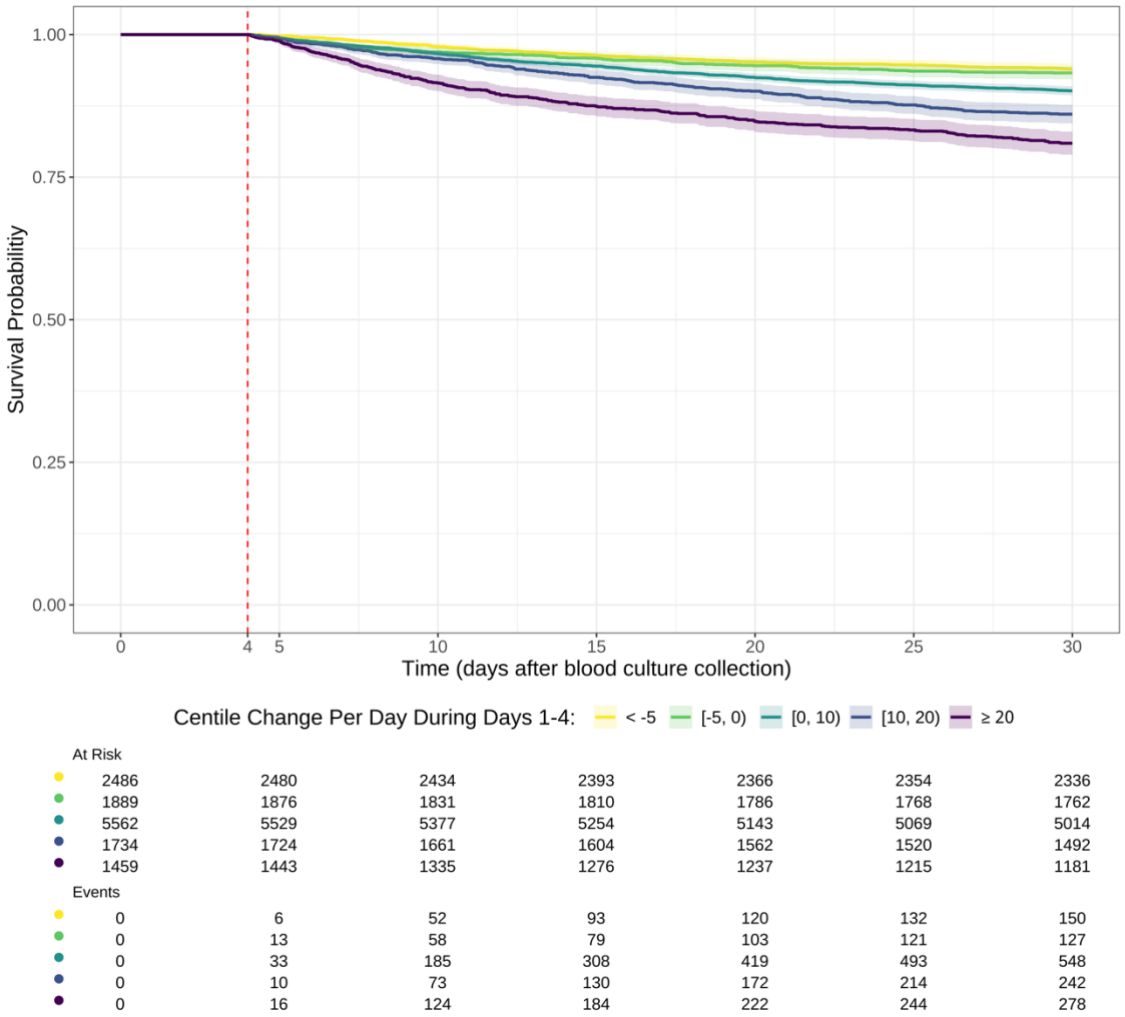


**Figure 5.12 Kaplan-Meier curves and risk tables for mortality from day 4-30 in episodes with different mean CRP centile change per day during days 1-4.**
The centile change per day was divided into 5 categories, <-5, -5 to 0, 0 to 10, 10 to 20, and ≥20.

## 5.4 Discussion

This study investigated the relationship between antibiotic prescribing patterns, changes in CRP centiles and patient outcomes in suspected BSI. My findings revealed significant variations in antibiotic use based on pathogen type, estimated the association between CRP centile changes and antibiotic decisions, and demonstrated the prognostic value of early changes in CRP centiles on mortality outcomes. However, many observed effects were modest, indicating the complexity of BSI management and the multifactorial influences on patient outcomes. Specifically, my analysis showed clearly the expected initial reliance on broad-spectrum antibiotics, with subsequent de-escalation within four days in Gram-positive infections. However, Gram-negative infections, polymicrobial infections and culture-negative episodes maintained broad-spectrum use. CRP centile changes were associated with subsequent antibiotic decisions, as were prescribing decisions on subsequent centile changes, although the effects were modest in size, and the latter relationship was complicated, varying strongly by time since the initial blood culture. Early CRP centile changes were also associated with 4-30 day all-cause mortality, demonstrating their prognostic value.

As above, the analysis of antibiotic prescribing patterns demonstrated a prevalent initial reliance on broad-spectrum antibiotics within the first three days after the index blood culture across infections regardless of blood culture result. This empirical approach reflects the urgency in managing potential BSI due to their high risk of morbidity and mortality [15]. For Gram-positive infections, there was a notable shift towards narrower-spectrum antibiotics within the first four days, with 28.0% of cases experiencing de-escalation. This trend aligns with contemporary stewardship guidelines advocating for

de-escalation to prevent the development of resistance and mitigate adverse drug effects [4]. Conversely, Gram-negative infections showed a slower decline in broad-spectrum antibiotic use, reflecting the complexity and high resistance potential associated with these pathogens [198]. Broad-spectrum antibiotics were also primarily used throughout the 14 days in polymicrobial infections, culture-negative episodes, and cases with potential contaminants. This use likely reflects the treatment complexities and the higher involvement of Gram-negative pathogens in polymicrobial infections, as well as a precautionary approach towards potential Gram-negative pathogens in culture-negative cases. This pattern underscores the inherent tension in BSI management: the need for rapid, empirically broad coverage versus the imperative to minimise unnecessary antibiotic exposure [15].

