Analysis of the Long-Term Outcomes of β -Lactam Allergies with Recommendations for Improving Erroneous β -Lactam Allergy Management using Mixed Methods

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Matthew Gray, PharmD, PhD

University of Pittsburgh, 2023

Allergies to β-Lactam (BL) antimicrobials are the most commonly reported medication allergy. Patients with documented BL allergies are more likely to receive second or third-line antimicrobials, and this altered antibiotic selection can result in clinical detriment and higher healthcare utilization. Most BL allergies are reported in error, and many patients with documented BL allergies can tolerate BL products. There has been an increase in understanding of the outcomes associated with BL allergies and methods for erroneous BL allergy delabeling, but gaps in the literature remain that may be hindering efforts to reduce the harm caused by erroneous BL allergies. The findings of this dissertation address critical gaps in literature by using a mixed methods approach to improve the understanding of BL evaluation processes and long-term clinical outcomes.

The first study used a qualitative study design to interview front-line clinicians on their perspectives and attitudes when evaluating the legitimacy of BL allergies. Through inductive and deductive analysis, interventions targeted at technology improvements and expanding the role of pharmacists in BL allergy evaluation were recommended. The second study used a retrospective cohort study design and clustered longitudinal analysis to examine the long-term outcomes of patients with BL allergies. Over 12 years of follow-up, patients with BL allergies experienced significantly higher rates of resistant infections. This finding supports delabeling efforts because of the substantial long-term detriment associated with BL allergy labeling. The third study used natural-language processing to develop a pipeline to identify clinical note segments indicating

instances where patients have previously tolerated BL products to promote the usage of these previously tolerated products despite documented allergies that can be used as a proof-of-concept for implementation by health systems. A survey indicated that confidence in using BL products increased when presented with information indicating previous BL tolerance.

The findings of this dissertation address critical gaps in the understanding of BL allergies and produce a tool to improve future allergy evaluation efforts. Implementation of tools to improve allergy documentation and enable informed allergy evaluation may empower clinicians to reduce the rate of erroneously documented BL allergies and improve the use of first-line BL antimicrobials.

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1.0 INTRODUCTION

β-lactam (BL) antibiotics are the most commonly used class of antibiotics in the world[1]. However, BL antibiotics are also the most commonly reported drug allergy in the United States, with between 5-13% of the population reporting an allergy to at least one BL antibiotic.[2-5] Despite the predominance of BL allergy labels, an overwhelming majority of reported BL allergies do not represent true allergic reactions[6]. Roughly 95% of patients with a reported BL allergy have been shown to not truly be allergic following skin testing, and upwards of 98% of BL allergies can be determined to be erroneous through gathering a thorough allergy history followed by an oral amoxicillin challenge.[7-9] Regardless of the legitimacy of a reported BL allergy, the presence of a BL allergy in a patient's medical record is associated with adverse outcomes including increased rates of resistant infections, higher medication costs, and increased all-cause mortality.[10-12]

Since alternative antibiotics are often available and there are too few allergists to meet the demand for challenging BL allergies, the legitimacy of most BL allergies is never challenged[13]. There has been increased emphasis on addressing erroneous BL allergies, but there remains significant areas for improvement.[14,15] The risks involved in challenging BL allergies are multifaceted and vary widely, leaving clinicians uncertain of appropriate courses of action, as well as to low rates in sustaining de-labeling efforts.[16,17] Tools such as risk stratification, improved allergy evaluation algorithms, and clinical decision support have been suggested as potential areas to help improve the rate of BL de-labeling, but there is a lack of consensus on the ideal method.[18,19] A mixed-methods approach employing a combination of improved understanding and education on the risks of BL allergy labeling, theory-informed interventions

that overcome current barriers in clinical practice, and computer-assisted targeted allergy review is needed to produce sustainable results in de-labeling erroneous BL allergies.

1.1 β-lactam Antibiotic Class Background & Allergy History

The accidental discovery of penicillin by Alexander Fleming in 1929 was one of the most influential events in modern medicine.[20] This discovery was followed in 1948 by the isolation of the first cephalosporin, which is a BL-based antibiotic with a fused dihydrothiazine ring and altered side chains which confer altered antimicrobial effects and resistance to degradation. Monobactams and carbapenems were then found through screening methods in the 1980s, and these products have more stable steric configurations which help overcome growing antibiotic resistance. The initial success of penicillin G, along with the later discoveries of more sophisticated β-lactam classes including cephalosporins and carbapenems have led β-lactam antibiotics to being the most widely used class of antibiotics worldwide.[1]

BL antibiotics rely on a β-lactam ring to inhibit the cross-linkage of peptidoglycan, which causes death of both gram-positive and gram-negative bacteria through increased susceptibility to cell lysis.[21] However, a major metabolite of the metabolism of BL products is penicillinoic acid, which can covalently link to lysine residues of proteins and cause immediate and severe hypersensitivity reactions.[22] T-cell mediated hypersensitivity is also possible which can cause an unpredictable range of both immediate and delayed reactions ranging from anaphylaxis or life-threatening skin reactions to minor skin rashes.[23] Historically, there was a concern for cross-reactivity of allergies between BL classes, although this concern has more recently been shown to be greatly overestimated.[24-26] The high historical use of BL antibiotics, along with the

overestimation of the severity of cross-class reactivity have led to BLs being the most commonly reported drug allergy in the United States, with between 5-13% of the population reporting a BL allergy nationally.[2,5,27,28]

1.2 'Penicillin' Allergies and BL Allergies

Figure 1-1 shows the classifications of the different medications within the full β-lactam class of antimicrobials.[29] Although the terms 'penicillin allergy' and 'β-lactam allergy' are used inconsistently by both patients healthcare professionals in allergy documentation, the terms refer to different groupings of medications, with 'β-lactam allergy' technically subsuming the smaller class of penicillins.[30] Research on the topic also uses both phrases, and the definitions used between studies are not well standardized. Among the 67 articles reviewed through a PubMed search on the topic (Section 2), 57 primarily used the phrase 'penicillin allergy' and 10 primarily used 'β-lactam allergy'. For the remainder of this dissertation, the phrase 'β-lactam allergy' (BL) will be used unless otherwise noted because we aim to broadly study the full class of medications, including penicillins, cephalosporins, carbapenems, and aztreonam. Because of this, some of our methods and results may not be able to be directly compared to studies which used narrower definitions, such as penicillin allergies, if the study did exclude non-penicillin class antimicrobials.

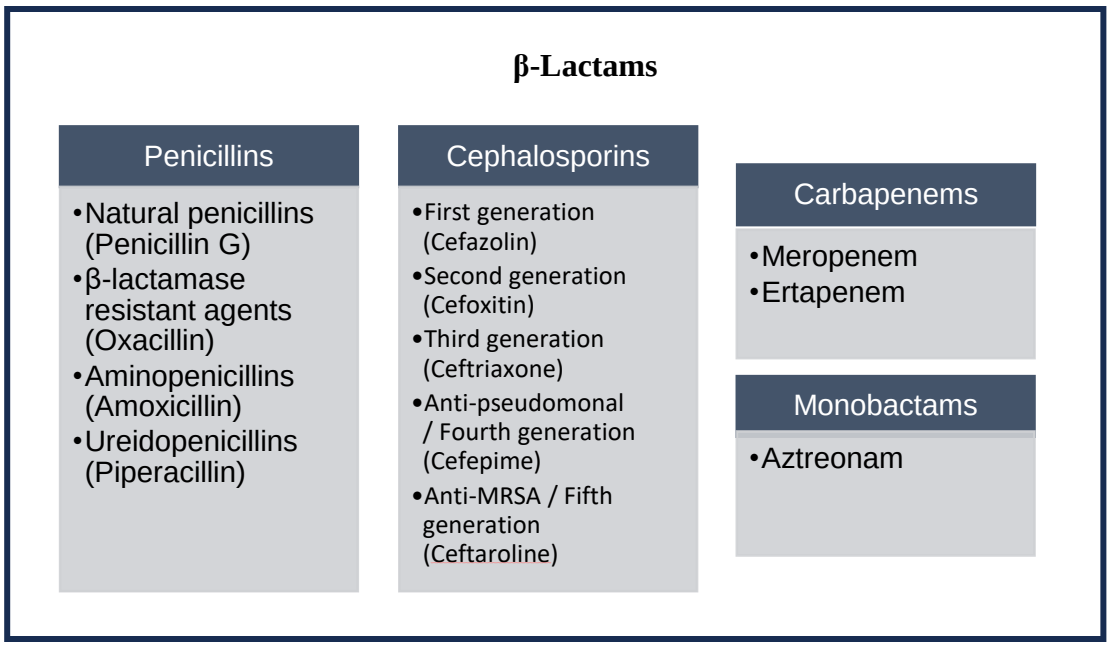


Figure 1-1: β-Lactam Allergy Classifications

1.3 The Inaccuracy of BL Allergy Labels

Although the frequency with which BL allergies are listed in electronic health records (EHR) is high, the majority of listed allergies do not correspond to true hypersensitivity reactions. Less than 10% of listed BL allergies are confirmed when challenged through skin testing or oral challenges.[7,31] Studies that have challenged patients labeled as BL-allergic through test-doses found that only 4% of patients experienced true hypersensitivity reactions, with the overwhelming majority of reactions being mild in nature.[32] The implementation of guidelines which target BL-allergic patients with test doses led to a large increase in BL-allergic patients receiving BLs, but did not increase the overall rate of hypersensitivity reactions compared to baseline.[33] The challenging of allergies through skin testing has been found to be overwhelmingly safe and sustainable, with the rate of re-emergence of BL allergies following successful de-labeling to be no higher than the overall incidence in the population.[34] Despite overwhelming evidence that

most BL allergies are erroneous in nature and de-labeling is a safe and effective process, most allergies are never evaluated, which is indicative of a systematic failure in allergy documentation and evaluation.[18,35]

The cause of erroneous BL allergy labels is multi-factorial, and some commonly reported causes are summarized in Table 1-1. A major factor is the lack or reliable allergy history information, with more than half of patients reporting a BL allergy not being able to provide reliable allergy histories.[36,37] There is also significant misunderstanding about what constitutes a true drug hypersensitivity reaction, leading to a large number of predictable adverse drug reactions being listed as allergies in patient records.[13,38] The current process utilized by most EHRs for allergy documentation, that usually records allergy information as free-text, and may be verbatim from the patient, is a large source of this ambiguity between intolerances, adverse drug reactions, and true hypersensitivities since patients are not experienced in distinguishing between the subtleties in these terms.[38-40] Moreover, up to 75% of BL allergy labels are acquired in childhood, causing confusion on the true allergy status of a patient once reaching adulthood.[41] The acquisition of an allergy label as a child may be a significant driver in the notoriously unreliable allergy history provided by patients, since even highly specialized allergists have been unable to reliably confirm BL allergies through medical history alone.[42] Additionally, it can be difficult to convince patients that they are not truly allergic to a BL and patients may continue to report the allergy and avoid BL-containing products despite de-labeling efforts.[42,43] Ultimately, a lack of scrutiny on allergy documentation, often occurring during childhood, has caused an overwhelming majority of BL allergy labels to be inaccurate, and the same limitations in documentation have stymied delabeling efforts through the lack of reliable clinical allergy history information.

Table 1-1: Causes of Erroneous β-Lactam Allergy Labels

• **Confusion between true hypersensitivity reaction and adverse drug reactions or intolerances (e.g. anaphylaxis vs. diarrhea)**
• **Inertia and persistence of existent inaccurate information**
• **Lack of patient knowledge about their own allergy status ("happened as a child")**
• **Technology limitations in allergy entry or removal process**
• **Desire for a patient to avoid β-lactam products (unwilling to be convinced otherwise)**
• **Documentation of a disease-related symptom following antibiotic administration as a potential allergy**

Adapted from: Wilcox et al. (2019).[16]

1.4 The Clinical and Economic Detriment of BL Allergy Labels

Regardless of the validity of a BL allergy label, the presence of being labeled as BL 'allergic' is sufficient to alter the standard course of care related to antimicrobial prescribing practices and cause clinical detriment.[44] An allergy to penicillin significantly alters the ability to prescribe BL-containing derivatives due to a theoretical cross-reactivity between BL classes.[45] Although there has been an increase in the understanding of side-chain structures and the true cross-reactivity rate being substantially lower than initially estimated, the lack of reliable allergy history information limits the ability of clinicians to utilize knowledge of which BL products have cross-allergic side-chains and safely prescribe cephalosporins in patients with a BL allergy label.[46] The avoidance of BL products due to a BL allergy label causes increased reliance on second and third-line antibiotics which incur higher rates of antibiotic resistance and toxicity.[47]

BL allergy labels have been associated with clinical detriment across a large number of clinical settings and scenarios. Penicillin allergy labels have been associated with a 23% increase in Cdiff, 14% increase in MRSA, and a 30% in VRE compared to inpatient controls without the allergy label.[35] Pregnant

women with penicillin allergies have shown a 10% increase in cesarean section rates and higher rates of adverse drug reactions.[48] Surgical prophylaxis guidelines rely heavily on the use of BL derivatives, and the utilization of second-line perioperative agents due to a penicillin allergy are associated with a 50% increase in surgical site infections.[49] Hospitalized patients with penicillin allergies show increases in total hospital days and higher rates of ICU admission.[50,51] Pediatric patients with penicillin allergies show longer lengths of stay, and an increased reliance on second-line antimicrobial agents secondary to penicillin allergies. Similar effects have also been demonstrated across veteran, outpatient, and emergency department settings.[52-55] In a general population of over 2.7 million patients across the United Kingdom, a penicillin allergy label was associated with an 8% increased risk of 1-year all-cause mortality.[56]

Patients with BL allergies are also more costly than non-allergic counterparts, and can lead to unnecessary economic consequences, particularly when applied to a system-level perspective. The antimicrobial regimens used in BL-allergic inpatient encounters incur up to $600 higher direct costs through both increased product cost and increased total antimicrobial utilization.[57-60] However, the aforementioned clinical consequences of BL allergy labeling also increases healthcare utilization more broadly such as increased length of stay and readmission risk, and the total increase in costs associated with a BL allergy label has been estimated to be between $1145 and $4254 per inpatient encounter.[60] When extrapolated to larger populations, the estimated cost of BL allergies is staggering. The broad implementation of a standardized perioperative penicillin allergy evaluation practice prior to knee and hip replacement alone could theoretically provide a system-level cost savings of $1.18 billion over a 20-year span.[61]

1.5 The Lack of Long-term Clinical Studies

The majority of studies analyzing the effect of BL allergies on clinical outcomes focus on the immediate needs of treatment, such as surgical prophylaxis, or initial management of suspected infection in the emergency department.[18] However, a BL allergy label is often a life-long, wide-reaching risk factor with historically low levels of successful and sustained de-labeling.[17] Instituting wide-reaching de-labeling efforts can successfully reduce the risk of using second-line broad-spectrum antibiotics and increase utilization of more preferred BL-class antibiotics.[32,62,63] However, there has not been much emphasis on examining the long-term benefit associated with BL-allergy removal, and the lack of understanding on these long-term effects may be limiting the uptake of sustained de-labelling efforts due to an inaccurate belief that BL-allergy labels are a singular and immediate obstacle in treatment.

There is a lack of long-term studies related to the clinical outcomes associated with penicillin allergy labels relative to the large number of studies analyzing singular hospital encounters or cohorts with under 5 years of follow-up.[64] One major cohort study followed patients over 20 years, and found a 14% increased risk of mortality, a 69% increase in the hazards of infection with methicillin-resistant *Staphylococcus aureus* (MRSA), and a 26% increase in the hazards of infection with *Clostridium difficile* (CDiff.) in BL-allergic patients compared to matched non-allergic counterparts.[65,66] In a mediation analysis from the same cohort study, between 35-55% of the increase in infections with MRSA and CDiff that was observed was attributable to altered BL utilization secondary to BL allergies.[66] However, this study is subject to unmeasured confounding, was limited to a UK population, and treated BL allergy status as a static variable which was not re-evaluated during the follow-up period. There is a need for an increased understanding in studies which analyze the long-term effects of BL allergies on clinical outcomes while

minimizing confounding since long-term models more closely mirror the true risk of a life-long BL allergy status compared to short-term evaluations.[25]

1.6 Increased Emphasis on Allergy Evaluation and Opportunities for Pharmacists

The increased understanding of the large economic and clinical consequences of spurious BL allergy labeling has led to a recent push in efforts to recognize and delabel erroneous BL allergies. The benefit to penicillin allergy evaluation and de-labeling has been increasingly recognized and encouraged by public health advocates and professional organizations, including: The Centers for Disease Control and Prevention, the Infectious Disease Society of America, and the Society for Healthcare Epidemiology of America.[14,18,67] This increased emphasis and recognition has led to a large increase in penicillin allergy evaluation methods and resources which can be tailored to specific populations and clinical settings to maximize their effectiveness.[68] Additionally, because penicillin allergies are a wide-reaching problem that are often encountered in a variety of settings, BL allergy evaluation has been identified as a key multidisciplinary opportunity where pharmacists in particular can act as a leader and subject matter expert.[68]

Clinical pharmacists have been shown to have the highest level of understanding on the topic of penicillin allergy histories and evaluation.[69] Pharmacists have been shown to be able to accurately collect patient medication histories and evaluate the legitimacy of penicillin allergies.[70,71] Pharmacists also have the knowledge and training to appropriately refer patients for additional testing or recommend the direct challenge of a suspected erroneous allergy with a high level of accuracy.[72,73] Pharmacist-led penicillin allergy de-labeling programs can reduce the use of restricted antibiotics and total antibiotic costs. [74-76] Given

the low number of allergists in the US (< 5000 total registered), pharmacists are uniquely positioned to supplement this gap and act as champions for accurate penicillin allergy evaluation and de-labeling.[68]

1.7 Summary

BL antimicrobials are the most widely used class of antimicrobials in the world and remain first-line treatment options for common diseases such as pneumonia and urinary tract infections because of their excellent spectrum of activity and safety profiles. Unfortunately, allergies to BL antimicrobials are also the most commonly reported drug allergy in the world. Many of these reported allergies are erroneous in nature due to misunderstandings on the constitution of true allergic reactions and overestimated cross-reactivity of BL products. However, regardless of the legitimacy of a documented BL allergy, patients who have BL allergies documented in their EHR ultimately incur increased risks of resistant infections and higher healthcare costs as a result of altered prescribing practices which avoid BL products. In the long-term, BL allergies have been associated with increased risks of all-cause mortality and resistant infections. The long-term outcomes of BL allergies remain an understudied area compared to short-term evaluations of the same outcomes. There has been an increase in initiatives to evaluate and delabel erroneous BL allergies, and pharmacists are well positioned to act as champions for the delabeling process given the shortage of allergy specialists.