Prescribing decisions in the subsequent 24h were associated with different categories of CRP centile changes over the preceding two days, albeit with small effect sizes. In most cases (63.9%) with CRP measurements over the preceding two consecutive days, prescribing decisions remained unchanged, regardless of the change in CRP centile. However, patients with sub-optimal recovery, arbitrarily defined by a CRP centile increase of more than 15 over two consecutive days, experienced higher rates of escalation (16.9% vs. 11.8% overall). This response implies a recognition of inadequate therapeutic response and a subsequent need for more aggressive intervention. Conversely, faster-than-expected recovery (CRP centile decrease of more than 15 over two consecutive days) were more frequently followed by de-escalation (24.0% vs. 18.4% overall). This pattern is consistent with emerging evidence supporting early de-escalation to reduce the risk of adverse outcomes linked to prolonged broad-spectrum

antibiotic use [192]. These findings complement existing studies that advocate for adaptable treatment strategies based on real-time clinical markers [15,193], thus emphasising the potential value of CRP monitoring in personalised infection management. However, it was worth noting that while these associations were identified at a population level, for many patients, these patterns were not seen, with some patients still having antibiotics escalated despite improving CRP centiles and de-escalated despite increasing CRP centiles.

Different antibiotic prescribing decisions were also modestly associated with subsequent changes in CRP centiles over the following 48h. Specifically, patients requiring escalation of antibiotics generally had higher CRP centiles, indicating worse clinical conditions. Also, escalation was counter-intuitively associated with an initial increase in CRP centiles, especially when escalation occurred in the first three days after blood culture collection. This could potentially be due to the long half-life of CRP, which delays the biomarker's response to therapeutic interventions. This initial increase may therefore reflect a persistent inflammatory response from the infection before the new antibiotic regimen takes effect. Similarly, stopping antibiotics generally led to increased CRP centiles, particularly 24-48 hours after the decision to discontinue. This could indicate that the underlying pathogen still persists or that only patients who deteriorated were continuously monitored with further CRP test after stopping antibiotics, introducing a potential bias into my estimate. However, over time, the decision to stop antibiotics increasingly approached the average centile, aligning with the clinical tendency to discontinue antibiotics around day 5. Similar estimates following de-escalation and no change at all days supported the goal of safe de-

escalation, as de-escalation involved replacing antibiotics with those of a narrower spectrum but were equally effective against the causative pathogen. It is essential to note that this analysis was conditional on having another antibiotic prescription. For example, patients prescribed co-amoxiclav for five days from the first day would not be included in this analysis, as the trajectories in **Figure** 5.8 reflect changes in prescription likely when there is concern about patient progress.

One limitation of this analysis is that in most cases, only one CRP measurement was performed within 48 hours after the prescribing decision, and the few instances of more frequent measurements may have preferentially occurred in deteriorating patients, as in the previously mentioned results after antibiotic discontinuation. This could be one reason that many of the centile trajectories showed an upward trend. Addressing this issue fully would require sampling regardless of clinical progress, which is unfeasible on a large scale. Excluding those with only one measurement is also not a solution, as it can lead to imprecise and biased estimates, particularly when the missing data mechanism is not completely at random [197]. Furthermore, the significant time-dependent confounding presents challenges in establishing causal relationships in this observational study. Although the CRP trajectories offer insightful information, they highlight the complexities involved in evaluating the impact of prescribing decisions. Future analyses should aim to address time-dependent confounding more rigorously. Additionally, these findings should be interpreted with caution, considering the dynamic nature of clinical decision-making and patient progression.

The association between mean CRP centile changes over the first 4 days and subsequent mortality outcomes highlights the prognostic value of early CRP changes. Kaplan-Meier analyses revealed that individuals with faster-than-expected recovery during days 1-4 consistently had the highest survival probabilities, while those with sub-optimal early recovery trajectories exhibited the poorest outcomes. This stratification persisted across the days 4-30, indicating the robustness of CRP centile changes as early indicators of subsequent mortality risk. This observation highlights the need for vigilant monitoring and timely therapeutic adjustments in patients exhibiting sub-optimal CRP trajectories. Similar associations between early CRP kinetics and patient outcomes have been noted in other studies, though most rely on CRP ratio calculations rather than more dynamic and visually intuitive methods of assessing treatment response [120,123,126].

Analyses in this chapter had several limitations that should be considered. The analysis of antibiotic prescribing patterns was limited to antibiotics prescribed in hospital, including those prescribed at discharge, with durations estimated from scheduled prescription orders. This analysis covered the first 14 days following the index blood culture collection, with prescription changes evaluated on a half-day or daily basis. This scope therefore does not include community antibiotic prescriptions prior to inpatient admission and may inaccurately reflect the duration of antibiotic use after discharge. Additionally, CRP has a relatively long half-life (~19h) [125,143,144], which delays its response to therapeutic interventions. This may make it difficult to fully capture the immediate effects of antibiotic changes on CRP changes, potentially limiting its utility in reflecting real-time treatment efficacy. Future research could also explore additional

biomarkers with faster response times to provide a more immediate assessment of therapeutic impact. Integrating other biomarkers, such as PCT, might provide a more comprehensive assessment of treatment response and outcomes. The goal would be to develop a data-driven metric to evaluate whether a patient is improving. This metric could combine various biomarkers, vital signs, clinical findings, and underlying factors like demographics, comorbidities, and the clinical syndrome. Such an integrated approach could offer a more nuanced and immediate picture of a patient's response to treatment.

Similar to the analysis in **Chapter 4**, I used multivariable logistic regression to examine the association between 4-30 day all-cause mortality with mean centile change per day between days 1-4. This approach facilitated the calculation of ROC and AUROC. Although survival analysis is generally preferable for time-to-event data due to its ability to appropriately handle censored data and avoid assumptions about individuals lost to follow-up, the minimal proportion of individuals lacking information 30 days post-index blood culture collection (1.9% [243/13,130]) suggests that the choice of logistic regression is unlikely to have significantly impacted the findings.

The study was retrospective and relied on existing medical records from one hospital group. Prospective studies with standardised protocols are needed to validate and extend these findings.

## 5.5 Conclusion

This study provides some insights into the dynamics of antibiotic prescribing patterns, CRP centile changes, and patient outcomes in the management of suspected BSI. The reliance on broad-spectrum antibiotics followed by targeted de-escalation in Gram-positive infections reflects a balanced approach to empirical therapy and personalised treatment. However, no significant de-escalation was observed in Gram-negative infections and polymicrobial infections. This highlights the complexity of these infections and emphasises the potential for patient response reference markers to aid in clinical decision-making. Although my analysis showed that changes in CRP centiles appeared to have modest impact in guiding clinical interventions, early changes were strongly associated with subsequent mortality risk. Future research should focus on integrating CRP monitoring with other response markers to refine and optimise recommendations for escalation/de-escalation. Such an integrated approach might be able to enhance patient outcomes while addressing the broader challenges of antimicrobial resistance. By leveraging insights gained from biomarker dynamics, it may be possible to move towards more personalised, effective, and judicious management of BSI, ultimately improving patient care and public health.

## 5.6 Supplementary Figures

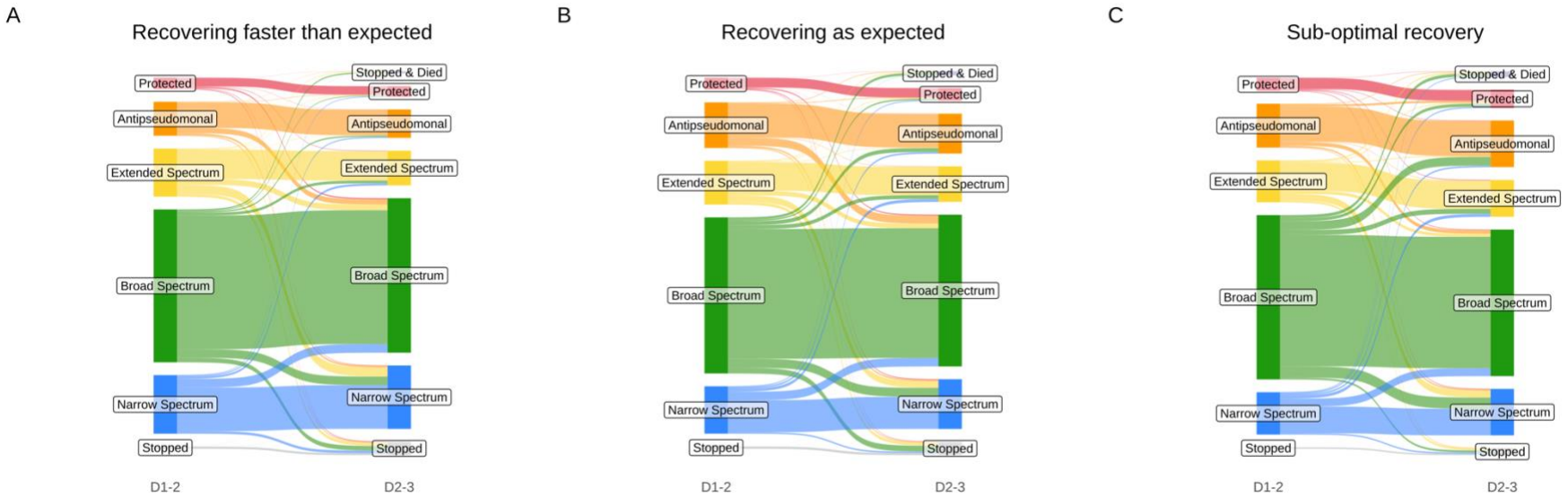


**Figure S5.1 Distribution of change in antibiotic groups from day 1 to day 2 following different CRP centile changes from day 0 to day 1.**
Centile changes of <−15, −15 to 15 and >15 were considered as recovering faster than expected, recovering as expected and sub-optimal recovery, respectively.