2.0 IMPROVEMENT AREAS FOR RECOGNIZING AND DE-LABELING ERRONEOUS BL ALLERGIES

2.1 Literature Review on the Evaluation of Erroneous BL Allergies

A targeted literature review was conducted to evaluate the current state of methods for evaluating and delabeling erroneous BL allergies. We sought to generate an understanding of the evaluation techniques that are being used, how each tool is implemented, and to describe the limitations and strengths inherent to each technique. We were also particularly interested in automated systems which aid in the evaluation of BL allergies. The goal of the review was to generate an understanding of the barriers associated with the tools and methods which are being used in the evaluation of BL allergies, and to use this understanding to design research studies which are specifically designed to address these barriers.

2.1.1 Search Strategy

A targeted search was conducted using Medline. The search was targeted to identify studies which explicitly involve the evaluation of potentially erroneous BL allergies, how and where evaluations occur in practice, what tools are used for evaluation, and the attitudes of clinicians and patients during evaluations. The following Medline search terms and descriptors were used to conduct the search: (penicillins, cephalosporins, carbapenems, monobactams, beta-lactams) AND (drug hypersensitivity, hypersensitivity, allergy, allergic reaction) AND (‘delabel’, ‘delabeling’, ‘removal’). Articles were limited to English language and 2018 or later. There have been many review articles written on the evaluation of BL allergies,

and references for identified reviews were also reviewed. All articles were reviewed by a single reviewer. The abstracts identified through review articles and the search strategy were reviewed to determine their relevance towards the goal of evaluating and delabeling erroneous BL allergies. Studies focused on evaluation with pediatric or pregnant populations were excluded since these populations each have unique needs and processes that differ from the general population. Cost evaluations were also excluded as not being focused on the evaluation process. The remaining articles relevant to the goal were then included for full-text review. The included studies were categorized based on whether they focused on qualitative or survey assessments, method/tool development and evaluation, or computer-assisted/ guideline-based evaluation.

2.1.2 Search Results

The Medline search produced 142 articles, and analyzing the abstracts for each article, 67 articles were relevant to the topics of the evaluation of potentially erroneous BL allergies, how and where evaluations occur in practice, what tools are used for evaluation, and the attitudes of clinicians and patients during evaluations. Twelve of these articles were reviews published within the past 5 years.

2.1.3 Qualitative and Survey Studies of BL Allergy Evaluation

Our search strategy found eight studies which included surveys or interviews of beliefs and attitudes of BL evaluation and delabeling summarized in Table 2-1. Wilson et al. surveyed patient perspectives on the BL allergy evaluation process in 2020, and found that most patients felt comfortable when going through the BL evaluation process, with 99% of patients feeling safe with the process and 99% reporting that they would recommend the testing process to others if appropriate.[77] Wilcock et al surveyed staff in a

UK-based hospital about their attitudes on delabeling BL allergies, and found that although clinicians had generally high knowledge on the benefits of delabeling, the most common barriers to evaluation were convincing the patient against preconceived beliefs, a lack of required time, and delabeling falling outside of the particular practitioner's scope, which was reported most often by nurses.[16] Another online survey by Elkhalifa et al. in 2021 identified similar barriers, with a lack of time, a desire to 'play it safe' in uncertain situations, and reporting that true allergy status cannot be attained from history alone. A case-based survey of clinician knowledge by Staicu et al found that more specific nuances of BL allergy evaluation such as when an allergist consults is required are not well known, and also found that over 85% of respondents almost never consult an allergist or immunologist for BL allergy evaluation even when the services are available.[69] Overall, clinicians reported dissatisfaction with the current status of allergy evaluation and documentation, as shown by Muylle et al in 2022, where only 15% of clinicians were satisfied with the current state of allergy documentation, 64% felt the current process was too time-consuming, and 95% were enthusiastic about being involved with the potential development of technology-based solutions to aid in BL allergy evaluation.[78]

Only three qualitative studies were found through the literature search, and the themes in each study largely mirror the survey study results. Wanat et al. conducted two qualitative evaluations of clinician and patient perspectives in a UK-based setting. In 2019, when focusing on the testing process itself, they found that while patients are generally likely to view the BL allergy testing process favorably, and had high confidence in the allergy specialists, some remained hesitant due to a fear of experiencing a reaction during the test.[79] The physicians reported that they infrequently referred patients for testing, and expressed doubts in convincing patients against preconceived beliefs of allergies, as well as hesitation permanently removing allergy labels when alternative antibiotics were available.[79] A study by the same group in 2021 found similar themes, where patients understood and appreciated the added safety afforded by allergy testing but their

anxiety of experiencing a reaction could sometimes outweigh the added benefit, and clinicians reported that BL allergy evaluation and testing isn't a high enough priority since there's almost always alternative antibiotics available.[80] Finally, a series of focus groups conducted by Powell et al. in 2021 with UK-based pharmacists, nurses, and physicians again showed similar results. The clinicians reported difficulty in convincing patients, and a lack of time and priority for BL allergy evaluation since alternative antibiotics were available.[81] Nurses also reported that their role in the BL allergy evaluation is in information gathering, and not necessarily evaluation.[81]

Table 2-1: Summary of Reviewed Qualitative and Survey Studies of BL Allergy Evaluation

Study	Design	Group(s) evaluated	Purpose	Results
Wilson et al 2020[77]	Phone survey	Patients who completed BL delabeling with oral challenge	Evaluate patient attitudes following completion of a BL allergy delabeling program	99% of patients completing testing felt safe and would recommend the procedure. 55% have since used BL products, but 2% of patients still considered themselves allergic.
Wilcock et al 2019[16]	Electronic survey	Physicians, nurses, and pharmacists at a single UK-based center	Determine health staff beliefs and attitudes of BL allergy de-labeling	37% of respondents felt patients were unlikely to be convinced against having an allergy. 31% felt they do not have adequate time, and 12% felt it was not within their scope.
Elkhalifa et al. 2021[82]	Electronic survey	Prescribers at a single UK-based center	Preliminary survey to help optimize planned implementation efforts for BL allergy delabeling	45% of prescribers agreed there was a lack of time for evaluation, but 43% also disagreed with this sentiment. 78% reported that it was not currently the duty of the pharmacist to evaluate drug histories.
Staicu et al. 2017[69]	Electronic survey	Inpatient prescribers at a New York-based tertiary health center	Evaluate prescriber knowledge on BL allergy evaluation	Pharmacists were more likely to appropriately identify low cross-reactivity rates between products. Skin-based reactions were the most challenging for prescribers to correctly evaluate.
Muylle et al. 2022[78]	Electronic survey	Physicians at a single teaching hospital in Belgium	Survey physicians about current allergy CDS alert expectations and opportunities for improvement	Only 15.4% of physicians were satisfied with the current state of allergy CDS alerts. 44% felt the information was both unclear and too limited. Most (84.6%) supported the use of allergy pop-up alerts, and 94.6% were enthusiastic about being involved in developing improvements to these alerts.
Wanat et al. 2019[79]	Interview study	31 patients (16 with a history of testing); 19 UK-based primary care physicians	Interview both patients and physicians on the attitudes on BL allergy testing	Patients rarely understood the benefit to BL allergy testing and the negative consequences associated with the allergy label. Clinicians did not feel confident removing an allergy label using clinical history alone, but rarely referred patients for testing and delabeling.
Wanat et al. 2021[80]	Interview study	31 patients (16 with a history of testing); 19 UK-based primary care physicians	Interview both patients and physicians on the attitudes of BL allergies when faced with an infection	Physicians reported difficulty distinguishing between true reactions using documented information, particularly skin reactions. Many physicians discussed the ease of using alternative antimicrobials in the setting of an infection.
Powerll et al. 2021	Focus group study	Two focus groups with physicians, nurses, and pharmacists at a UK-based center	Explore barriers for delabelling erroneous BL allergies in hospital-based practice	BL allergy evaluation was identified as low priority in most cases. When presented with accurate information, delabeling was not challenging, but gathering this information may be time consuming. There was frustration with the poor state of allergy documentation in the EHR.

2.1.4 Comparison of Clinician Pathways and Tools for Evaluation of BL Allergies

The responsibility of roles throughout the BL allergy evaluation process within the care team has recently evolved. Although most formal BL allergy evaluations and allergy skin testing services are still performed by allergy specialists, there is a major shortfall in the number of allergists available, and this is expected to worsen in the upcoming years.[83,84] Only 44% of surveyed hospitals have an allergy specialist available, and as few as 15% of community hospitals report having an allergy specialist on staff.[83] To make up for this shortfall in allergists while still providing BL allergy evaluation services, there has been a large movement towards an interdisciplinary approach which empowers non-specialist healthcare professionals to undertake this role.[68,85] BL allergy evaluation is increasingly being performed outside of allergist offices, with programs expanding in areas such as inpatient care, emergency departments, and even dental clinics.[86] Pharmacists have increasingly been shown to be effective in appropriately using BL allergy evaluation tools and accurately delabeling or referring BL-allergic patients.[74,87-90] Nurses can also reliably follow allergy evaluation algorithms, but some nurses reported their role in allergy evaluation to largely be an information gathering, and not evaluation, role.[81,91]

One of the most critical first steps in BL allergy evaluation is to risk stratify a patient's reported allergy based upon risk factors including the severity of the reaction and how long ago the reaction occurred.[92,93] This risk stratification step is vital because it helps guide what resources will be required in order to appropriately evaluate the legitimacy of a BL allergy. While there remains some controversy in the area, there is growing evidence that patients with 'low risk' allergies that are likely to be erroneous in nature can proceed with a direct oral challenge, and bypass more resource intensive routes which require skin testing or specialist evaluation.[76,94-96] Many programs have found significant success in challenging low risk BL allergies with direct oral challenges, bypassing the use of skin tests, and have not seen significant differences safety endpoints.[97-103] A 2019 randomized controlled-trial by Mustafa et al. concluded that direct

oral challenge can be equal in effectiveness and safety among low-risk patients compared to skin-testing followed by oral challenge, and bypassing the skin-testing step is quicker, more cost effective, and produced less false-positives.[104] However, other programs have used more conservative programs which include skin-testing as an intermediary step, or a hybrid stratification process where the resources used depends on the patient's individual risk factors.[37,43,74,87,88,105-110]

Risk stratification of BL allergies is often completed using validated questionnaires or stratification algorithms to determine the risk of a BL allergy being legitimate in a repeatable and standardized manner. There are many tools that have been developed for this purpose, many of which differ slightly in the factors that are evaluated and how the tool was validated, and the lack of consensus and harmonization among tools is a major source of hesitation in promoting the bypassing of skin testing in the BL allergy evaluation process. Sixteen articles were identified which created tools or processes for BL allergy evaluation.[19,43,82,91,93,95,104,106,111-118] A comparison of the differences between a selected sample of reviewed tools, and how the same patient may receive different recommendations depending upon the tool that is used, are shown in Table 2-2. The columns in this table represent simulated allergy statuses, and the rows correspond to individual stratification algorithms. The results show whether the patient would be initially recommended to receive direct oral challenge, skin testing, or allergist referral.

Table 2-2: Comparison of Recommendations Provided for Risk Stratification Tools

	Allergy = "Penicillin" Reaction = "Rash" Last occurred: Childhood	**Allergy = "Penicillin" Reaction = "Rash" Last occurred: 4 years ago**	**Allergy = "Penicillin" Reaction = "Unknown" Last occurred: Childhood**	**Allergy = "Penicillin" Reaction = "Unknown" Last occurred: 4 years ago**
Bourke et al. 2015[118]	Oral challenge	Oral challenge	Skin testing	Skin testing
Kuruvilla et al. 2018[116]	Oral challenge	Oral challenge	Oral challenge	Oral challenge
Devchand et al. 2019[115]	Oral challenge	Skin testing	Allergist referral	Allergist referral
Mustafa et al. 2019[104]	Oral challenge / Skin testing*	Skin testing	Allergist referral	Allergist referral
Blumenthal et al. 2019[111]	Oral challenge	Oral challenge	Oral challenge	Oral challenge
Trubiano et al. 2020[19] (PEN-FAST)	Oral challenge**	Oral challenge**	Allergist referral**	Allergist referral**
Stevenson et al. 2020[117]	Oral challenge	Oral challenge	Skin testing /Allergist referral	Skin testing / Allergist referral

Legend: Cells show the first step in BL evaluation which would be recommended using each risk stratification algorithm. The reaction of "Rash" was assumed to be a benign, localized, self-resolving (without treatment) rash which occurred within 1 hour of receiving the penicillin product. The reaction of "Unknown" assumed that other aspects such as the timing of the reaction, resolution, severity, and treatment required are all also unknown.
* Patients meeting this criteria were randomized to either oral challenge or skin testing
**The PEN-FAST does not directly provide recommendations corresponding to each score. Previous studies have used a score of 2 or less for oral challenge, 3 for skin testing, and 4-5 for referral.[47]

2.1.5 Standardization and Computer-Assisted Methods in BL Evaluation

There is a lack of standardization across many aspects of BL evaluation, but one of the areas that has seen a significant push for standardization is in allergy and reaction documentation.[119] Drug intolerances and true allergies are often documented interchangeably, but it is important to clearly delineate true allergic reactions from drug intolerances since single-product intolerances have been shown to have much less effect on detrimental prescribing practices.[120] Inglis et al found that the distinction between allergies and intolerances within EHR systems could not be reliably interpreted, which was confirmed by Foreman et al.

in 2021 who found that foundpowe only 45% of BL intolerances were correctly identified as intolerances instead of allergies.[38,121] In an effort to improve these allergy documentation shortcomings, Goss et al. used natural language processing (NLP) to create a value set of standardized allergy reactions consisting of SNOMED-CT terms, which was improved by Wang et al. in 2021 through the creation of a dynamic pick-list for allergy reactions that could adapt to meet the changing needs of allergy documentation in various care settings.[122,123] Inglis et al in 2021 also used NLP to categorize allergy documentation information, and their model had a reported 99% accuracy in distinguishing allergies from intolerances.[124]

Computer-assisted evaluation programs and algorithms have shown great potential in standardizing the process of BL allergy evaluation. A major component of computer-assistance in this process is the use of clinical decision support (CDS) alerts, which are commonly used to alert clinicians to the presence of a BL allergy at the time of medication prescribing or verification.[119] Since cross-reactivity between penicillin derivatives and cephalosporins has been shown to be much lower than initially estimated, many CDS systems can be significantly improved simply by turning off cephalosporin cross-sensitivity alerts for patients with allergies to penicillin-class products. Boesch et al and Macy et al have found that penicillin-allergic patients saw a 47-90% increase in BL utilization once the cross-sensitivity alerts were turned off with no difference in treatment failure or safety concerns.[125,126] CDS alerts can also be improved by directing clinicians to consult allergy services on low risk patients.[127] There have been attempts to build applications and fully-automated processes to assist with risk stratification and standardizing the evaluation process. A 2018 predictive model created by Chiriac et al. was not able to accurately stratify patient allergies using clinical history alone derived from structured EHR data.[128] While this fully-automated process wasn't successful, applications which guide clinicians in BL allergy evaluation have seen success. Elkhalifa et al created and validated a mobile-phone application in 2021 which standardizes BL evaluation and supports appropriate prescribing decisions.[82]

2.1.6 Discussion

Relative to the large size of studies published on delabeling programs at individual institutions or health systems, there has been a much smaller number of studies which qualitatively examine the barriers in place to implementing and sustaining such programs. The three qualitative interview studies which have been conducted on the topic of BL allergy evaluation have all been focused on UK populations, and it is highly likely that there are major differences between regional practices that need further explored to ensure delabeling programs are designed to overcome regional barriers. Additionally, these three studies have not explored the dynamics surrounding clinician-specific role assignments in BL evaluation in depth. The lack of clear oversight and direction in role assignments throughout the BL allergy evaluation process was noted in clinician surveys on the topic, where one of the most commonly reported barriers for not evaluating BL allergies was a belief that it was not within the particular clinician's scope of practice. While a multidisciplinary approach is the ideal method to implement a BL delabeling workflow, the clinician-specific roles throughout this process need to be further explored, and health systems could greatly benefit from studies which explore the primary responsibility for organizing allergy evaluation team dynamics, role assignments, and leadership on the delabeling process when specialists are not available.

The literature has well-established that BL evaluation programs are effective at reducing erroneous BL allergies and promoting the use of first-line BL antimicrobials. One of the less explored aspects of these programs is their sustainability and effect over time. Relabeling of BL allergies which have been previously delabeled is fairly common due to limitations in allergy documentation.[129] Lutfeali et al described examples of successful initiatives that can sustain delabeling programs, such as EHR alerts to prevent re-introduction of delabeled allergies and providing patients with pocket cards explaining their allergy status.[130] Sustainability of delabeling programs is vital because the long-term aspects associated with a BL allergy label are much less well understood than the short-term detriment. The only study examining the outcomes

of patients with BL allergies over a period greater than five years found a 14% increase in mortality associated with the BL allergy status and an increase in resistant infections.[10,66] However, health systems may be able to be better justify the upfront cost of implementing BL allergy delabeling initiatives if the long-term detriments associated with BL allergies such as acute kidney injury (AKI) were better understood.

Finally, the lack of standardization in BL evaluation remains a significant issue, and automation presents a promising route to standardize the evaluation process. Accurate and repeatable risk stratification is a pivotal step in ensuring that appropriate resources are being allocated to BL allergies that are low, moderate, or high risk for being true reactions. However, the large increase in the number of available resources for risk stratification has led to a lack of consensus on how to best implement these tools since similar patients can be recommended to proceed down highly differing delabeling pathways using different tools. The only previous attempt to fully automate the risk stratification process was unsuccessful, but was conducted in 2017, prior to the publication of many newer risk stratification tools, including the PEN-FAST. It is likely that a future attempt to automize the risk stratification process that utilizes these resources could yield significantly more success and reduce the time constraints that are currently associated with BL allergy evaluation. Improvements made in automized risk stratification could then be implemented electronically to continue the advancements which have been made in BL allergy CDS systems or stand-alone applications such as those created by Elkhalifa et al.

2.1.7 Summary

There is an increasing number of studies examining the outcomes of patients with BL allergies and the delabeling and evaluation of erroneous allergies, as well as advances in tools to assist in the evaluation process, but some areas in the literature remain underexplored. The number and breadth of qualitative studies, in particular, are severely lacking when compared the large number of quantitative and programmatic evaluations, and more international examinations of clinician beliefs and BL allergy evaluation pathways are needed. There is also a lack of studies examining the long-term outcomes of patients with BL allergies, which is needed to support justification to health systems that BL allergy evaluation programs can lead to significant clinical impact and long-term cost savings. Standardization of allergy processes remains a significant outstanding limitation with delabeling initiatives, and automized processes which make use of newly developed tools and resources are well-suited for improving BL allergy evaluation, as well as improve allergy CDS systems.

3.0 RESEARCH SUMMARY

3.1 Dissertation Overview and Specific Aims

The goal of this dissertation is to improve the evaluation and delabeling of erroneous BL allergies and the understanding of the long-term impact of BL allergies. This goal was achieved through 3 independent studies that each focused on separate aspects of BL allergy evaluation and outcomes. Each aim was specifically designed to target a current gap in understanding regarding BL allergy evaluation and outcomes. First, clinicians were interviewed to generate targeted interventions for implementation in practice for BL evaluation. Next, a cohort of patients from a regional health system were used to examine the long-term outcomes associated with BL allergies. Finally, clinical notes from the same cohort of patient encounters were used to develop a machine-learning pipeline to promote the use of previously tolerated BL products despite the presence of an allergy. The specific aims and hypotheses evaluated in this dissertation are summarized below:

Aim 1: Attitudes and beliefs on the evaluation of beta-lactam allergies in practice: a qualitative study of front-line clinicians:

Hypothesis 1: There are unaddressed limitations in the current processes of BL evaluation which are currently impeding the progress of efforts to evaluate and delabel erroneous BL allergies.

Approach: Semi-structured interviews will be used to summarize clinician attitudes and practices when evaluating BL allergies. Next, a structured framework will be employed to translate these beliefs into theory-informed, targeted interventions to overcome the barriers that are being experienced which are limiting BL evaluation and delabeling.

Aim 2: Long-term clinical outcomes associated with beta-lactam allergies using mixed-model survival analysis:

Hypothesis 2: BL allergies will be associated with a long-term increase in the hazards of all-cause mortality, resistant infections, and acute kidney injury.

Approach**:** A 12-year longitudinal cohort of patient encounters from a regional health system will be used to examine the long-term outcomes of patients with BL allergies using a repeated-measures, mixed-model survival analysis design to determine long-term mortality, resistant infections, and acute kidney injury associated with BL allergies.

Aim 3: Natural-language processing of clinical notes to promote the use of previously tolerated beta-lactam products in beta-lactam-allergic patients:

Hypothesis 3: Automated risk stratification processes using natural-language processing can provide clinicians with an accurate estimate of the likelihood that a patient's reported BL allergy is legitimate.

Approach: A natural-language processing pipeline will be created using a corpus of clinical notes which identifies instances where patients have previously used BL products Simulated CDS alerts will be used as a proof-of-concept for implementation into health system EHRs.

4.0 ATTITUDES AND BELIEFS ON THE EVALUATION OF BETA-LACTAM ALLERGIES IN PRACTICE: A QUALITATIVE STUDY OF FRONT-LINE CLINICIANS

4.1 ABSTRACT

More than 90% of reported BL allergies have been recognized as erroneous in nature, and there have been improvements in the methods for identifying and delabeling erroneous allergies. However, less than half of all documented BL allergies are ever delabeled even through it is widely recognized that most are erroneous in nature, and the rate of delabeling has remained stagnant despite advances in BL evaluation, which necessitates a deeper understanding of the attitudes and beliefs associated with the current practices for BL evaluation.

A semi-structured interview-guide designed to align with the domains within the Theoretical Domains Framework (TDF) was used to interview 25 clinicians on their beliefs and practices when evaluating beta-lactam allergies. A minimum of two physicians and pharmacists from each of the following specialties were interviewed: critical care, emergency medicine, general practice, and infectious disease / infection prevention. At least two nurses from the same specialties were also interviewed with the exception of emergency medicine. The interviews were recorded and transcribed, and the transcripts were then analyzed using deductive and inductive analysis to identify belief statements which were categorized according to the TDF. The behavior change wheel was then used to translate the identified beliefs into theory-informed intervention recommendations.

Clinicians reported frustration with the inconsistency and unreliability of documented allergy information within the electronic health record. Clinicians felt comfortable in their personal ability to determine the legitimacy of a BL allergy, but were often hesitant to make permanent changes to the patients' allergy documentation, often preferring a more conservative approach "just in case". The allergy reaction was reported as the most influential factor in determining an allergy's legitimacy. There was a persistent belief that it was important for patient care to accurately evaluate all allergies, but that the clinician may personally not have the needed time or resources available to perform the evaluation in their care setting. Pharmacists were overwhelmingly identified as the clinician that is the most equipped to evaluate the legitimacy of BL allergies.

Two interventions were strongly supported by the identified belief statements. First, pharmacists should be empowered to take on a more direct role in BL allergy evaluation, as well as leading delabeling efforts, particularly when specialists are not available. Previous studies have implemented pharmacist-led BL delabeling with significant success, and since pharmacist-led BL allergy evaluation can be successful even without large time and financial investment, health systems should adopt models of pharmacist-led BL allergy evaluation when possible. Second, EHRs should completely overhaul how allergy information is documented and updated through the inclusion of unambiguous reaction selection using picklists which will clarify the distinctions between true immune-mediated reactions and drug sensitivities. Additionally, it would be beneficial if EHRs supported clinicians in delabeling efforts and amending existing allergies by identifying agents that patients have previously tolerated which would conflict with existing allergies.

4.2 INTRODUCTION

Upwards of 35% of patients have at least one medication allergy listed in their EHR, and BL allergies are the most commonly reported drug allergy.[5] However, over 90% of all EHR allergy alerts are overridden by providers, showing that there is a clear disconnect between the allergy information contained in the EHR and the interpretation of that allergy information by providers.[131] Surveys of provider knowledge and attitudes have shown continued reluctance in challenging BL allergies despite rising levels of understanding on the frequency of erroneous BL allergies.[69,132,133] The discrepancy between advances in the knowledge of best practices for allergy evaluation and the actual practices that are being employed by front-line clinicians indicates that there may be structural limitations in implementing BL allergy delabeling programs. It is important to thoroughly analyze these limitations in order for advances in BL allergy evaluation to achieve their intended effect and begin reducing the damage caused by erroneous BL allergies.

Qualitative studies are particularly well-suited for analyzing this disconnect through the use of interviews and focus groups with the care teams which are on the front-lines of BL allergy evaluation. Interviews have been conducted with UK primary care providers, and have shown that providers are reluctant to remove allergies from patients' health records using their personal clinical judgement alone.[79] An additional focus group, also conducted with UK-based clinicians, concluded that many felt that delabeling BL allergies is not a high priority in their clinical setting despite representing a relatively broad group of clinicians and care settings consisting of generalists, pharmacists, nurses, and specialists.[81] However, attitudes and resources may vary significantly by country, and it is unknown whether similar issues are being encountered in other health systems since there has yet to be an attempt to conduct interviews with a non UK-based group of clinicians and evaluate the attitudes around BL allergy evaluation and delabeling.

In order to address this gap in the literature, we sought to use semi-structured interviews with a diverse group of mostly US-based clinicians, including pharmacists, nurses, and physicians who are on the front-line of BL allergy evaluation. There may be significant differences in attitudes represented by different specialties, so we also sought to include specialists from the fields of critical care, emergency medicine, and infectious disease. Additionally, we will design the interview guide to algin with a structured framework for behavior change in order to increase the reliability and interpretability of our results. Through the use of thematic analysis, we will conclude by proposing targeted interventions which are specifically designed to overcome the barriers in current practice models that are limiting BL allergy evaluation and delabeling.

4.3 METHODS

4.3.1 Goals, Study Design, and Review Board Approval

The goal of this study was to evaluate the current attitudes held by front-line clinicians (hereafter, the phrase 'clinicians' will be used to include physicians, pharmacists, and nurses for brevity) when encountering a patient with a listed BL allergy and develop targeted intervention recommendations to overcome the current barriers and limitations that are hindering the recognition and de-labelling of erroneous BL allergies. The evaluation of clinician attitudes was conducted through the use of semi-structured interviews and a standardized interview guide. The interview guide was developed to target beliefs across the behavior domains within the Theoretical Domains Framework to ensure both the interview guide's rigor and comprehensiveness.[134] A diverse population comprised of nurses, pharmacists and physicians was identified. The clinician groups were further stratified by the specialties of general or hospital care, emergency medicine (EM), infectious disease / infection prevention (ID), and intensive / critical care (ICU). The goal was to recruit and interview at least two clinicians from each profession and specialty (e.g. two hospital pharmacists, two critical care pharmacists, etc..) in order to assess how attitudes and practices may be influenced by profession and practice setting. The study was approved as exempt for posing no greater than minimal risk by the University of Pittsburgh International Review Board (Study 20120059).

4.3.2 The Behaviour Change Wheel and Theoretical Domains Framework

The behavior change process outlined Michie in "*The Behaviour Change Wheel – A Guide to Designing Interventions"* was used as a conceptual framework while designing the study.[135] This behavior change process is organized into eight stages, and can be seen below in Figure 4.1. Steps 1-3 are focused on defining, selecting, and specifying in behavioral terms the problem that is targeted for intervention. These three steps are completed using worksheets and preliminary information to help direct the focus towards a selected target behavior. Following the completion of the first three steps, the target behavior selected was "healthcare providers evaluating the legitimacy of beta-lactam allergies listed in electronic medical records".

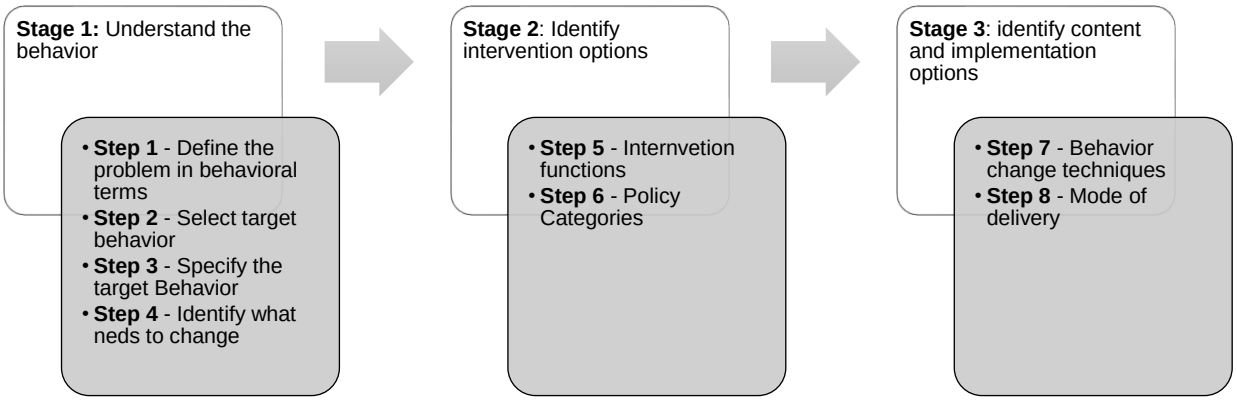


Figure 4-1: The Eight Steps for Intervention Design from The Behaviour Change Wheel

Reproduced from Michie et al.[135]

Using the targeted behavior as a focal point, step four of the behavior change wheel was to identify the areas of the behavior that needed to change, which were evaluated through semi-structured interviews. To help organize the interview process and ensure its comprehensiveness in understanding the behavior, the decision was made to structure the interview guide to align with the fourteen domains within the Theoretical Domains Framework (TDF), which is a common tool in implementation science that assists in modeling complex behavior making decisions according to behavior influence domains.[134] We chose to use the TDF

because of its ability to evaluate both individual and organizational-level constructs, which is ideal for our targeted behavior which was expected to contain complicated system and individual-level influence overlap. The definition of the fourteen domains in the TDF, along with their theoretical constructs, are shown in Table 4.1. The theoretical constructs are divisions within each domain which comprise more specific attitudes and activities related to the domain. The constructs were used to help guide the development of the interview guide through the inclusion of questions targeted at particular constructs that were thought to be particularly important to the evaluation of BL allergies.[136]

Table 4-1: The Domains and Constructs of the Theoretical Domains Framework

Domain (definition)	Constructs
1. Knowledge **(An awareness of the existence of something)**	Knowledge (including knowledge of condition/scientific rationale) Procedural knowledge Knowledge of task environment
2. Skills **(An ability or proficiency acquired through practice)**	Skills Skills development Competence Ability Interpersonal skills Practice Skill assessment
3. Social/professional role and identity **(A coherent set of behaviors and displayed personal qualities of an individual in a social or work setting)**	Professional identity Professional role Social identity Identity Professional boundaries Professional confidence Group identity Leadership Organizational commitment
4. Beliefs about capabilities **(Acceptance of the truth, reality or validity about an ability, talent or facility that a person can put to constructive use)**	Self-confidence Perceived competence Self-efficacy Perceived behavioral control Beliefs Self-esteem Empowerment Professional confidence
5. Optimism **(The confidence that things will happen for the best or that desired goals will be attained)**	Optimism Pessimism Unrealistic optimism Identity
6. Beliefs about Consequences **(Acceptance of the truth, reality, or validity about outcomes of a behavior in a given situation)**	Beliefs Outcome expectancies Characteristics of outcome expectancies Anticipated regret Consequents
7. Reinforcement **(Increasing the probability of a response by arranging a dependent relationship, or contingency, between the response and a given stimulus)**	Rewards (proximal/distal, valued/not valued, probable/improbable) Incentives Punishment Consequents Reinforcement Contingencies Sanctions

Table 4-1 (Continued)

8. Intentions **(A conscious decision to perform a behavior or a resolve to act in a certain way)**	**Stability of intentions** **Stages of change model** **Transtheoretical model and stages of change**
9. Goals **(Mental representations of outcomes or end states that an individual wants to achieve)**	Goals (distal/proximal) Goal priority Goal/target setting Goals (autonomous/controlled) Action planning Implementation intention
10. Memory, attention and decision processes **(The ability to retain information, focus selectively on aspects of the environment and choose between two or more alternatives)**	Memory Attention Attention control Decision making Cognitive overload/tiredness
11. Environmental context and resources **(Any circumstance of a person's situation or environment that discourages or encourages the development of skills and abilities, independence, social competence and adaptive behavior)**	Environmental stressors Resources/material resources Organizational culture/climate Salient events/critical incidents Person × environment interaction Barriers and facilitators
12. Social influences **(Those interpersonal processes that can cause individuals to change their thoughts, feelings, or behaviors)**	Social pressure Social norms Group conformity Social comparisons Group norms Social support Power Intergroup conflict Alienation Group identity Modelling
13. Emotion **(A complex reaction pattern, involving experiential, behavioral, and physiological elements, by which the individual attempts to deal with a personally significant matter or event)**	Fear Anxiety Affect Stress Depression Positive/negative affect Burn-out
14. Behavioral regulation **(Anything aimed at managing or changing objectively observed or measured actions)**	Self-monitoring Breaking habit Action planning

4.3.3 Interview Guide Development and Field Testing

Semi-structured interviews were used because of their ability to be highly adaptable to a diverse group of interviewees with greatly differing perceptions, which was expected of our interview population consisting of up to 11 combinations of specialties and practitioners.[137] An initial interview guide was created which consisted of high-level questions relating to particular constructs within the TDM as well as follow-up probing questions which were meant to maintain interview flow and encourage a thorough thought process from the interviewee.[138] The high-level questions were focused on identifying major opportunities and limitations related to the target behavior and were organized according to the domains within the TDM. The lower-level questions were subsumed within the higher-level question / TDM domain and consisted of probes related to specific attitudes and beliefs regarding the target behavior.

The initial interview guide was then field tested by interviewing a generalist pharmacist who is experienced in conducting qualitative and implementation research. Field testing is the process of simulating a real interview situation by interviewing a potential study participant, which is an important step in ensuring the understandability and relevance of the interview questions as well as ensuring the interview can be completed in a timely manner.[139] Based on the pilot-tester's feedback, the interview guide was refined to include further probing questions and improved clarity in distinguishing between the decision to investigate a BL allergy and the evaluation process itself. The completed interview guide was used for all completed interviews in the study, and is presented in its entirety in Appendix 4-1.