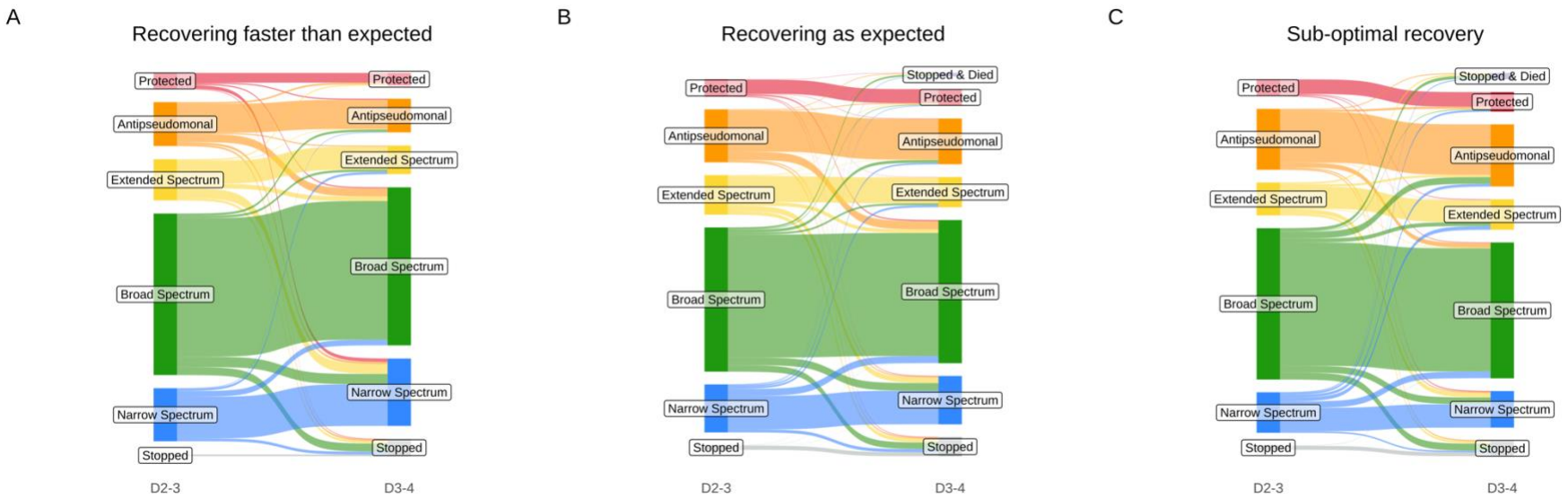


**Figure S5.2 Distribution of change in antibiotic groups from day 2 to day 3 following different CRP centile changes from day 1 to day 2.**

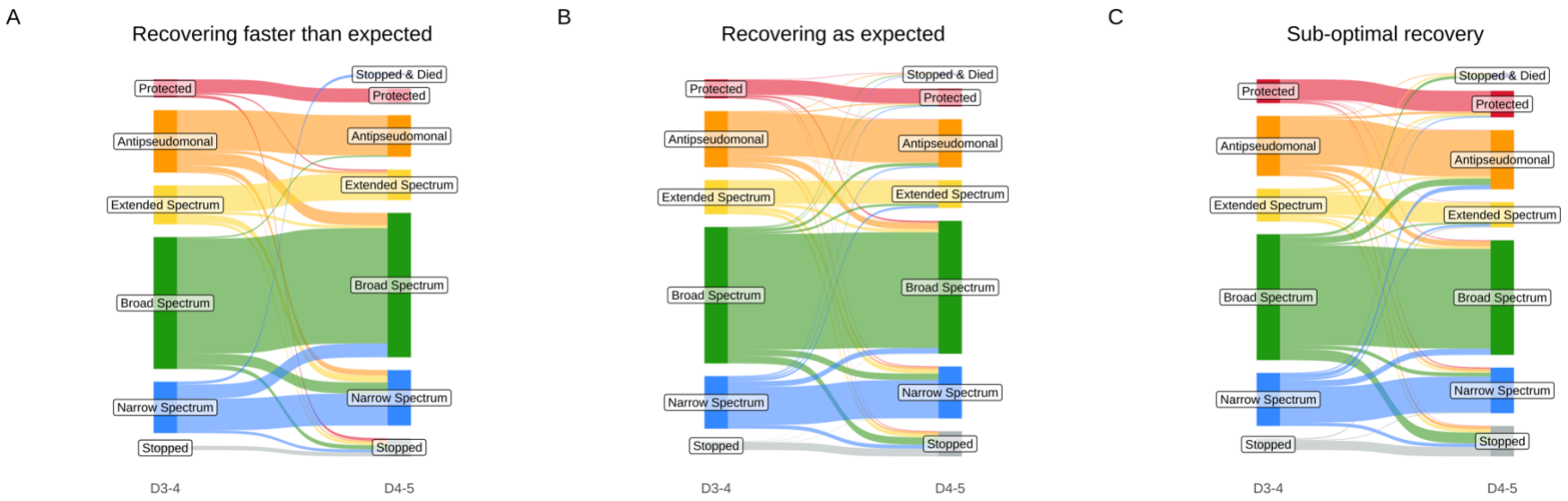


**Figure S5.3 Distribution of change in antibiotic groups from day 3 to day 4 following different CRP centile changes from day 2 to day 3.**