4.3.4 Participant Enrollment and Interview Process

Beginning with known clinician contacts familiar to the study team, a snowball method was used to contact additional participants by asking initial contacts to recommend receptive clinicians to the research

team.[140] Participants were initially contacted through an email describing the purpose of the study, the interview process, and the study team information. Participants indicating a desire to participate were further contacted to schedule an interview. In total, two clinicians each from following groups were initially interviewed: general pharmacists, emergency medicine (EM) pharmacists, infectious disease (ID) pharmacists, intensive-care unit (ICU) pharmacists, general physicians, EM physicians, ID physicians, ICU physicians, general nurses, ID nurses, ICU nurses; for an initial total of 22 completed interviews. These clinical groups were identified because each respective care setting has been an area of emphasis for BL allergy evaluation and delabeling.[68] In order to meet our original goal of 24 completed interviews, three more interviews were conducted, one each with a general pharmacist, general physician, and ICU nurse. A total of 25 interviews were conducted. At the time of being interviewed, 23 of 25 interviewees were working at US-based health systems (one ID Physician was practicing in Canada, and one physician was trained in the US but was practicing in Europe). Notably, the only group not meeting the participant goal was EM nurses, which the study team had difficulty in contacting likely due to the additional stressors associated with the COVID-19 pandemic which exacerbated a pre-existing shortage of EM nurses.[141]

Interviews occurred between September 2021 and June 2023. All interviews occurred online using Zoom with the audio of the interviews recorded.[142] Each interviewee verbally consented to the audio recording of each interview prior to the first interview question. The completed interview guide was used to conduct the interviews. A second-year pharmacy student assisted in conducting the interviews and was trained on the use of the interview guide by simulating interview and question responses, and this student also observed multiple interviews prior to conducting their first interview.

4.3.5 Thematic Analysis

Following the completion of the interviews, the audio recording of each interview was manually transcribed into a text format by the primary investigator (MG). NVivo version 12 was then used for thematic analysis.[143] Two reviewers participated in the thematic analysis process. The first reviewer was the primary investigator who conducted the majority of the interviews (MG). The second-year pharmacy student who assisted in the conduction of the interviews acted as the second reviewer (ND). First, a coding guideline was developed to facilitate the coding of transcript text segments into appropriate TDF domains in a standardized manner.[144] The coding guideline was developed through an iterative process involving both reviewers. First, each reviewer independently reviewed the interview transcripts to develop definitions and examples for how each TDF domain related to the interview questions and responses. Next, the results of these reviews were pooled and compared, consensus was used to resolve disagreement, and this resulted in a mutually agreed-upon coding guideline. The coding guideline was then used for the deductive analysis of all transcripts, through which text segments relating to the target behavior were coded by each reviewer into one of the 17 domains within the TDF. In order to evaluate the utility of the coding guideline, this process was done independently by each reviewer, and the results of this process were evaluated for kappa agreement and reliability.

There is poor consensus on sample size recommendations when conducting qualitative research, but it is generally recommended that the sample size be designed to sufficiently evaluate the scope of the problem and the quality of the data.[145] The initial goal for our sample size was to interview at least two persons from each clinician-specialty group, and to supplement the relatively low number of interviews in each group by conducting in-depth, comprehensive interviews. The study achieved its initial sample size goal in 11 of 12 clinician-specialty groups, with ED nurses not meeting the enrollment goal. Data saturation was defined as being met when the completion of at least two additional interviews did not result in the

identification of any new beliefs, which aligns with recommendations for evaluating data saturation and adequate sample size.[146]

Prior to the inductive analysis process, two randomly selected transcripts were held-out to assess for data saturation. Three additional interviews were also conducted after the initial set of 22, with all three of these interviews held out to enhance the confidence in achieving thematic saturation and to reach the initial interview goal of 24 interviews. Following the deductive analysis, inductive analysis was used to translate the TDF-coded transcripts into belief statements, which relate the overarching motivation or attitude underlying groups of responses in each transcript to the targeted behavior. The process of deriving these beliefs was completed using a process where one reviewer initially derives the set of beliefs and a second reviewer independently confirms those beliefs, which has been recommended as an efficient approach to inductive analysis.[134,147] Reviewer A (MG) performed the initial inductive analysis on the corpus consisting of twenty transcripts and generated the initial set of belief statements. The belief statements were categorized according to the TDF domain from the coded transcripts that led to the generation of the belief. For example, the belief statement "Evaluating allergies is too time consuming" was categorized under the TDF domain of Environmental Context and Resources because the majority of responses that were expressing this belief were coded under the Environmental Context and Resources domain. A total of 70 unique belief statements describing underlying beliefs were identified and are shown according to their overarching TDF domain in Table 4.2.[148] Reviewer B (ND) then coded the transcribed statements from the transcripts according this list of 70 belief statements in order to confirm the appropriateness of the belief statements.[134]

Table 4-2: Belief Statements Identified Through Inductive Analysis

TDF Domain	Beliefs Statements
Environmental Context and Resources	Evaluating allergies is too time consuming
	I have higher priorities in my care setting
	There are safeguards/alerts that assist me
	Patients and family are unavailable or unreliable
	Severe reactions are better remembered and documented
	Documentation of information is missing or unreliable
	I am confident in the information provided when it is available
	Additional forms of testing would be beneficial
	I refer to external resources for the evaluation process
Beliefs about Capabilities	Most allergies can be determined with the proper tools and information
	I am confident in my ability to evaluate an allergy
	Evaluating allergies is not difficult
	I am confident in removing/amending allergy documentation
	I am not confident in removing/amending allergy documentation
	I am comfortable challenging erroneous allergies
Behavioral Regulation	There is no policy or it is only informal
	I do not know if we have a policy
	I am not confident in the current policy/procedure
	A formal policy would be beneficial
	We do have a formal policy
	Policies do not dictate my evaluations
Beliefs about Consequences	I prefer to be safe if I am unsure
	Evaluating allergies will improve patient outcomes and safety
	I have seen negative consequences from allergy evaluation/challenging
Emotion	I am worried I may hurt the patient
	This process is not stressful
	This process is stressful
Goals	My goal is to provide high quality care
	My goal is to clarify the allergy
	My goal is to immediately treat the patient
Intentions	Every allergy needs evaluated every time
	Allergy evaluation is very high priority in some circumstances
	The allergy does not need evaluated unless a penicillin is being given
	The allergy reaction is the most important factor for evaluation

Table 4-2 (Continued)

	I do not evaluate well-documented allergies
Knowledge	There is confusion between side effects and allergies
	I know what a true allergy is
	There is a lack of knowledge / education on this topic
	Beta lactams are the optimal choice for some infections
	I know which beta lactams I can use based on side chain activity
Memory, Attention, and Decision Process	I can use alternative non-beta-lactam antibiotics (or generally other options)
	I can use alternative beta-lactam antibiotics
	I can use anything a patient has previously received
	Every patient has different needs
Optimism	It is not possible to confidently evaluate some allergies
	Most documented allergies are not true allergic reactions
	Allergies are not evaluated as often as they should be
Reinforcement	There is little to no oversight on allergy evaluation
	There is no reward or recognition for evaluating allergies
	I am unlikely to be reprimanded whether or not I evaluate allergies
	I am personally satisfied by providing good care to the patient
Skills	I am guided by what others have taught me
	I have experience evaluating allergies
	Evaluating allergies requires experience
	Navigating the EHR is an important skill
	Interviewing patients/family is an important skill
Social and Professional Role and Identity	Nurses are too busy to evaluate allergies
	Nurses are relied on for information gathering, not evaluation
	All clinicians should know how to evaluate allergies
	It is the prescriber's job to evaluate allergies
	It is everyone's job to evaluate allergies
	Pharmacists are the most equipped to evaluate allergies
	Evaluating allergies is part of my job
Social Influences	I have colleagues I can consult when needed
	I am confident in my colleagues
	Evaluating allergies is a team effort
	I am prompted by others to evaluate allergies
	I rely on others to make the final decision
	Evaluating allergies is a high priority to my employer / supervisor
	Evaluating allergies is not a high priority to my employer / supervisor

4.3.6 Data Saturation

Prior to the inductive analysis, but following the completion of the deductive analysis, two randomly-selected transcripts were held out to assess for data saturation. Data saturation was defined as being met when the addition of at least two interviews did not lead to new beliefs being identified.[146] As our initial goal of enrollment included a minimum of two clinicians from each clinician-specialty group for a total of 24 clinicians, we planned to evaluate data saturation only after the completion of this first set of interviews to ensure we were achieving a representative sample of clinician attitudes. After the initial set of 22 interviews was completed, it was decided to conduct three additional interviews, which were held-out in a similar manner and considered for data saturation, for a total of five interviews evaluated for data saturation. Data saturation was evaluated following inductive analysis using the two hold-out interviews and three additional interviews as specified above, through which reviewer B (ND) independently reviewed the five hold-out transcripts and investigated for new belief statements which were not represented through the initial inductive analysis process that was completed with the set of twenty interviews. No new belief statements were identified during this step, meeting the definition that had been set for data saturation, and no additional interviews were conducted.

4.4 RESULTS

4.4.1 Interviewee Demographics

Table 4.3 shows the demographics and clinical backgrounds for the 25 clinicians who were interviewed on their attitudes about BL allergy evaluation in practice. Slightly more female clinicians were interviewed (60%), and almost all clinicians were practicing in the US (92%), with only one clinician each practicing in Canada (4%) and Europe (4%). The initial recruitment goals with regard to clinician specialty were met with the exception of nurses working in emergency medicine, with a total of at least 2 clinician-specialists in each area being interviewed.

Table 4-3: Interviewee Demographics and Clinical Background

Characteristic	Healthcare Provider Count, N (%) (N = 25)
Sex	
Female	15 (60%)
Practice Location	
United States	23 (92%)
Pennsylvania	16 (64%)
Ohio	1 (4%)
New York	2 (8%)
North Carolina	1 (4%)
Georgia	1 (4%)
Illinois	2 (8%)
Canada	1 (4%)
Europe	1 (4%)
Clinical Profession	
Physician	9 (36%)
Pharmacist	9 (36%)
Nurse	7 (28%)
Clinical Specialty	
General Practice*	8 (32%)
Infectious Disease / Infection Prevention	6 (24%)
Emergency Medicine	4 (16%)
Intensive Care	7 (28%)

*General practice included hospitalist physicians, family medicine physicians, hospital staff pharmacists, and hospital staff nurses

4.4.2 Inter-Rater Reliability

Table 4-4 shows the Inter-rater reliability (IRR) measures between both reviewers when performing deductive analysis (coding text segments according to the TDF domains).[149] Overall, kappa scores were lower than the desired range of 0.6 for achieving IRR; however, this is not surprising given the relatively large number of domains.[134,150] In contrast, the percent agreement rating in each category was excellent, with all TDF domains achieving a percent agreement above 90%. There were some notable differences in IRR across some TDF domains, particularly "beliefs about consequences" and "memory, attention, and decision process," which all had kappa ratings close to 0.22, indicating generally poor agreement. The differences in these groups are likely due to ambiguity in the domains' definition and application which have been noted by other researchers as an outstanding issue with the TDF.[136] The level of IRR seen was considered acceptable due to the excellent percent agreement despite the relatively lower Kappa coefficients.[134]

Table 4-4: Inter-rater Reliability of Transcript Coding by TDF Domains

TDF Domain (n of beliefs)	Cohen's Kappa Coefficient	Percent Agreement	Percent Disagreement
Behavioral Regulation (6)	0.368	90.5%	9.5%
Beliefs about Capabilities (6)	0.481	95.8%	4.2%
Beliefs about Consequences (3)	0.221	94.0%	6.0%
Emotion (3)	0.848	99.7%	0.3%
Environmental Context & Resources (9)	0.454	91.4%	8.6%
Goals (3)	0.403	98.0%	2.0%
Intentions (5)	0.202	93.1%	6.9%
Knowledge (5)	0.306	93.7%	6.3%
Memory, Attention, and Decision Process (4)	0.229	92.7%	7.3%
Optimism (3)	0.279	96.8%	3.2%
Reinforcement (4)	0.661	96.9%	3.1%
Skills (5)	0.511	97.2%	2.8%
Social & Professional Role and Identify (7)	0.662	95.1%	4.9%
Social Influences (7)	0.452	95.5%	4.5%
Overall (70)	0.434	95.0%	5.0%

4.4.3 Selected Quotes and Frequency of Identified Belief Statements

The tables below show the total belief statement response frequency organized by their overarching TDF domain. Due to the nature of semi-structured interviews, every belief was not necessarily inquired about in every interview since the identified beliefs were derived following interview completion. Additionally, the frequency that each belief was expressed within each interview is not considered in these frequencies (Each belief was counted as all/none per interview). The tables also show a selected quote which highlights the conceptual idea of the belief's relation to the targeted behavior and the interview that generated the quote. Each table is then followed by a brief summary highlighting the selected quotes and the belief statement sentiment that was expressed by interviewees related to each TDF domain.

Table Set 4-5: Belief Statement Selected Quotes by TDF Domain

Table 4-5-1: Behavioral Regulation

Belief Statements (n interviews belief was expressed)	Selected Quote
We do have a formal policy (6)	"If they [the patient] don't know, we do have a protocol to try a small dose, depending on the acuity. If not, I will default to a different antibiotic". -ID Physician 2
There is no policy or it is only informal (18)	"So I wouldn't say we have an official in our organization, policy and procedure. In fact, we don't have an official policy or procedure." -General Physician 2
Policies do not dictate my evaluations (3)	"I don't know that I've ever used a resource to make that determination other than my previous experience and learning." -ICU Nurse 2
I do not know if we have a policy (11)	"I actually don't know if there's a formal hospital policy on that process, that's generally what I do." -ICU Nurse 2
I am not confident in the current policy/procedure (6)	"OK, so that from a pharmacist standpoint... Yeah, I'm not that confident, especially considering our current model in our hospital is more of a centralized staff pharmacies model, so a lot of times there's not a direct interaction with the patients". -ED Pharmacist 1
A formal policy would be beneficial (9)	"I would like a formal de-labeling program. And I would like our ID stewardship program to take more ownership of the process system wide." -ED Pharmacist 2

- There was a sentiment that there is a lack of formal policies regarding the evaluation of BL allergies to help guide front-line clinicians. Importantly, this should not be interpreted to mean that there necessarily is not a guiding policy in actuality, but does imply that there is a broad lack of awareness of such policies if they do exist. Additionally, interviewees expressed that they did not know if there was a formal policy and that the implementation of a formal policy would be beneficial. Among the clinicians that were aware of the current policies and procedures for BL evaluation, there was some expression that they were not confident in these procedures.

Table 4-5-2: Beliefs about Capabilities

Belief Statement (n interviews belief was expressed)	Selected Quote
Most allergies can be determined with the proper tools and information (20)	"I think with a proper history and a proper patient interview it definitely can be determined, right?" -ID Pharmacist 1
I am not confident in removing/amending allergy documentation (6)	"No, I wouldn't. I'm not confident. I would not remove it from the MAR just in case." -Gen Nurse 1
I am confident in removing/amending allergy documentation (20)	"So, in myself, my confidence is medium to high in that I feel confident my own abilities of doing such a thing." -General Pharmacist 1
I am confident in my ability to evaluate an allergy (24)	"I always feel confident in my decision. If it looks like there's anything questionable, I'll go ahead and investigate it." -General Pharmacist 2
I am comfortable challenging erroneous allergies (5)	"I would say I have a lot of experience with, kind of, changing from an inappropriate regimen to a more appropriate regimen by utilizing beta lactams." -ED Pharmacist 2
Evaluating allergies is not difficult (13)	"You know, I don't think it's very difficult. It just takes a little extra time." -ID Pharmacist 1

- There does not appear to be a knowledge deficit in the evaluation of BL allergies, with respondents reporting they are confident in their ability to evaluate erroneous BL allergies. Instead, there is a lack of confidence in clinicians challenging erroneous allergies and updating documentation of existing allergies, regardless of their personal confidence in evaluating the allergy's legitimacy. This sentiment is echoed in the results seen in the domain Beliefs about Consequences, where clinicians may feel personal confidence in evaluating and making a justifiable treatment decision in the moment, but do not feel confident in assuming personal liability in permanently removing an allergy from a patients' electronic health record.

Table 4-5-3: Beliefs about Consequences

Belief Statement (n interviews belief was expressed)	Selected Quote
I prefer to be safe if I am unsure (11)	"But nobody wants to take that chance, right? Would you want to know what anaphylaxis feels like? I don't." -ID Nurse 1
I have seen negative consequences from allergy evaluation/challenging (3)	"You know, I had somebody once with a penicillin allergy. I thought it was bogus. I gave somebody penicillin and their throat closed and almost died. That person's not going to give somebody penicillin again. I don't care what the guideline says." -ED Physician 1
Evaluating allergies will improve patient outcomes and safety (5)	"As I mentioned before, that helps future decision makers for that patient. And then the more we document, the easier the process is. So that's important." -ID Pharmacist 2

- The results seen for this domain are similar to those seen for Beliefs about Capabilities in showing a proclivity for conservative management of suspected erroneous BL allergies and a desire to err on the side of caution. The quote seen for the belief "I prefer to be safe if I am unsure" is an excellent example of this hesitancy, and may also point to a desire to avoid causing what the clinicians may view as unnecessary harm if the challenging of a BL allergy resulted in a deleterious effect such as anaphylaxis, even if the clinician was justified in challenging the allergy.

Table 4-5-4: Emotion

Belief Statement (n interviews belief was expressed)	Selected Quote
This process is stressful (3)	"Stressful. I immediately call the clinical coverage. Like I'll talk to the patient, gather information, call the pharmacist." -General Nurse 1
This process is not stressful (23)	"I don't think stressful. I don't I don't think the majority are. There some that can be frustrating, especially if we can't resolve or clarify their reaction." -ICU Pharmacist 2
I am worried I may hurt the patient (5)	"I guess just protecting my license. I'm so terrified that I'm going to do something wrong and hurt somebody." -ICU Nurse 1

- Clinicians generally reported that the process of evaluating a BL allergy is not a stressful process, with the process being described as more "frustrating" than "stressful". There were some negative emotions that were reported, including a fear that the clinicians would make a mistake that could lead to harm for the patient, or that BL allergy evaluation may be stressful at times, and this stress may be particularly related to the amount of resources and persons involved to evaluate an unclear BL allergy.

Table 4-5-5: Environmental Context and Resources

Belief Statement (n interviews belief was expressed)	Selected Quote
There are safeguards/alerts that assist me (4)	"And then our electronic health record would identify any cross-reactivity at that point and warn the provider about that." -General Physician 2
Severe reactions are better remembered and documented (10)	"People will remember what almost killed them, but the little ones maybe not so much." – ID Nurse 2
Patients and family are unavailable or unreliable (22)	"The degree to which histories from patients can be variable, unpredictable, unreliable, confusing, seems to know very few limits." -General Physician 1
I refer to external resources for the evaluation process (11)	"In this case, we usually refer for an outpatient allergy testing and a specialist that will do the skin test, the prick tests and all to figure out if there are also other allergies." -ICU Physician 2
I have higher priorities in my care setting (12)	"And it's very time based that if you have a 20 minute office visit and you have things like a colon screening and blood pressure and diabetes and things you're trying to do. Blowing past their allergies can be pretty easy. And take a low priority in terms of fact finding of things." -General Physician 2
I am confident in the information provided when it is available (18)	"But, you know, I think the majority of the time I'm confident that if there is a reaction listed in there, then it occurred." -ICU Pharmacist 2
Evaluating allergies is too time consuming (11)	"Most people aren't going to get to the bottom of it either, you know, like it's just too labor intensive." -ED Physician 1
Documentation of information is missing or unreliable (20)	"I mean, as I said, patient histories are always flawed and charts are notoriously either missing or missing parts, so it's not great." -ID Physician 1
Additional forms of testing would be beneficial (9)	"I'd like having a tool where you could do the test right there, and know. That would be great. Or a way to calculate your risk factor of developing something, right? So more, I guess, technical tools than time." -ID Physician 2

- The domain of Environmental Context and Resources resulted in the identification of the largest number of belief statements, with a total of nine being related to this TDF domain. Many identified beliefs were related to frustration expressed at a lack of needed resources and reliable information to accurately evaluate a BL allergy's legitimacy. The beliefs "Evaluating allergies is too time consuming", "Documentation of information is missing or unreliable", "Additional forms of testing would be beneficial," and "Severe reactions are better remembered and documented" all fall into this category, and the lack of reliable information from patients and family was frequently reported across all clinician groups and specialties. However, in contrast to this belief, there was an

indication that the clinicians tended to trust the information which was able to be provided and was available in the EHR through the belief "I am confident in the information provided when it is available." There was also a sentiment that the clinician felt that although BL evaluation was important and should be conducted, their care setting involved more emergent problems which had to take precedence in acute situations.

Table 4-5-6: Goals

Belief Statement (n interviews belief was expressed)	Selected Quote
My goal is to provide high quality care (12)	"My goal is really to optimize their therapy to give them some sort of beta lactam if possible." -ID Pharmacist 1
My goal is to immediately treat the patient (8)	"Usually, if I am evaluating the legitimacy, I already have the drug at the bedside, so it's just to determine whether or not it's safe to give." -ICU Nurse 1
My goal is to clarify the allergy (13)	"To get to the bottom of it. To really try to figure out why it's on the chart and whether or not it's true." -ICU Nurse 2

- The domain of Goals resulted in only three belief statements. Clinicians expressed a desire to clarify the allergy, and "why it's [the allergy] on the chart". Additionally, clinicians emphasized the importance of providing high-quality care and to "optimize therapy". Lastly, there were some clinicians who reported that the lack of time in their care setting required immediate treatment decisions, and their goal was more directly related to making a suitable treatment decision in the moment.

Table 4-5-7: Intentions

Belief Statement	Selected Quote
The allergy reaction is the most important factor for evaluation (20)	"If they do have a penicillin allergy, the next things we're asking is, well, "what type of reaction did the patient have when they had penicillin previously?" -ID Pharmacist 2
The allergy does not need evaluated unless a penicillin is being given (16)	"If I'm getting the patient from another nurse or if they're not ordered the medication, I'm not going in-depth on their allergies." -General Nurse 1
I do not evaluate well-documented allergies (5)	"But if there's a class, an agent, a description, I think that's pretty good documentation. Which we rarely have an agent. It's usually just penicillins or cephalosporins or something like that. I'll always at least bring it up when I'm talking to teams, but I think that the better the documentation, the less probing that I do." -ID Pharmacist 1
Every allergy needs evaluated every time (6)	"I mean, it's just - you've got to do it for every patient." -ED Pharmacist 2
Allergy evaluation is very high priority in some circumstances (18)	"I think it's important, but not necessarily acutely in the emergency department, right? I think if I have to give somebody an antibiotic and I don't have a good alternative, it becomes very high on my list." -ED Physician 1

- The belief statements identified in the Intention domain focused on two main concepts: first, the relative priority of evaluating beta-lactam allergies, and second, the patient and environment-related factors which are intrinsic to the decision of whether or not to further evaluate a particular allergy. For the prior category, it was expressed that there are some situations where allergies must be evaluated and others where it is lower priority. The differences in priority may be affected by care setting, shown by ED Physician 1 stating that "It's important but not necessarily acutely in the emergency department". Regarding the second category, there was a sentiment that the allergy does not need evaluated unless there is an immediate plan for the patient to receive a BL-containing product, but others expressed that it is important to evaluate every allergy every time and "for every patient". Finally, it was expressed that the reaction to the allergy itself is a strong influence in whether or not the clinician further evaluates an allergy, with many indicating that reactions such as rash and itching are the most troublesome and prompt the most evaluation due to their ambiguous nature.

Table 4-5-8: Knowledge

Belief Statement (n interviews belief was expressed)	Selected Quote
There is confusion between side effects and allergies (14)	"It is my experience that the majority of documented allergies are not actually true allergies, as opposed to somebody thought maybe it was an allergy, so it gets put into the record just in case." -ICU Nurse 2
There is a lack of knowledge / education on this topic (9)	"But as a nurse, I don't think a nurse is really ever going to go too much beyond because they don't understand it. They don't have the knowledge base. That in depth anyway." -ID Nurse 1
I know which beta lactams I can use based on side chain activity (8)	"And then the second part that I think would be most important is being able to interpret cross sensitivity between the allergy and whatever medication that is ordered." -General Pharmacist 1
I know what a true allergy is (6)	"I think I have a pretty good handle on being able to chart check and determine if that if that's true anaphylaxis, or true IGE-mediated reactions versus an intolerance." -ICU Pharmacist 1
Beta lactams are the optimal choice for some infections (12)	"So, I mean, if I can use penicillin and that's the optimal agent for the patient, then I would change to it as long as I can use it." -ID Physician 1

- The beliefs identified in the Knowledge domain focused on the understanding of BL medications and the true definition of drug allergies. It was expressed that patients are not commonly able to differentiate between allergies and side effects, and that a large amount of this confusion is reflected in the poor documentation entered into the EHR. An important quote reflecting this belief is that the allergy may be documented "Just in case", which echoes some hesitancy shown in the Beliefs about Consequences domain. There were a few beliefs identified which were relating to unique aspects of BL medications, such as the lack of education on the topic, side chain activity, and BL agents being the optimal choice for some infections. Lastly, there were clinicians who expressed a personal aptitude for recognizing and distinguishing a true allergic reaction from an erroneous allergy.

Table 4-5-9: Memory, Attention, and Decision Process

Belief Statement (n interviews belief was expressed)	Selected Quote
I can use alternative non-beta-lactam antibiotics (or generally other options) (9)	"Generally, if I'm considering prescribing a beta lactam and somebody says they've had an allergy. First, it's - do we have an easy switch? That's not a beta lactam to treat this? And then we'll go with the easiest switch." – General Physician 2
I can use alternative beta-lactam antibiotics (10)	"We generally will give beta lactams to patients that have these kind of histories of penicillin allergies, for example." -ED Pharmacist 1
I can use anything a patient has previously received (8)	"If I clearly see that they've received similar antibiotics safely in the past than I do very little to no further investigation at that point." -ICU Pharmacist 2
Every patient has different needs (8)	"So again, it will vary from patient to patient, depending on what's documented in the electronic medical record." -ID Pharmacist 2

- The beliefs derived from the Memory, Attention, and Decision Process domain largely focused on the ability to determine which agents were appropriate to use given the details that were uncovered about the patient and the allergy in question. For example, there was recognition that it would be appropriate to use any agent which a patient has already previously tolerated with "little to no further investigation". Referencing a more general approach, there was also sentiment that clinicians were able to use alternative agents, both other BL-antibiotics and non-BL antibiotics depending on the situation. Some clinicians emphasized the importance of understanding that every patient has unique needs and it may not be best to approach any complicated situation such as this with a broad brush, and it is instead better to evaluate "patient to patient".

Table 4-5-10: Optimism

Belief Statement (n interviews belief was expressed)	Selected Quote
It is not possible to confidently evaluate some allergies (7)	"Unfortunately, a lot of the time, there's not an absolute answer, and the legitimacy remains nebulous or unclear." -ICU Nurse 2
Most documented allergies are not true allergic reactions (7)	"Nah. It's pretty clear that most people that have documented penicillin allergies are not real, or at least they're not true allergies." -ED Physician 1
Allergies are not evaluated as often as they should be (8)	"I think it gets missed a lot. I think, on the front lines, it doesn't necessarily happen as much as we would like it to upfront." -ID Pharmacist 1

- Similar to the Emotion domain, the beliefs identified through the Optimism domain did not elicit powerful positive or negative responses. All three belief statements identified through this domain focused on pessimism around the ability to evaluate some allergies and the situations surrounding them. Some interviewees identified that most BL allergies they see are "not true allergies", and consistent with this belief, felt that the allergies were not being evaluated as often as they ought to be and that it "gets missed a lot". Clinicians also reported the belief that despite following what they believed to be the best practices, some allergy evaluations would ultimately end in an educated guess and that "a lot of the time, there's not an absolute answer".

Table 4-5-11: Reinforcement

Belief Statement	Selected Quote
There is no reward or recognition for evaluating allergies (17)	"But then from the institution, no reward. Nothing." -ICU Physician 2
There is little to no oversight on allergy evaluation (4)	"I don't think that somebody would ever know that you didn't evaluate it, to be honest with you." -ICU Nurse 1
I am unlikely to be reprimanded whether or not I evaluate allergies (16)	"No, nope. it's a free for all. Since COVID, it's been the Wild West." -ED Pharmacist 2
I am personally satisfied by providing good care to the patient (5)	"Well, I guess my goals of doing an investigation would be that the treatment team as a whole can feel more comfortable about providing safer care for the patient." -General Physician 1

- The belief statements related to the Reinforcement domain highlighted that there is a general lack of oversight and emphasis placed on BL allergy evaluation. It was expressed that clinicians were unlikely to be reprimanded for not evaluating an allergy, which is likely related to the lack of monitoring on BL evaluation by institutions, where one clinician reported "I don't think that somebody would ever know that you didn't evaluate it." There was also some sentiment that adherence to best practices may have worsened significantly secondary to COVID-19 as well, as evinced by the quote provided by ED pharmacist 2 reporting that "Since COVID, it's been the wild west." The positive reinforcement that was reported was in the form of personal satisfaction on the side of the clinician through "providing safer care for the patient".

Table 4-5-12: Skills

Belief Statement (n interviews belief was expressed)	Selected Quote
Navigating the EHR is an important skill (10)	"I guess maybe navigating through the chart a little bit better. And learning where to find everything." -General Pharmacist 2
Interviewing patients/family is an important skill (11)	"But that interviewing skills and how to ask sufficient open-ended questions. It would be is really important." -General Physician 1
I have experience evaluating allergies (16)	"I probably have more prior experience than many other subspecialties. But I would say it's even more strong in the last few years because of the emphasis we put on this very topic." -ID Pharmacist 2
I am guided by what others have taught me (3)	"How I do that practice, I learned from my senior resident. When I was a young resident, from my tutor, the attending physician how to do that." -ICU Physician 2
Evaluating allergies requires experience (5)	"But I don't even know, if brand new nurses [would know how to evaluate a BL allergy]. Experienced ones learn that in experience, right? I don't know that a brand-new nurse would even know to be weary of a cephalosporin." -ID Nurse 1

- The belief statements identified from the domain of Skills did not suggest many skills that were uniquely required for BL allergy evaluation. Clinicians did express a general familiarity and experience with evaluating BL allergies, and there were some clinicians who highlighted the importance of having this experience when evaluating BL allergies. This experience may come in the form of mentorship by residents or other training experiences, as expressed by ICU Physician 2 stating "I learned from my senior resident. When I was a young resident". The second set of beliefs related to skills were focused on information gathering and "where to find everything", either through navigating the EHR or through interviewing patients and family members for allergy-related information.

Table 4-5-13: Social Influences

Belief Statement	Selected Quote
I rely on others to make the final decision (7)	“I would think ultimately it comes down to the prescriber who chooses what we're going to order.” -General Pharmacist 2
I have colleagues I can consult when needed (12)	“And if that's the case, then the processes to communicate that with the other care providers, as well as with the parents.” -ICU Nurse 2
I am prompted by others to evaluate allergies (5)	“Because I think we rely on the pharmacist a lot for the allergies because they'll call me and say "This patient has this is allergy" and they'll reject the medication.” -General Nurse 1
I am confident in my colleagues (13)	“But with other infectious diseases pharmacists, I think they're all very good at assessing allergies and investigating further.” -ID Pharmacist 2
Evaluating allergies is not a high priority to my employer / supervisor (7)	“Reviewing them, yes. To say whether or not there is one. But as far as investigating to determine whether it's actually one, I wouldn't say that's something that we actively push or promote.” -ICU Nurse 1
Evaluating allergies is a team effort (9)	“So generally, it's a two-person job. Because you might not have all the knowledge, so one part is the health care provider and the other one is the pharmacist.” -ID Physician 2
Evaluating allergies is a high priority to my employer / supervisor (12)	“I think from a departmental standpoint, from our ID group, there's a push towards evaluating beta lactam allergies.” -ID Pharmacist 1

- The belief statements identified through the Social Influences domain highlight interesting influences between practitioners and their expectations on evaluating BL allergies. Some clinicians reported that regardless of any information they discovered related to the evaluation of a BL allergy, they may rely on others to make the final decision, and that in particular it "comes down to the prescriber". There was a persistent feeling that clinicians had colleagues they could consult when needed, and that they had a high degree of confidence in those colleagues, which is a positive finding since there was also a sentiment that the evaluation of BL allergies is a team effort. Some clinicians are prompted by others to evaluate allergies, such as General Nurse 1 reporting that calls from pharmacists may be the trigger to further evaluate a BL allergy. From a supervisory / employer standpoint, there was a conflicting sentiment between those who felt that there was a significant push to evaluate BL allergies and those who did not feel it was a high priority. There were some clinicians who expressed both sides of this belief through reporting that BL evaluating was important at a "departmental standpoint" but not emphasized from an organizational standpoint.

Table 4-5-14: Social and Professional Role and Identity

Belief Statement (n interviews belief was expressed)	Selected Quote
Pharmacists are the most equipped to evaluate allergies (18)	"I do think that the pharmacists are better than most of us about doing these things because, they deal with meds. They understand the cross-reactivity between different meds and everything else. They're much better looking at the med histories than most of us are." -ED Physician 1
Nurses are too busy to evaluate allergies (2)	"I try not to make it mine, but it is usually mine and the nurses in general. They're so busy right now. We have like three of them in the whole hospital, I think right now. So, I try not to put that on them." -ED Physician 1
Nurses are relied on for information gathering, not evaluation (5)	"As far as nurses go, because again, we just confirm the allergy, confirm the reaction and it kind of ends there for us." -General Nurse 2
It is the prescriber's job to evaluate allergies (11)	"I think that should rest with the provider or the advanced practitioner that's working with the provider." -General Physician 2
It is everyone's job to evaluate allergies (11)	"I mean, everybody on the team. The nurse, especially the nurses and the doctors. I work with interns, so the interns do that work a lot of the time." -General Nurse 1
Evaluating allergies is part of my job (8)	"I just find it to be part of my job and making sure the patient is on the right antibiotic." -ID Pharmacist 2
All clinicians should know how to evaluate allergies (4)	"But I think it is basic medical knowledge, so every medical doctor should know how to evaluate the legitimacy of an allergic reaction and so on." -ICU Physician 2

- The patterns of beliefs identified from the Social and Professional Role and Identify domain are highly complementary to the Social Influences beliefs. An important belief was expressed relating to the expectations of nursing in BL allergy evaluation where it was expressed that "[nurses] just confirm the allergy, confirm the reaction, and it kind of ends there for us", which was complementary to clinicians reporting that the physician who was prescribing the BL product was ultimately responsible for the evaluation process. In contrast, other clinicians expressed that BL evaluation was a part of their role and "to be part of my job". There was also a sentiment that evaluating BL allergies was a team effort which should be manageable by any member of the care team, but particularly "every medical doctor". Finally, it was expressed that pharmacists were the most equipped to evaluate allergies because "they deal with meds", despite the underlying belief that the final decision and responsibility ultimately rested upon the prescribing physician.