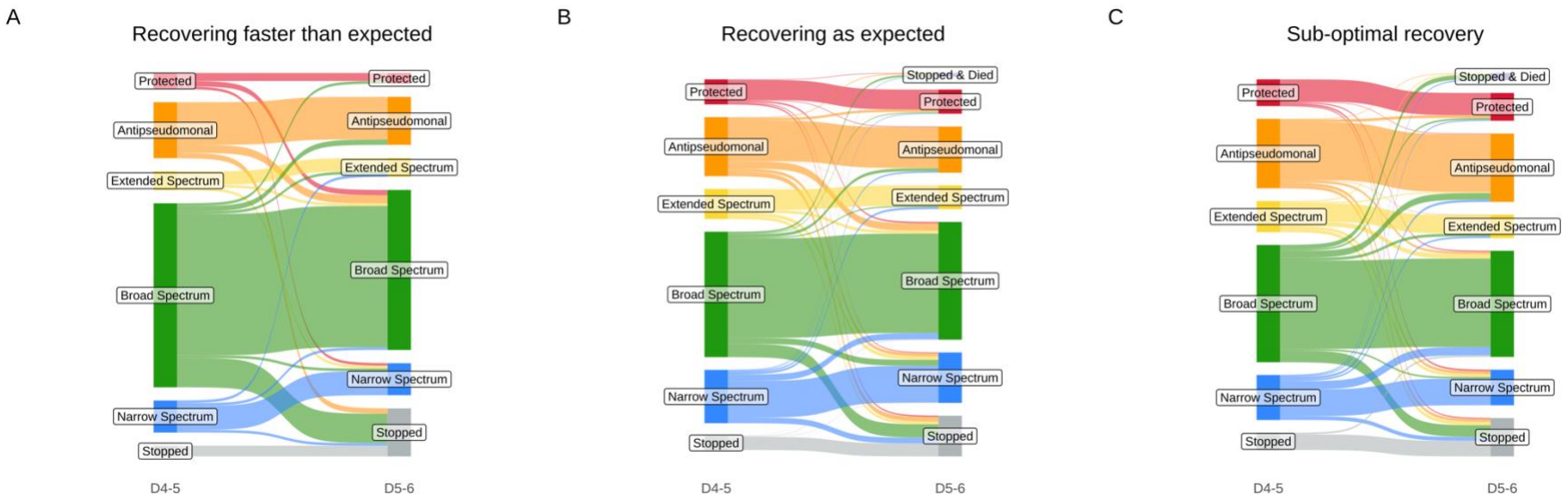


**Figure S5.4 Distribution of change in antibiotic groups from day 4 to day 5 following different CRP centile changes from day 3 to day 4.**

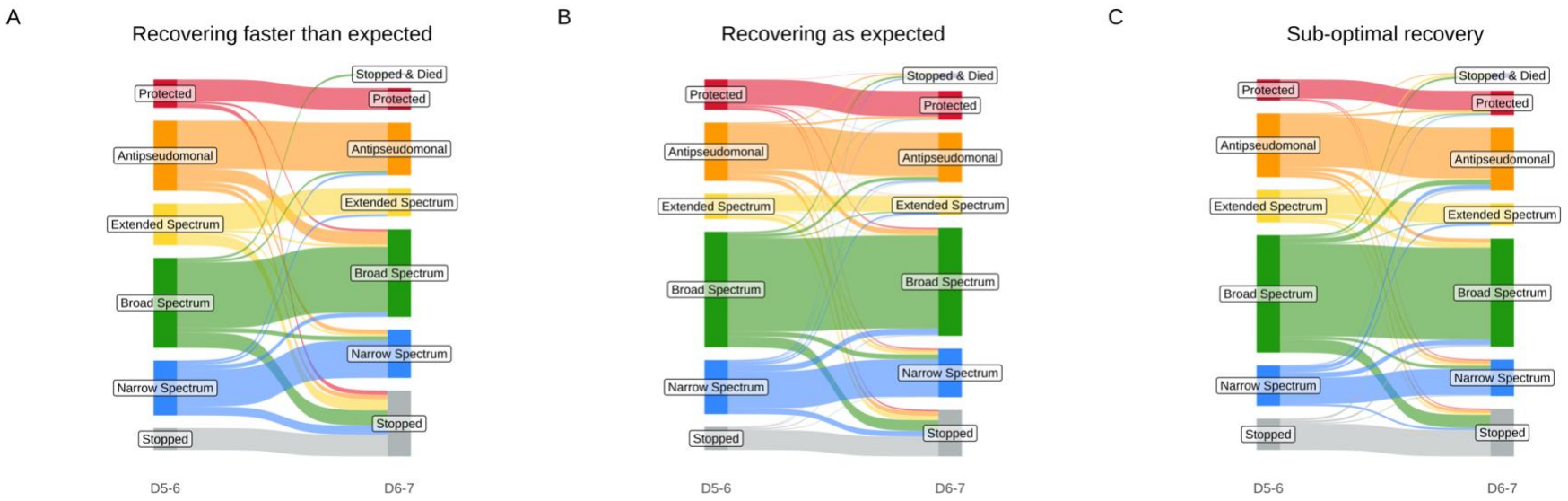


**Figure S5.5 Distribution of change in antibiotic groups from day 5 to day 6 following different CRP centile changes from day 4 to day 5.**