4-5: INTERVENTION RECOMMENDATION AND DISCUSSION

4.5.1 Belief Statement Interpretation and Intervention Recommendations

To begin the process of translating the identified belief statements into recommendations, the overall strength and sentiment of the belief statements from each TDF domain will be considered as a whole and evaluated as either important or not important for BL allergy evaluation. This will provide a preliminary group of domains and beliefs to target for intervention design. Additionally, since many beliefs that were reported are complementary in influencing behavior, domains with beliefs that had similar sentiment, such as Social Influences and Social and Professional Role and Identity, will be evaluated together. The interpretation of the belief statements and translation into intervention recommendations invariably requires an amount of subjective interpretation of the relative importance of each belief that was identified throughout the interview process.[135] In order to minimize this subjective interpretation, the belief statements were reported with their overall frequency, which has been previously used as a method to gauge the relative strength that each belief was expressed.[148] However, since each belief was not necessarily evaluated in each interview due to the nature of semi-structured interviews, the frequency of each belief statement must then be interpreted in accordance with selected quotes and overall sentiment of each belief in influencing the targeted behavior, and the justification for evaluating each domain as important or not important will be based on both the frequency that each belief was reported and the quotes from each belief. Finally, literature which supports the link between the identified belief statements and the evaluation of BL evaluation will be provided and considered while evaluating the importance of each domain.

Important Domains for BL Allergy Evaluation

Social Influences / Social and Professional Role and Identity / Behavioral Regulation

The belief statements and strength of the beliefs identified from the domains of behavioral regulation, social influences, and social and professional role and identity are highly inter-connected, and will be interpreted together. Some of the most strongly expressed beliefs from these three domains involved feelings that although each individual clinician was confident in themselves and their teams in evaluating allergies, there was differing opinions on who should bear the final responsibility. Many clinicians (18/25) expressed the belief that pharmacists were the most equipped to evaluate BL allergies, and it's a natural extension to support pharmacists in acting as the primary clinician responsible for BL allergy evaluation. Pharmacists have been previously identified as equally or more knowledgeable than other care providers, including physicians and advanced practice providers, in the proper evaluation of BL allergies.[69] Additionally, programs of pharmacist-led BL evaluation have been shown to be highly successful and within the expected scope of practice for pharmacists, with between 58-96 % of tested patients being able to have erroneous BL allergies successfully delabeled by pharmacist-led programs.[70,72-74]

This restriction and environmental restructuring intervention would involve assigning and empowering pharmacists with the required time and resources required with the patient and other care team members to evaluate BL allergies. By acting as the clinician-champion in this role, they would also be modeling the proper evaluation behaviors to other care team members. Implementing this intervention would also alleviate much of the confusion regarding role assignments in allergy evaluation, where nurses were self-reporting that they did not see themselves in a direct evaluator capacity but instead as information gatherers and allergy confirmers. In assigning pharmacists to act in this role, it would be beneficial to outline and widely disseminate a clear organizational policy indicating this change in responsibility, which was the strongest belief identified through the behavioral regulation domain.

Environmental Context and Resources / Beliefs about Capabilities / Memory, Attention, and Decision Process / Intentions / Knowledge

Similar to the previous three domains, the domains of environmental context and resources, beliefs about capabilities, and memory, attention, and decision process, intentions, and knowledge all identified a set of belief statements which are useful to consider together while designing an intervention that would be targeted at all five domains simultaneously. Many clinicians strongly indicated that they were confident in challenging and removing erroneous BL allergies when presented with the knowledge that was required to make that decision. However, the beliefs identified through the environmental context and resources domain stressed the unreliability of current resources due to unclear and missing EHR documentation and unreliable patient and family histories. A previous examination of BL allergy documentation quantified this documentation issue, and found that over 20% of documented allergies did not contain a reaction, and over 50% of documented allergies warranted further evaluation due to reporting low-risk reactions that are inconsistent with true immune-mediated reactions.[38] A survey of physicians also found that over 85% of physicians are unsatisfied with the current state of allergy documentation, with over 40% believing it was either too limited to unclear how and where to document allergies.[78]

In order to address this problem, we recommend that an environmental restructuring take place regarding the EHR process for documenting allergies, and that it be reworked to require the inclusion of more relevant information such as the date of the last time the allergy occurred, who is reporting allergy-related information, and whether they have ever previously tolerated any related medications such as cephalosporins or carbapenems. In particular the EHR process for entering allergies should stress the importance of having a clearly defined reaction, as this was consistently identified as the key factor in determining the legitimacy and severity of an allergy through the Intentions domain. When reporting an ambiguous reaction such as rash or itching, the EHR should prompt the evaluator to add as much additional

context regarding the severity of the reaction as possible from the allergy reporter. Recent improvements in allergy reaction picklists could be implemented with this rework to help standardize reaction documentation.[123] The use of picklists in allergy evaluation have also been supported by a 2022 Work Group by the American Association of Allergy, Asthma, and Immunology.[151]

The results of memory, attention, and decision process domains indicated that clinicians were comfortable utilizing alternative agents to meet the immediate needs of the patient, but this may sometimes lead to an increased utilization of non-BL antimicrobials. In order to address this, a potential rework of the allergy portion of the EHR should also empower clinicians in prescribing ideal antimicrobials whenever possible despite the presence of an allergy by assisting in the medication history process and having clear processes available for identifying what agents a patient has tolerated in the past despite the presence of the allergy. Guidelines by Canadian Society of Allergy and Clinician Immunology have supported the use of previously tolerated BL products, indicating that after tolerating a medication without reaction, the patient is "low risk" and may be prescribed the same medication again.[152] Side chain cross-reactivities can help inform the use of which BL products are most and least likely to react to a particular allergy.[153] In particular, promoting the availability and use of side chain cross-reactivity charts can help alleviate some of the ambiguity associated with unclear allergies, such as identifying which alternative agents might be appropriate if the patient has an allergy documented as "penicillin", instead of to a specific agent. The EHR can also assist the clinician in making judgement-based decisions through the inclusion of preferred agent suggestions for particular conditions in the setting of an allergy and the corresponding information regarding the allergy, while also integrating side-chain tables to estimate the likelihood that an allergy to one BL agent would preclude the use of other antimicrobials, both of which were important beliefs identified through the knowledge domain.

Domains Not Identified as Important for BL Allergy Evaluation

Beliefs about Consequences / Goals

The beliefs from these two domains emphasized the underlying belief that it is important to provide high-quality care and that ambiguity in allergy evaluation should be addressed by taking the most conservative approach and avoiding BL-containing products. Increased utilization of clear evaluation techniques and reliable access to information through the two suggested interventions should address much of the uncertainty in BL allergy evaluation and provide clinicians with the confidence needed to interpret the results of a BL allergy evaluation as an actionable recommendation which will improve patient care. A prior qualitative evaluation of BL allergy-related beliefs also found that both patients and clinicians were not worried about the immediate consequences of being labeled with a BL allergy because of the ease of prescribing alternatives, so it is unlikely that this domain would be high influential in motivating behavior change.[80]

Optimism / Emotion

BL allergy evaluation was not seen as a high emotional task, and future intervention efforts should attempt to avoid introducing added stress into what is currently understood to be a low-stress evaluation. There was a moderate amount of prevailing pessimism regarding the likelihood that BL allergies were able to be properly evaluated, and although the two suggested interventions could help improve this underlying belief, the current pessimism is not seen as a large barrier to the evaluation of BL allergies and is instead likely a result of frustration with current unsatisfactory practices and resources. However, a previous survey found that 37% of clinical staff evaluating allergies felt that the patient was "unlikely to be convinced" as a reason for not discussing an erroneous allergy, and the importance of patient-related beliefs should be further evaluated in future interventions.[16]

Reinforcement

There was a belief that there is little reinforcement, whether positive or negative, surrounding the evaluation of BL allergies. However, clinicians were already likely to indicate that they personally viewed proper allergy evaluation as being important for patient care. Because of this, it is unlikely that any intervention aimed at rewarding proper evaluation or remediating improper evaluation would have any significant effect, and would not address the underlying environmental and structural issues with the allergy evaluation process.

Skills

Many beliefs resulting from the skills domain were positive in nature and indicated an acceptable level of ability to evaluate BL allergies. Some specific skills such as EHR navigation and collection of patient allergy histories were emphasized, but were not reported with the same strength as the resource and protocol-based beliefs as being large factors which are currently inhibiting the evaluation of BL allergies. It would be beneficial for training programs to increase the amount of teaching offered on the topic of BL evaluation and true allergy constitution since there is currently a lack of available allergy training programs.[154] However, it is not known how additional training on this topic from a health-system perspective would compare to modifying current behaviors. Additionally, there is a moderate level of misunderstanding on the best clinical practices in specific instances of BL evaluation, but this is likely best addressed through interventions targeting the Knowledge domain.[69]

4.5.2 Translating Beliefs to Intervention Functions, Behavior Change Techniques and Proposed Interventions

The capability, opportunity, motivation, behavior (COM-B) framework for motivation change underlies the domains in the TDF and can help guide the process of evaluating how influential each domain is in influencing the targeted behavior. A benefit of using the TDF combined with the BCW is the ability to

use the intervention function categories provided in the BCW, along with the COM-B behavior influences, to assist in translating inductive analysis results into theory-informed interventions. The BCW maps these intervention functions directly to the TDF domains, allowing for a straightforward mapping process. The TDF themes for the barriers identified in the interview were mapped to the intervention functions following the framework according to the final two steps of the 8-step process described in the COM-B/BCW framework. This process is outlined in Table 4-6. Further, these intervention functions were then translated to behavior change techniques using the same COM-B/BCW framework. Finally, based on practical experience, the sentiment of the reported beliefs, and the findings of previous published work as highlighted in each domain summary above, a list of proposed implementation interventions was produced. While formulating the proposed interventions, the five key areas within the Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) framework were also considered to ensure that interventions which were recommended would be amenable to effective and reproducible evaluation and implementation methods at both the individual and organizational level. The results of considering how each area in RE-AIM would apply to the proposed interventions are highlighted in Table Set 4-7. The full process of conducting, transcribing, and analyzing the data to produce the proposed interventions is summarized in Figure 4-2.

Table 4-6: Belief Statement Intervention Recommendation Translation Summary using the Capability, Opportunity, Moviation, Behavior Model and Behavior Change Wheel Function Categories

COM-B Component	TDF Domain	Relevant Belief Statement(s)	Behavior Change Wheel Intervention Function Categories	Behavior Change Techniques	Proposed Intervention
Psychological Capability	Behavioral Regulation	• There is no policy or it is only informal • I do not know if we have a policy	• Training • Environmental Restructuring	• Demonstration of the behavior • Social Support • Restructuring the physical environment	Develop and disseminate a policy for BL allergy evaluation while promoting the use of pharmacists in drug allergy evaluation
Opportunity	Social Influences	• I have colleagues I can consult when needed • I am confident in my colleagues	• Enablement		
Reflective Motivation	Social and Professional Role and Identity	• Pharmacists are the most equipped to evaluate allergies	• Modelling • Restriction		

Table 4-6 (Continued)

Reflective Motivation	**Beliefs about Capabilities**	• **Most allergies can be determined with the proper tools and information** • **I am confident in my ability to evaluate an allergy** • **I am confident in removing / amending allergy documentation**	• **Enablement**	• **Restructuring the physical environment** • **Review the behavior goal** • **Review the outcome goal** • **Adding objects to the environment** • **Self-monitoring of behavior** • **Instruction on how to perform a behavior**	**Rework of the EHR process for documentin g and accessing allergy information**
Psychological Capability	Knowledge	• There is confusion between side effects and allergies • Beta-lactams are the optimal choice for some infections	• Education		
Reflective Motivation	Intentions	• The allergy reaction is the most important factor for evaluation • The allergy does not need evaluated unless a penicillin is being given	• Modeling		
Psychological Capability	Memory, Attention, and Decision Process	• I can use alternative agents (both beta-lactams and non-beta-lactams) • I can use anything a patient has previously tolerated	• Training • Environmental Restructuring • Enablement		
Physical Opportunity	Environmental Context and Resources	• Patients and family are unavailable or unreliable • Documentation of information is missing or unreliable • I am confident in the information provided when it is available	• Environmental Restructuring • Enablement		

Table Set 4-7: RE-AIM Criteria Applied to BL Allergy Proposed Interventions

Table 4-7-1: RE-AIM Criteria Applied to Intervention 1

Intervention 1: Develop and disseminate a policy for BL allergy evaluation while promoting the use of pharmacists in drug allergy evaluation

Dimension	Application to Proposed Intervention	Potential issues / future directions
Reach	Local policies apply broadly within their own system setting	Local policies may conflict with society-level recommendations
Effectiveness	Policies can clarify processes and standardize steps in BL allergy process Pharmacists can effectively evaluate and BL allergies	Allergists remain the gold-standard for allergy evaluation and should be utilized when appropriate
Adoption	System-level policies do not require further approval Evaluating allergies is within pharmacist scope of practice	Individual-level buy-in is required to identify and train staff on new policies Pharmacists must be identified to undertake initiative
Implementation	Local BL-allergy champions can assist in implementation and ensure uptake through departments	Different departments may be different implementation needs, complicating uptake of policies
Maintenance	Policies can be periodically re-evaluated for effectiveness or evidence updates	Staff must remain abreast of new policy changes

Table 4-7-2: RE-AIM Criteria Applied to Intervention 2

Intervention 2: Rework of the EHR process for documenting and accessing allergy information

Dimension	Application to Proposed Intervention	Potential issues / future directions
Reach	EHRs are used widely and allow for broad standardization across health systems	Processes may differ between EHRs, causing confusion
Effectiveness	Previous literature has identified that current documentation of allergy information is lacking Documentation of allergies has been targeted by expert groups as an area of focus	New evidence must be periodically updated, such as cross-reactivity charts Any allergy-related decision-support alerts must be evaluated for effectiveness and revised appropriately
Adoption	EHR use and format is mandated at the system-level	Staff may bypass alerts if they are ineffective
Implementation	EHR use and format is mandated at the system-level	Technical challenges may limit some EHR capabilities for allergy documentation
Maintenance	Once functioning and standardized, new documentation processes will require little maintenance as mostly static portions of the EHR	Processes should be evaluated after implementation and feedback from clinicians should be considered for ongoing revisions

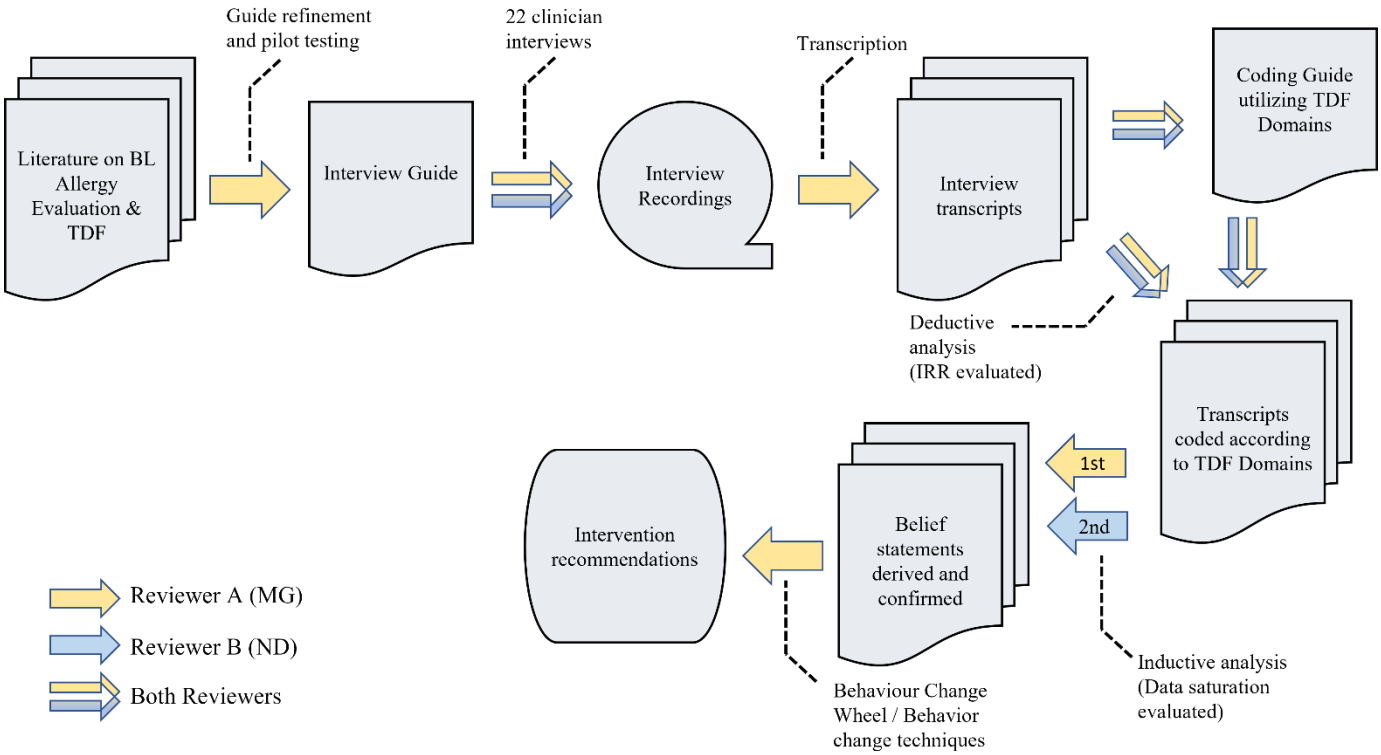


Figure 4-2: Flowchart for Interview, Transcription, and Analysis Process

BL = β-lactam
TDF = Theoretical domains framework

4.5.3 Intervention Summary Recommendations

The first recommendation that is supported by the results of our interviews is that pharmacists should be on the forefront of BL allergy evaluation and act as the clinician-champion on the topic. Pharmacists and pharmacy students have been the target of educational programs aimed at improving the accurate evaluation of BL allergies, which may be a factor in explaining why the interviewed clinicians overwhelming reporting pharmacists as the most equipped for this task.[155,156] Pharmacist-led BL allergy delabeling has been found to be highly safe and moderately-to-highly successful through the use of structured clinical histories alone, without the need for oral amoxicillin challenges or skin testing.[73] Pharmacists can accurately stratify the risk of a BL allergy and appropriately de-escalate antimicrobial coverage away from carbapenems, and between 74 and 88% of pharmacist recommendations based on patient interviews were accepted by providers.[157,158] As a secondary benefit to empowering pharmacists to evaluate BL allergies, it has been shown that the documentation of allergies also improves with pharmacist involvement, such as an over 3-fold increase (8.8% vs. 28.4%) in the number of allergies which have additional documentation describing patients' historical tolerances to BL medications.[159]

Pharmacist-led and pharmacy-technician-assisted models for BL allergy evaluation have been well described and can be tailored uniquely for a health systems' particular needs and resources.[75,90,160] Education can be provided to participating staff by infectious disease pharmacists or allergists to train on the proper methods for allergy evaluation through structured medical history, and may further include guidelines for obtaining skin testing if resources are available to support such testing services.[90] The availability of skin testing services can lead to mildly higher rates of successful delabeling over structured history alone, but health systems which lack the ability to support this resource-intensive service can still achieve successful increases in BL-usage through structured history alone.[160] Direct oral challenges are also an option to supplement structured history alone and require less resources than a skin test.[161] There was a belief

identified that additional resources would be valuable for BL allergy evaluation such as skin testing, and hospitals should consider expanding these resources where possible. However, even hospitals which lack specialists or personal required for more skin testing and oral challenges should consider investing in additional pharmacy services to manage BL allergies since only an average of 0.15 full-time pharmacists were required to offer pharmacist-led BL allergy evaluation in a large university hospital.[162] BL evaluation has also been found to be highly cost-effective, and may result in substantial cost savings through a reduction in adverse drug events.[163,164] Overall, the high confidence shown by colleagues in pharmacist-led BL allergy evaluation, in combination with the relatively low resource investment required and proven success of previous implementations strongly supports the expansion of pharmacist-led BL allergy evaluation programs.

The current process for allergy documentation in EHR systems is enamored with inconsistencies and leads to a large amount of confusion for clinicians in applying allergy knowledge to patient care.[151] There is a lack of consensus on what constitutes an 'allergy' that warrants entry into the EHR, as well as how drug intolerances should be documented compared to true drug allergies.[165] The inability for clinicians to properly utilize documented allergy information leads to high rates of allergy alerts being bypassed, including life-threatening allergy alerts, which are overridden over 70% of the time they occur.[166,167] It is likely that without major changes, the current process for allergy documentation will only continue to deteriorate since over 80% of drug allergies are never deleted, and allergy lists generally only tend to grow over time.[168] Many of these complaints and concerns were mirrored through the belief statements that were identified from the interviews, such as a lack of consistency in documented allergy information and frustration that the EHR was often hindering their ability to evaluate allergies instead of enabling it. These sentiments strongly support the initiatives proposed by a recent 2022 work group by the American

Academy of Allergy, Asthma, and Immunology which highlight the need for standardized terminologies for allergy reactions, an EHR rework, and expanded training for allergy documentation.[151]

This work group recommended an EHR rework which steers away from the use of free-text allergy documentation, instead using a hierarchical categorization system which will automatically delineate between immune-mediated reactions, patient preferences, and other important hypersensitivity information at the time of the clinician entering the allergy. A system such as this which incorporates the severity would be highly beneficial and could alleviate a large amount of the frustration expressed by clinicians in attempting to determine when some documented reactions, such as rash, are clinically significant enough to warrant an alteration in therapy. Additionally, it was recommended that EHR systems incorporate clinical decision support alerts to identify medications which have been previously tolerated, which was a belief identified through our interviews. Finally, the group recommended that all clinicians with access to the EHR should receive training on proper allergy documentation and the use of the improved allergy section. This EHR rework would also offer an opportunity to incorporate cross-reactivities into EHR allergy systems, which can direct prescribers to which agents are most likely to be tolerated given the details of the allergic reaction. Importantly, while our study focused on the evaluation of "BL allergies" as a whole, allergies are most likely to be reported to a singular agent or class, such as "penicillin", and cross-reactivities are particularly useful for distinguishing between which agents may be likely to be tolerated in the setting of an agent or class-specific allergy.[18]

4.5.4 Limitations

Our study has some notable limitations, many of which are inherent to the use of semi-structured interviews and a qualitative study design. First, we sought to interview a diverse population of clinicians in order to capture a wider picture of the beliefs that front-line clinicians hold on BL allergy evaluation.

However, we were only able to interview two clinicians in most provider-specialty groups, and failed to interview any nurses working in emergency medicine. A larger number of interviews would increase the confidence that our sample was not skewed due to low sample size. Additionally, our sample of clinicians may be subject to response bias since clinicians with the most knowledge on the topic of BL allergy evaluation may also be those most inclined to agree to be interviewed on the topic, resulting in beliefs that are skewed towards clinicians with a higher level of understanding on the topic. Second, there is an amount of subjective interpretation that must be done through the deductive and inductive analysis process, but we did attempt to minimize the risk for bias by including a second reviewer. There was a degree of disagreement due to the large number of domains in the TDF, and some lower kappa values such as those for Beliefs about Consequences which had particularly lower agreement may have less reliable translation into belief statements. Interviewees were aware that the research team consisted of pharmacists through the initial recruitment email, and this may have led to more positive views on pharmacists to be expressed. Finally, we used the Behavior Change Wheel and the Theoretical Domains Framework as a basis for understanding current limitations in practice and formulating intervention strategies, but it should be mentioned that these are other frameworks for intervention design and behavior change, including the Consolidated Framework for Implementation Research.[169]

4.6: CONCLUSIONS

This qualitative study identified beliefs which are currently limiting the proper evaluation and delabeling of BL allergies in practice. Frustration was expressed with the poor consistency in allergy documentation and a lack of necessary resources such as time to perform BL allergy evaluation and delabeling. Pharmacists are uniquely positioned to take on a more direct role in BL allergy evaluation, and

health systems should incorporate models which empower pharmacists to act in this role. The process for documenting allergies and interpreting allergy information in EHRs should be reworked to remove ambiguity in how reactions are listed and assist clinicians in determining historical medication usage and cross-reactivities.

5.0 LONG-TERM CLINICAL OUTCOMES ASSOCIATED WITH BETA-LACTAM ALLERGIES USING MIXED-MODEL SURVIVAL ANLYSIS

5.1 ABSTRACT

BL allergies alter prescribing decisions, and a patient who has a BL allergy listed in their electronic health record has a higher likelihood to receive second-line antimicrobials. It has been well-established that these altered prescribing pathways incur adverse outcomes such as increased healthcare utilization and higher rates of resistant infections compared to treatment pathways that utilize BL-containing products. However, the presence of a BL allergy is often a life-long risk factor, and only one study has examined patients for a period of more than 5 years to determine the long-term outcomes for patients who have a BL allergy listed in their EHR compared to those who do not.

We used a retrospective cohort study design, including patients who had an index healthcare encounter within in a single regional western Pennsylvania health system with a diagnosis of sepsis, pneumonia, or urinary tract infection between the years of 2007-2008. Patients meeting this inclusion criteria were then followed from the time of the index encounter to each patient's latest observed healthcare encounter, the end of 2018, or death. The primary outcome of interest was the hazard of all-cause mortality. Secondary outcomes included occurrence and severity of acute kidney injury, and hazards of resistant infections with methicillin-resistant *staphylcococus aureus*, *clostridium difficile*, and vancomycin-resistant *enterococcus*. Parametric mixed-effect survival models were used to conduct a time-to-event analysis while using each individual patient as a cluster variable. Control variables included age, race, sex, Elixhauser (Van Walraven) comorbidity scores, baseline serum creatinine, total number of healthcare encounters, incident

use of hemodialysis, and intensive care hospital encounters. Secondary analyses were conducted which analyzed beta-lactam allergy status as a time-varying indicator variable, and which compared the outcomes of beta-lactam-allergic patients to patients with non-beta-lactam antimicrobial allergies and multi-allergic patients.

A total of 4211 BL-allergic patients (52607 encounters) and 15881 non-BL-allergic patients (168327 encounters) were included in the analysis. BL-allergic patients were more likely to be female, white, and have multiple antimicrobial allergies. Death occurred in 2635 (62.6%) and 9602 (60.5%) of patients with and without BL allergies, respectively. MRSA (28.7% BL-allergic vs. 24.4% non-BL-allergic), CDiff (9.2% vs. 8.8%), and VRE (9.1% vs. 7.5%) all occurred in higher rates in BL-allergic patients, but the rate of stage 2/3 AKI (68.8% vs. 72.5%) and stage 3 AKI (68.1% vs. 72.1%) occurred more frequently in the non-allergic patients. In the primary analysis using parametric mixed-effect survival models, all-cause mortality was not significantly associated with the status of a BL allergy (HR 1.01, 95%CI 0.96 – 1.07). Resistant infections with MRSA (HR 1.50, 95%CI 1.34 – 1.68) and VRE (HR 1.23, 95%CI 107 – 1.42) were also significantly higher in the BL-allergic patients, but rates of AKI and CDiff did not differ. In the secondary analysis, all effects seen in the primary analysis were seen at higher rates when analyzing BL-allergy status as a time-varying indicator, with MRSA, and VRE all being significantly associated with BL allergies. Additionally, BL allergies were significantly associated with all-cause mortality when modeling BL allergy status as a time-varying indicator (HR 1.08; 95%CI 1.02 – 1.14). Patients with multiple antimicrobial allergies showed the highest risk for mortality (HR 1.21, 95%CI 1.10 – 1.33), MRSA (HR 1.55, 95%CI 1.29 – 1.86), and VRE (HR 1.38, 95%CI 1.09-1.76).

Our analysis showed that in a cohort of patients initially identified with a diagnosis of sepsis, pneumonia, or UTI, BL allergies were a statistically significant long-term risk factor for increased rates of resistant infections and may be associated with an increase in all-cause mortality. Patients with both BL and

non-BL antimicrobial allergies should be considered at particularly high risk and receive scrutiny to ensure they are receiving the most ideal antimicrobial options which can be tolerated. Health systems should emphasize the evaluation and delabeling of possibly erroneous allergies in order to reduce the harm caused through unnecessary BL antimicrobial avoidance. Future efforts should support risk stratification efforts by determining what risk factors can be synergistic in predisposing patients to harm in the setting of a BL allergy.

5.2 INTRODUCTION

It has been shown extensively that the listing of a beta-lactam allergy during an inpatient healthcare encounter is associated with increased rates of readmission, risk for resistant infections, length of stay, and adverse events.[4,35,58,60] The labeling of a beta-lactam allergy is not just a one-time risk as it is often considered in single-admission or short-term analyses, but is instead often a life-long status that causes harm during each healthcare encounter a patient experiences. There has been a large increase in initiatives to emphasize the de-labeling of erroneous BL allergies due to the mounting evidence of their risks.[170] However the long-term risks associated with BL allergies are poorly described and have received little emphasis in comparison.[171]

There has been only one previous cohort study to examine the long-term (>5 years) outcomes associated with the labeling of a beta-lactam allergy.[10,66] Beta-lactam allergies were associated with a 14% increase in the hazard of mortality over a 6-year span.[65] For comparison, the annualized hazard ratio for mortality is increased by 40% for someone with hypertension compared to a normotensive individual, and 25.4% for a smoker compared to a never-smoker, meaning the increase in mortality due to the presence of a beta-lactam allergy could be upwards of more than half the same risk as a standard tobacco smoker.[172,173]

This is a strikingly large increase in mortality, and is of significant concern because over 90% of beta-lactam allergies are erroneous in nature, meaning that the majority of beta-lactam allergy labels have little-to-no true basis in modifying the standards of care a patient receives.[7]

Despite overwhelming evidence of the safety and effectiveness of challenging questionable beta-lactam allergies, the majority of allergies are never questioned, and instead cause continual and lifelong damage, particularly in those who are already predisposed due to opportunistic and resistant infections due to immunocompromising conditions.[13,174-178] The poor documentation of beta-lactam allergies, which in many instances is decades old and might have occurred when the patient was a child, may be leading to one-time solutions for immediate management, while allowing the allergy to remain in the chart to cause insidious damage.[38,121,129,179,180] There are also instances where previously removed allergies have been reintroduced to charts due to a lack of patient understanding regarding their true allergy status.[181] The lack of knowledge on the long-term outcomes of may be impeding the sustainability and uptake of de-labeling programs if erroneous allergies are being perceived as a singularly occurring instance instead of a life-long risk factor.

We sought to expand the understanding of the long-term clinical outcomes associated with patients who have a documented beta-lactam allergy. Currently, there is limited information about the long-term outcomes of resistant infections or AKI due to beta-lactam allergy labeling, and only one study that examined all-cause mortality. Our study used mixed-model survival analysis to provide estimates of the effects of patients with documented beta-lactam allergy labels over the course of twelve years and enables health systems to expand delabeling efforts by providing an enhanced understanding of the long-term detriment of being labeled with a beta-lactam allergy.

5.3 METHODS

5.3.1 Study Design, Data Source & Review Board Approval

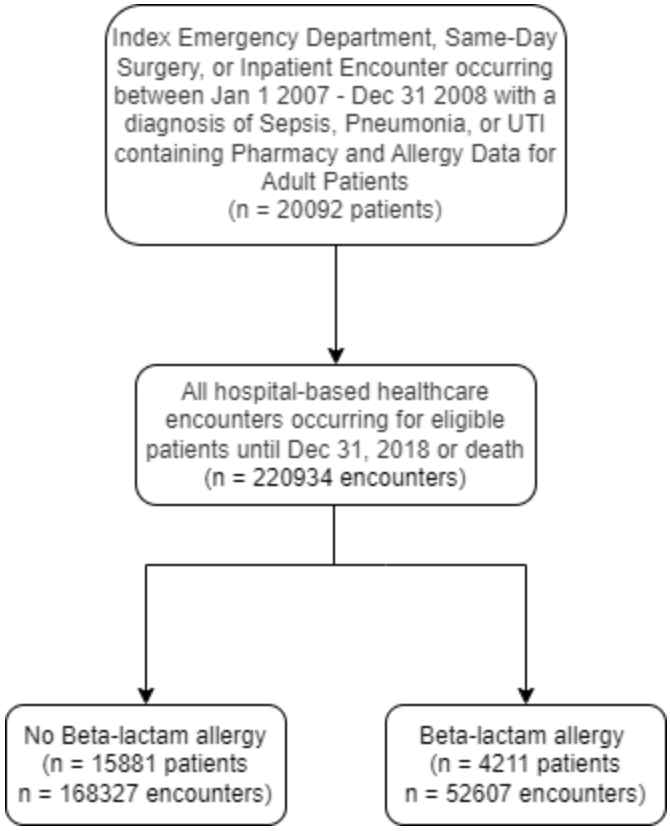
This study utilized a retrospective cohort design. A cohort of patients was identified from the Medical Archival Retrieval System (MARS), an electronic medical record data repository which contains integrated clinical, financial and administrative records for patients from UPMC, a regional health system in western Pennsylvania.[182] An honest broker obtained patient-level data with a waiver of informed consent. Patient data was de-identified to maintain patient confidentiality using De-ID™ software (University of Pittsburgh, Pittsburgh, PA), this study and process was approved as exempt by the University of Pittsburgh's International Review Board.[183]

5.3.2 Inclusion/Exclusion Criteria and Cohort Definition

Patients were identified for inclusion into the cohort through a hospital-based healthcare encounter between 2007-2008 with a diagnosis of sepsis, pneumonia, or urinary tract infection (UTI). Instances of sepsis, pneumonia, and UTI were identified through the use of ICD-9 codes through previously published methods. Sepsis was defined as an ICD-9 diagnosis of infection plus a code indicating organ dysfunction (excluding mechanical ventilation codes) (Appendix 5-1).[184] Pneumonia and UTI were identified using ICD-9 codes 480-487 and 599.0 and their child codes, respectively (excluding 487.1 – Viral Pneumonia; Full pneumonia codes seen in Appendix 5-1).[185,186] The methods used for identifying sepsis, pneumonia, and UTI have been found to have variable sensitivities, but generally high positive predictive values (PPV), with the methods used to identify sepsis and pneumonia achieving a PPV of 71% and 88% respectively.[185-

[187] The goal of the cohort was to identify a sample of temporally-related patients who would have a high likelihood of having their care affected by the presence of a BL allergy because the three selected indications include a majority of BL products as first and second-line products within their standards of care.[188-190] The patient selection process can be seen in Figure 5-1.

Figure 5-1: Patient Selection Process and Exclusion Criteria



Data was obtained for patients meeting the inclusion criteria from Jan 1, 2007 (starting with index encounter) through December 31, 2018. Patients were excluded if they were under the age of 18 during the index admission or if no allergy information was available for the index visit. The final cohort for analysis consisted of 20092 patients, of which 4211 reported a BL allergy and 15881 did not (Figure 5-1). Medication use and drug allergies were characterized using pharmacy discharge summaries which summarized net dispenses and credits at the medication level and listed allergies as free-text. Laboratory results were obtained from MARS and discrepancies in inter-hospital codes were manually harmonized using a system-level lab dictionary. Microbiology results were used to determine infection status. Data management and analysis procedures were conducted in accordance with the RECORD reporting guidelines for observational research (Appendix 5-5).[191] During this time period, UPMC hospitals were in

the process of migrating to the use of an electronic health record which was recorded in MARS, and data for each UPMC hospital was utilized as it was migrated (Appendix 5-2). Patients were followed from the beginning of the index encounter until death. Patients who did not die over the follow-up period were censored at the time of their last observed healthcare encounter or the end of 2018.