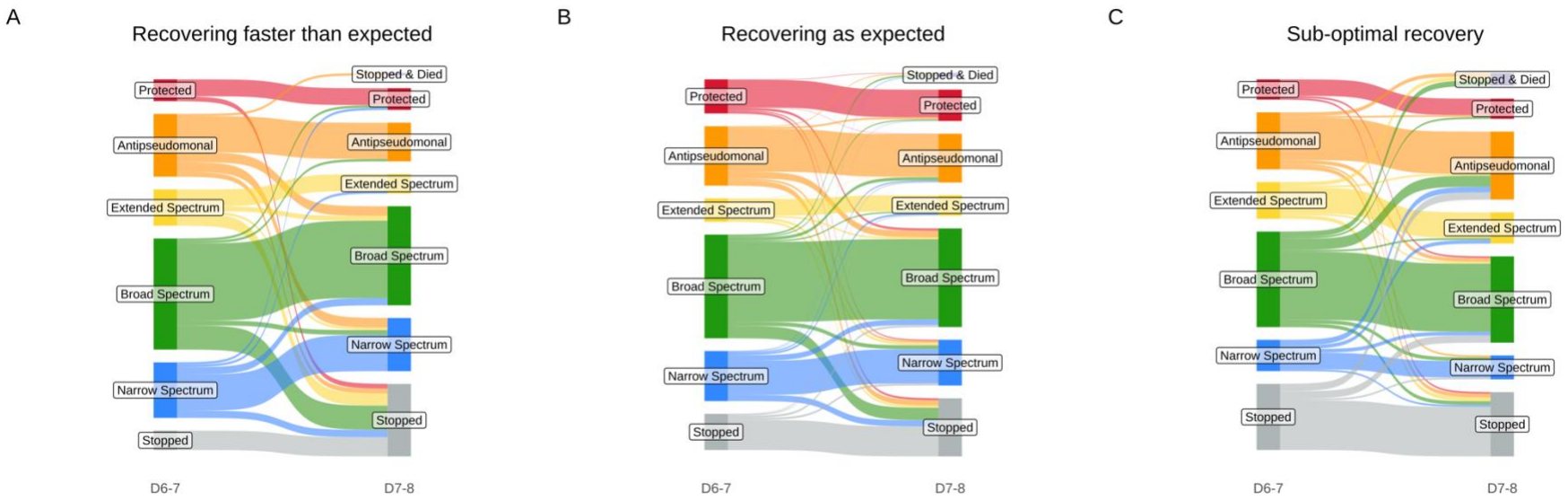


**Figure S5.6 Distribution of change in antibiotic groups from day 6 to day 7 following different CRP centile changes from day 5 to day 6.**

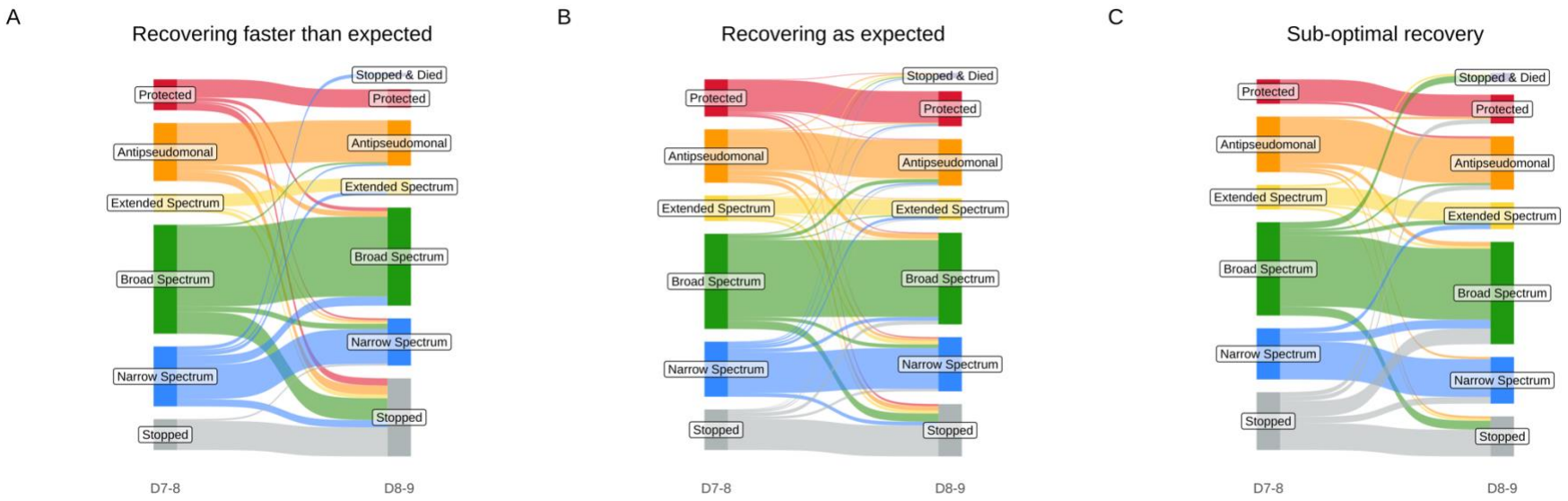


**Figure S5.7 Distribution of change in antibiotic groups from day 7 to day 8 following different CRP centile changes from day 6 to day 7.**

# Chapter 6 Conclusions and future work

The transformative role of EHRs in healthcare delivery and research has already impacted infection management and has huge potential to improve it further [199]. Integration of diverse clinical data combined with high precision data analytics will likely enable more effective and personalised patient care. This thesis explored how EHR data can be leveraged to refine antimicrobial prescribing practices, monitor infection response trajectories, and ultimately improve patient outcomes. Through the chapters presented, the research collectively underscores the potential and challenges of using EHRs to improve infection management.

In my first results Chapter, I evaluated the impact of introducing new guidelines for vancomycin dosing at OUH using EHR to determine their effectiveness in real-world settings. Despite high compliance rates with the new guideline, the proportion of drug levels within the target therapeutic range remained suboptimal. This chapter demonstrated the intrinsic complexity of antimicrobial stewardship — even with high adherence to guidelines, optimal therapeutic drug levels were not consistently achieved, with most patients under-dosed, suggesting that current guidelines may need revision and need to account for other patient factors, including age. In fact, standard dosing guidelines are often developed from clinical trials based on selected patient populations, making specific patient subgroups potentially under-represented [200]. Changing demographics, such as an ageing population and rising obesity rates, can further complicate dosing regimens. My analysis revealed that blood drug levels were independently lower and more likely to be below target in younger patients, those

without morbidities and those with normal renal function. Such findings resonate with the broader literature showing limited achievement of therapeutic targets, indicating the challenges of standardising antibiotic dosing regimens [30,86].

By applying multivariable regression models on EHR-derived pharmacokinetic data, I proposed personalised dosing recommendations, accounting for patient-specific factors such as age, weight, and renal function. The updated recommendations aimed to narrow the gap between compliance and optimal drug levels, and a validation using published pharmacokinetic models supported the proposed adjustments, with estimated $AUC_{24h}$/MIC ratios achieving the target range for nearly all patient subgroups. This chapter demonstrated the value of using real-world pharmacokinetic data collected from EHR systems to inform and improve antimicrobial prescribing practices. By leveraging extensive patient data, clinicians can make more informed adjustments to dosing regimens, thus potentially enhancing therapeutic effectiveness and minimising the risks of nephrotoxicity and antimicrobial resistance.

Subsequent chapters delve into the heterogeneity of patients' clinical responses to suspected BSI and the underlying dynamic patterns of response. **Chapter 3** used routinely collected EHR data to characterise the temporal dynamics of several clinical parameters, including CRP, WBC counts, heart rate, respiratory rate, and temperature. The findings highlighted significant heterogeneity in these response trajectories, driven at least in part by pathogen types, sources of infection, and individual patient characteristics. These variations provide critical insights into the differential manifestations of infections and underscore the need for tailored therapeutic

strategies. They also explain why definitively answering questions such as ‘is my patient recovering as expected’ or ‘are they responding appropriately to antibiotics’ is so challenging. Clinicians may instinctively ‘integrate over’ all this individual variation when making assessments of patients’ responses, however how well this is done may vary from patient to patient, and context to context.

As an example of the heterogeneity seen, infections caused by *Streptococcus pneumoniae* and beta-haemolytic Streptococci exhibited pronounced acute responses, whereas polymicrobial and *Candida* infections were associated with slower recovery trajectories. These nuances facilitate a better understanding of infection progression and potentially enable clinicians to make informed decisions based on specific causative agents. This chapter’s findings highlight the complexity of the host response to BSI and the value of integrating comprehensive databases like EHRs in clinical epidemiological research. Identifying distinct infection response patterns through these databases could be pivotal in developing algorithms for early identification and targeted management of infections.

In **Chapter 4**, my focus shifted to developing reference tools to standardise the assessment of clinical responses. By applying latent class mixed models, five distinct CRP response trajectory subgroups were identified among patients with suspected BSI. The majority of episodes exhibited a peak in CRP levels on days 1 or 2, reflecting a “normal” response to effective antimicrobial treatment. Conversely, a smaller proportion of cases demonstrated delayed or low responses, or slow recovery. These findings enabled the construction of centile reference charts based on the standard

responders, providing a visual and quantitative tool for clinicians to benchmark patient recovery against expected clinical response trajectories (**Figure** 4.10).

The implementation of these centile charts could potentially aid infection management. They could, at least in theory, provide a means of early detection of deviations from standard recovery patterns, facilitating timely escalation, de-escalation or adjustment of duration of antimicrobial therapy in patients with suspected BSI, especially when blood cultures are negative or results are not yet available (**Figure** 4.10). Traditional biomarker-guided antimicrobial treatment protocols have often relied on absolute biomarker values or arbitrary change thresholds, which might account for poor clinician compliance in some clinical trials examining biomarker-guided antibiotic stewardship (**Table** 4.1) [164,166,169,175]. Compared to using absolute values or calculating CRP ratios recommended by existing studies [120,123,126], visually tracking CRP response trajectories using centile charts provides a dynamic and intuitive approach to incorporating evidence-based benchmarking into daily clinical decision-making, and this method is applicable to a wide range of clinical parameters. My analysis of individual patients' CRP changes against the population-level centile showed that most patients tended to track along the centile curves during the recovery stage, with only a minority deteriorating relative to what was expected, demonstrating the potential utility of the centile chart.

**Chapter 5** provided a detailed investigation into the interplay between empirical antibiotic prescribing patterns, CRP dynamics, and patient outcomes. Empirical broad-spectrum antibiotics are usually used in the early stages of suspected infection

because of the high risks of adverse outcomes associated with under-treatment. However, de-escalating to narrower-spectrum agents should be considered as soon as pathogen-specific susceptibilities are identified [15]. The analysis of current antibiotic prescribing patterns for suspected BSI demonstrated a notable shift towards narrower-spectrum antibiotics within the initial treatment period for Gram-positive infections, aligning with current stewardship guidelines advocating for de-escalation to prevent the development of resistance and mitigate adverse drug effects [4]. However, there was a much slower decline in the use of broad-spectrum antibiotics for Gram-negative infections during the 14-day treatment period. Similar predominant use of broad-spectrum antibiotics was also observed for polymicrobial infections. This likely reflects the high resistance potential associated with Gram-negative pathogens and treatment complexities in polymicrobial infections (for example, where the isolated pathogen may only be part of an intra-abdominal polymicrobial infection), emphasising the need for patient response reference markers to aid in effective antibiotic prescribing decisions.

The analysis in **Chapter 5** sought not only to map current prescribing trends, but also to explore the possibility of using the centile chart-based approach developed in **Chapter 4** to dynamically optimise antibiotic use and track treatment response. The analysis revealed that CRP centile changes were associated with subsequent antibiotic decisions, as were prescribing decisions associated with subsequent centile changes, but that the effects were modest. Patients showing sub-optimal recovery, defined by a CRP centile increase exceeding 15 percentiles, were more likely to have their antibiotics escalated. Conversely, a CRP centile decrease of more than 15 percentiles, reflecting a faster-than-expected recovery, often led to the de-escalation or cessation of antibiotics.

However, although these associations were evident at a population level, they might not be observed at individual level. Some patients experienced antibiotic escalation despite improving CRP values, and vice versa.

The impact of various prescribing decisions on subsequent centile changes was more complex and challenging to estimate. Major limitations of this analysis include the time lag in changes in CRP levels caused by its prolonged half-life potentially affecting associations and the increased frequency of CRP measurements in deteriorating patients or lack of repeat CRP testing in patients who stopped antibiotics and doing well. Prospective studies with standardised protocols may be needed to validate the effectiveness of the centile reference charts in tracking patients' responses to infection.

Analyses in this chapter also established a strong association between early CRP centile changes and subsequent mortality. Faster-than-expected recovery trajectories over the first 4 days were consistently linked to higher subsequent survival probabilities, while suboptimal early recovery correlated with increased mortality risk. These findings highlight the prognostic value of early CRP centile changes and emphasise the need for monitoring and timely therapeutic modifications in patients exhibiting sub-optimal CRP trajectories. However, it is important to acknowledge that these early CRP centile changes did not significantly add to the predictive ability over baseline characteristics alone. Notably, the baseline characteristics demonstrated a high AUC of 0.86 for predicting subsequent mortality, suggesting that much of the predictive power is explainable by baseline factors. What remains particularly interesting is understanding how the inclusion of CRP centiles might alter the effects of baseline factors on

outcomes. This represents an intriguing question for future research, as it could potentially reveal new insights into the dynamics of disease progression and treatment response that are not captured by baseline characteristics alone. Exploring this could lead to more refined predictive models that integrate both static and dynamic patient information.

Despite the demonstrated potential, the use of EHR data in clinical research is not without its challenges. Data completeness and consistency are critical concerns that can impact the reliability of the findings. In the context of this thesis, serial measurements of biomarkers like CRP are less frequently obtained in patients who are recovering well, leading to potential biases in the interpretation of response trajectories. Additionally, potentially informative information on patient recoveries documented by clinicians, nurses and other health professionals may be present in unstructured text, which was not included in my analyses. This is challenging to retrieve and code; for example, it may require manual annotation, although emerging large language models may make such text or derived features available for analysis in future, providing resource, governance and privacy concerns can be addressed.

Another notable limitation is the complexity involved in integrating disparate data sources within EHR. Linking prescription data with laboratory test results requires meticulous data management and correct definitions based on a good understanding of clinical practice, an endeavour that is both time-consuming and challenging. Standardising EHR data extraction and providing professional guidance on processing in

a clinical context are essential for enhancing the reproducibility and generalisability of findings.

Moreover, the generalisability of findings from single-centre studies, such as those conducted in this thesis, may be limited. Differences in patient demographics, clinical practices, and healthcare infrastructure across institutions necessitate replication of studies in diverse settings to validate the applicability of the findings more broadly. Addressing these challenges requires concerted efforts to develop robust methodologies and establish standardised protocols for the use of EHR data and external validation in clinical research.

The findings from this thesis open several promising avenues for future research and practical implementation. A key next step involves the clinical validation of the updated vancomycin dosing recommendations and centile reference charts in diverse patient populations and clinical settings. This could involve implementing the updated recommendations and centile charts in a real-world setting and monitoring their impact on clinical outcomes and healthcare resource utilisation, similar to the methodology used in this thesis. Studies would need to both understand the impact of following any guidance on patient outcomes, and also the interplay between the tools and the clinicians who use them. Implementing these tools within EHR systems could facilitate their integration into routine clinical workflows, potentially providing real-time decision support and promoting personalised patient care. However, understanding how they influence clinician behaviour is key to obtaining successful impact.

On a broader scale, the integration of EHR-based analytics with other emerging technologies offers exciting prospects. For instance, combining clinical data with genomic, proteomic, and microbiome data could offer an even more comprehensive understanding of infection pathogenesis and treatment responses. Such multidisciplinary approaches may identify novel biomarkers and potential therapeutic targets, further refining and personalising infection management strategies.

Artificial intelligence and machine learning algorithms also hold significant potential in this context. Advanced predictive models can be developed to identify patients at high risk of infection, predict antimicrobial resistance patterns, and optimise treatment regimens based on real-time data inputs. The integration of machine learning algorithms with EHR data could potentially transform infection management from a reactive to a proactive practice, enabling early interventions and preventing adverse outcomes. To underpin this, substantial data, compute and expertise are required, as well as clear systems for evaluating and monitoring the impact of these innovations, as well as engagement to ensure public and healthcare worker support.

Leveraging real-world data to conduct health services research on the impact of EHR-integrated decision support tools on clinical outcomes and healthcare resource utilisation is another important area. Such research can provide valuable insights into the cost-effectiveness and scalability of these innovations, informing policy decisions and guiding the allocation of healthcare resources. Furthermore, there is considerable scope for developing educational initiatives to enhance the clinical adoption of evidence-based tools derived from EHR analytics. Training programs that equip

healthcare providers with the skills to effectively interpret and apply data-driven insights in clinical practice are essential. This will ensure guideline adherence and the optimal utilisation of EHR-based decision support tools.

A central goal of effective infection management is to prescribe antimicrobials with an appropriate spectrum to combat the infecting pathogen and with optimal dosing regimens that are adjusted to specific patient subgroups. This thesis highlights the transformative potential of leveraging EHR to enhance these objectives. Specifically, by assessing and optimising the vancomycin dosing guidelines at OUH, my study provided an example of how real-world pharmacokinetics based on EHR data can be used to suggest improved dosing regimens. Using large-scale EHR data, I have shown that response trajectories of clinical parameters are associated with both specific blood culture results and infection sources in individuals with suspected BSI. The expected response can be summarised using centile reference charts, potentially offering clinicians a valuable tool to evaluate individual patients' clinical responses and adjust treatment decisions appropriately in the absence of definitive microbiological diagnoses.

The continuing evolution of EHR technologies and analytic capabilities promises to mitigate some of the current limitations of data completeness and consistency in EHR studies, thereby increasing the reliability of clinical insights derived from EHR data. Rigorous validation and robust data governance will be crucial in realising the full potential of EHRs in improving healthcare outcomes. The integration of EHR-based decision support tools into routine clinical practice represents a significant potential

future advancement in infection management. As the healthcare landscape evolves, the integration of EHR, advanced analytics, and personalised medicine principles will play a pivotal role in shaping the future of infection management and improving patient care on a global scale.

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