5.3.3 Dependent Variable

The presence of a BL allergy was defined as the listing of any penicillin, cephalosporin, carbapenem, or aztreonam as an allergy in the patient's allergy list.[45] Allergy lists were recorded as free text, necessitating manual review and assignment into correct allergy groups. Both brand and generic names were included through the manual review process, and an online repository of medications was utilized to ensure comprehensive inclusion.[192] Other allergy classes, such as fluoroquinolones and macrolide antibiotics were coded similarly (Appendix 5-3). Allergies are not necessarily evaluated and updated in practice during every healthcare encounter, and patients without available allergy information during the index admission were not included for evaluation since this was required for analysis. There were also instances where the initial BL allergy status of a patient changed during the follow-up period (e.g. an initially BL allergic patient later became non-allergic or vice versa). In total, 177 patients initially documented as beta-lactam allergic became non-allergic, and 778 patients initially documented as beta-lactam non-allergic became beta-lactam allergic during the follow-up period. When this occurred, the patient's initial allergy status was carried forward for the full follow-up period for the primary analysis. A sensitivity analysis was conducted where these patients were excluded instead of carrying forward the initial allergy status, and a second sensitivity analysis included these patients using a time-varying allergy status.

5.3.4 Directed Acyclic Graph and Causal Model

The directed acyclic graph (DAG) for the theoretical relationship between the presence of a beta-lactam allergy and the outcomes are shown in Figure 5-2. Antibiotic allergies primarily affect clinical outcomes through altered antibiotic selection involving inferior antibiotic selection including reduced beta-lactam usage and increased overall antibiotic utilization.[193] It has been previously reported that the presence of a penicillin allergy is associated with increased healthcare utilization and an increase in readmissions.[4,47] Healthcare utilization is also highly impactful on all-cause mortality, creating the potential for healthcare utilization to serve as a mediator between beta-lactam allergy labeling and mortality. An alternate DAG is provided in Figure 5-2 highlighting this theoretical effect by displaying the total number of healthcare encounters as a mediator instead of a covariate, and a mediation analysis was performed to explore this relationship more deeply. The independent variables selected were guided by previous studies examining the impact of beta-lactam allergies on mortality.[56,194]

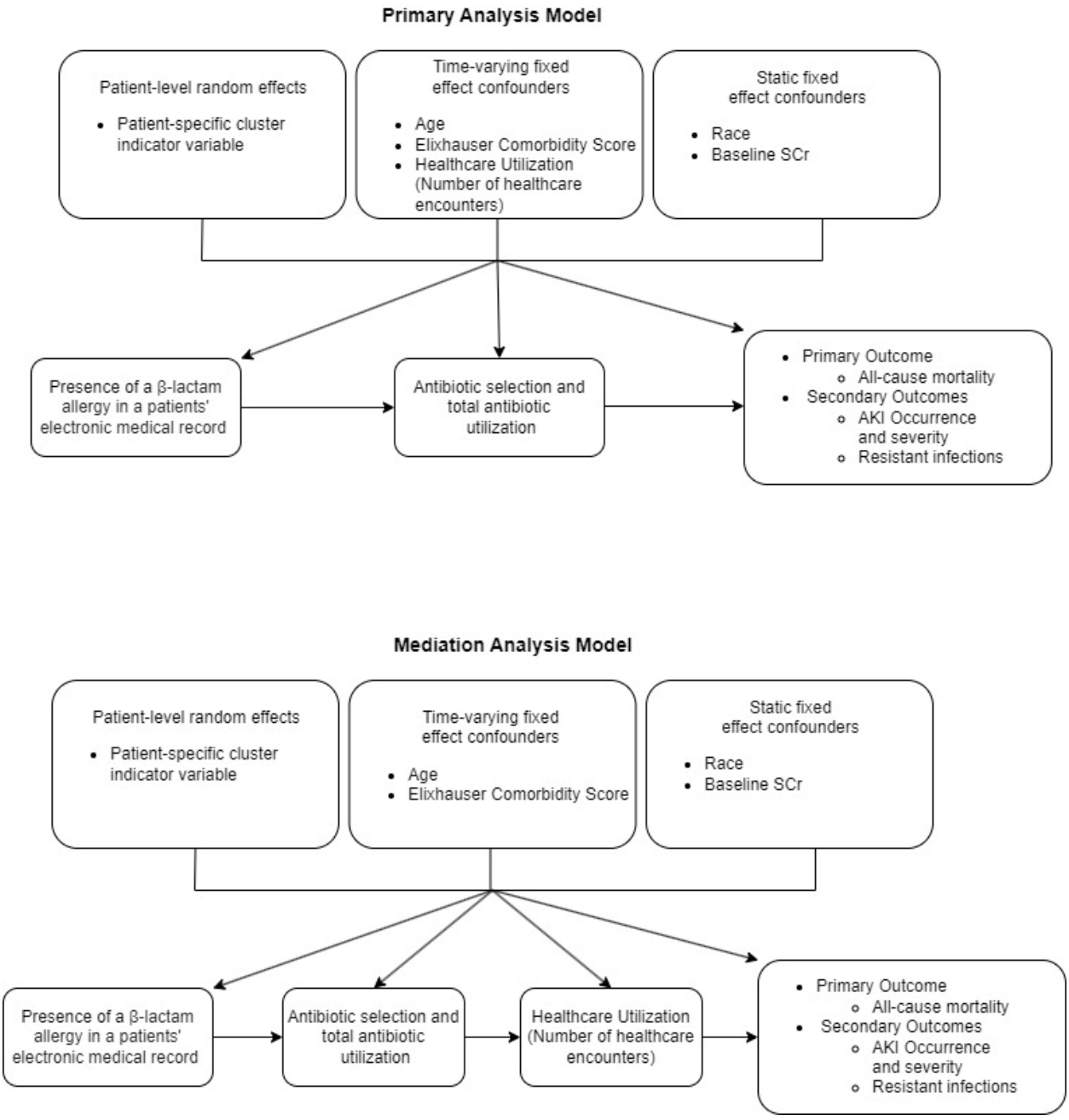


Figure 5-2: Directed Acyclic Graph of Theoretical Causal Model Between Beta-Lactam Allergy Status and Clinical Outcomes

5.3.5 Independent Variables

Independent variables included in the analysis were age, sex, race, baseline serum creatinine, Van Walraven-Elixhauser comorbidity score, the number of healthcare encounters during the study period, intensive care unit (ICU) admissions, and utilization of hemodialysis (coded as a binary variable as present / not present during each encounter). Patient race was condensed into to three categories: white, black or other. Baseline SCr was calculated using a combination of two criteria. First, patients were determined to have either stable or unstable admission Scr, with unstable Scr defined as a change in Scr >0.3 mg/dL within 48 hours following the first recorded Scr. Those with stable admission Scr had their first admission Scr used as the baseline. Those with unstable admission Scr had a baseline Scr calculated using the MDRD equation.[195] There is a lack of consensus on the ideal method to estimate a baseline serum creatinine, and estimation using well-established methods is recommended by the Kidney Disease, Improving Global Outcomes (KDIGO) consensus guidelines.[196] Van Walraven scores, a modified version of the Elixhauser comorbidity score with updated weights were calculated using ICD-9 and ICD-10 scores for each patient at each encounter.[197-199]

5.3.6 Outcomes

The primary outcome of interest was all-cause mortality at any time during the study period. Secondary outcomes included the occurrence and severity of acute kidney injury and the occurrence of resistant or opportunistic infections of methicillin-resistant *staphylococcus aureus, clostridium difficile,* vancomycin-resistant *enterococcus* (VRE), and a pooled outcome of any resistant infection (first occurring MRSA, CDiff, or VRE). AKI was stratified by severity into stage 1 (Scr 1.5-1.9x baseline or ≥0.3mg/dL increase), stage 2 (Scr 2.0-2.9x baseline) , or stage 3 (Scr ≥ 3.0x baseline or Scr ≥ 4.0 mg/dL), defined using

the KDIGO 2012 guidelines.[196] Since data on urine output was not available, only serum creatinine criteria was used to evaluate for AKI outcomes. MRSA was defined as a positive blood test indicating the presence of MRSA bacteria using inpatient health system microbiology codes. CDiff was defined as a positive stool sample for the presence of the *clostridium difficile* toxin.[200] VRE was defined as an infection with *enterococcus faecalis* which was resistant to vancomycin.[201] The corresponding microbiology codes used are shown in Appendix 5-4.

5.3.7 Statistical Analysis

Baseline demographics and clinical characteristics of interest were evaluated at the earliest occurring encounter per patient, and included age, race, sex, baseline Scr, encounter type (e.g. elective, emergency, trauma, etc.), antibiotic allergy status, and Elixhauser Comorbidity Score. These variables were compared for significance at baseline using ANOVA for continuous variables and Chi-squared tests for binary variables. The total number of healthcare encounters per patient during the study period was also evaluated. Missingness for the baseline characteristics was then evaluated at each encounter over the full study period, and missingness was identified in age (<1%) and baseline Scr (22%). Missing values in age and baseline Scr were imputed through multiple imputation (MI) by chained equation utilizing predictive mean matching.[202,203] The use of MI was required because the model used for analysis does not allow gaps in data and would lead to large losses in statistical power, particularly if the 22% of baseline Scr which was missing were not imputed.

Mixed-effect parametric survival models were used to generate a time-to-event model for the outcomes of interest.[204,205] Each patient was followed from their first admission to the first time point where an outcome occurred (mortality, MRSA infection, etc..) or censoring through reaching the end of the study period (final observed encounter or Dec 31, 2018). In instances where an outcome may have occurred more

than once, such as MRSA infection, the patient was censored upon the first instance of the outcome. A cluster variable was created at the patient-level to attempt to control for unmeasured patient-level characteristics that may influence the outcome. The model was refined by fitting models including only BL-allergy status, age, race, and sex to determine the ideal distribution for the main analysis (Table 5-3-1). Through this process, Weibull distributions were identified as the more robust model for its lowest AIC and BIC values (Table 5-3-1). Additionally, unstructured covariance structures were used for all models since the large sample size of this population did not restrict the allocation of degrees of freedom required for an unstructured covariance matrix.

Table 5-1: Comparison of AIC/BIC Values to Idneitfy Ideal Distribution

Distribution	**Weibull**	**Loglogistic**	**Exponential**	**Lognormal**
AIC / BIC	63331.97 / 63404.11	65310.52 / 53382.66	64118.06 / 64190.2	Failed Maximization

Legend: Models included: BL-allergy status, age, sex, and race. All models used unstructured covariance.

Next, multivariate models were generated, with each covariate being measured at each healthcare encounter during the study period. This created two sets of covariates: 1) variables that did not change over time including sex, race, baseline SCr, and the number of healthcare encounters and 2) variables that changed over time including age, Elixhauser comorbidity score, and length of stay. A benefit to the mixed-effect parametric survival model is the ability to accurately model the effects of both time-changing and non-changing variables simultaneously. The mixed-effect parametric survival model is described in detail in Equation 5-1.

Equation 5-1: Mixed Effect Parametric Survival Model[205]

$$h(t_{ji}) = h_0(t_{ji})\exp(x_{ji}\beta + z_{ji}u_j)$$

Where:

- $h(t_{ji})$ = Hazard function for visit *i for* patient *j* at time t
- $h_0(t)$ = Baseline Hazard Function (parameterized with survival distribution)
- t_{ji} = visit *i* for patient *j* at time t
- x_{ji} = Covariate vector for patient fixed effects
- β = Regression coefficient for fixed effects
- z_{ji} = Covariate vector for patient random effects (including error term)
- u_j = Random effects coefficients

Mixed-effect parametric survival models have some notable assumptions and limitations. This model assumes normality of the covariates being used. Given the large number of observations, the parametric models used are not highly sensitive to non-normally distributed variables, but the Stata command *gladder* was used to visually test for normality.[206] (Appendix 5-5) Another requirement is the assumption of proportional hazards over time, although this assumption is more flexible through the inclusion of a patient-level cluster variable. The proportional hazards assumption is a requirement in many survival models which requires that survival between groups remain proportional over time.[207] For example, if the relative difference in mortality between those with BL allergies and those without is 2% at year one of follow-up, then this difference should remain generally at 2% at ten years of follow-up as well, even if the absolute risk of mortality changes over this time. This assumption was tested graphically through the use of a

proportional hazards plot for the primary outcome of all-cause mortality, and formally tested using Schoenfeld residuals.

Another limitation of mixed-effect parametric survival models is that it is not straightforward to interpret the results and apply them broadly when compared to more traditional models. Similar to the patient-level associations used in shared frailty models, each cluster (patient) has unique random effects within its own cluster, which can provide more accurate predictions at the patient-level, but causes difficulty in interpreting marginal effects because the population-level effect is not necessarily proportional to the effect seen at the patient level.[208] For example, a hazard ratio (HR) of 1.06 for the presence of a beta-lactam allergy can be interpreted as meaning that for a given patient, the annual hazard of death increases by 6% as a result of having a beta-lactam allergy, but cannot be interpreted as meaning that in general, the presence of a beta-lactam allergy in an electronic medical record increases the annual risk of mortality by 6%. However, the estimates provided are proportional to one another in direction, such that a HR of 1.06 for the presence of a beta-lactam allergy can be understood as meaning that the hazard rate is on average higher in the beta-lactam-allergic group than in the non-allergic group, even though the individual estimates of this effect vary. Survival curves were generated to visually model the effect of beta-lactam allergies on each outcome. As each patient has their own random effects, the survival curve attempts to approximate the marginal effect by modeling the mean effect of each covariate to provide an overall representation of the marginal effects in the population, and as a result, the survival curves show what is estimated to be an 'average' patient.

We conducted k-fold cross-validation in order to test the validity of our model and the explanatory value of the covariate selection. Multivariate Cox proportional hazards models using the same list of covariates as the primary model were used, along with a clustered robust error measure (clustered at the patient-level) were used to estimate pseudo R-squared values to determine both the stability and the

estimated explanatory value of our model. Five folds and five replications were used to predict all-cause mortality estimates and the results are shown in Table 5-2.

Table 5-2: K-fold Cross-Validation Results

	ESTIMATE 1 PSEUDO R^2	ESTIMATE 2 PSEUDO R^2	ESTIMATE 3 PSEUDO R^2	ESTIMATE 4 PSEUDO R^2	ESTIMATE 5 PSEUDO R^2
ALL-CAUSE MORTALITY	0.0154	0.0123	0.0139	0.0132	0.0131

The Cox proportional hazard models did have relatively low, but stable pseudo R-squared values, with the highest replication only reaching 0.0154. While this is not fully unexpected since mortality is a complicated outcome, it should be noted that our model may still be subject to a significant amount of confounding bias and the results should be interpreted accordingly.

5.3.8 Sensitivity Analysis

A sensitivity analysis was completed repeating the analysis above using Cox proportional hazard models with a shared frailty term instead of mixed-effect parametric survival models. A benefit to the use of Cox proportional hazard models with mixed effects is that the hazard function is allowed to vary over time, which may more accurately model the risk of death over time. Another benefit to a robustness analysis using Cox models is the ability to easily compute Schoenfeld residuals to check the proportional hazard assumption of the model covariates.[209] The null hypothesis of this test is that the covariate does not violate the proportional hazards assumption, and a significant test statistic indicates that the covariate likely does violate this assumption. Patients whose beta-lactam allergy status changed throughout follow-up had their original allergy status carried forward for the primary analysis. To test the appropriateness of this decision,

we repeated the analysis by fully excluding these patients instead of including them with the extrapolated allergy status. A final sensitivity analysis was conducted to compare the outcome results while limiting the cohort of patients to those with the highest and lowest available baseline morbidities, as measured using the first available Elixhauser score. The roughly 30% patients with the highest and lowest baseline Elixhauser scores (rounded to the nearest whole number score) were used to determine whether the measured outcome differences associated with BL allergies are influenced by the severity of a patient's baseline morbidity status.

5.3.9 Mediation Analysis

A mediation analysis was conducted to evaluate the potential for healthcare utilization to mediate the effect of a beta-lactam allergy on the clinical outcomes of interest. Mediation effects were estimated using the Stata module *paramed* which utilizes parametric regression models to model the individual relationships between the exposure, mediator, and the desired outcome while including the effects of covariates.[210] Binary beta-lactam allergy status was assigned as the exposure, binary death during the analysis period was assigned as the outcome, and the covariates included were age, race and sex. Total number of healthcare encounters was assigned as the mediator in individual analyses. Standard error estimation was enhanced with bootstrapping using 1000 replications (seed 123). The outcome of death was modeled as logistic regression and the effect of beta-lactam allergy status on healthcare utilization was modeled as linear regression. Bias-corrected estimates were calculated for the controlled direct effect, natural direct effect, natural indirect effect, and marginal total effect for the structured relationships.[211]

5.3.10 Secondary Analysis

There were two primary goals in the secondary analyses that were conducted. First, we sought to understand how the effect of non-beta-lactam antimicrobial allergies would compare to the effect beta-lactam allergies seen in the primary analysis. The potential for non-beta-lactam antimicrobial allergies to alter long-term clinical outcomes has not been previously described.[212] The present analysis can be extended to examine this relationship and determine whether beta-lactam allergies represent a unique long-term risk, or if the presence of any antimicrobial allergy in general can alter antimicrobial prescribing to a substantial enough to degree to alter clinical outcomes. Additional allergy groups were derived through the same process as that used to define beta-lactam allergies using both brand and generic name for the following antimicrobial classes: glycopeptides, lincosamides, macrolides, quinolones, peptides, tetracyclines, and miscellaneous antimicrobials. Since patients often reported multiple allergies and groups could not be defined exclusively, there was the need to define combination allergy groups for patients having more than one non-beta-lactam allergy, and those with both a non-beta-lactam and non-beta-lactam allergy present. Following the creation of these groups, it was determined that some allergy groups did not contain sample sizes which were sufficient to obtain meaningful statistical estimates. To account for this, the allergy groups were refined into four independent groups: no antibiotic allergy, beta-lactam allergy only, non-beta-lactam allergy only, and both beta-lactam and non-beta-lactam allergy. The primary analysis was repeated using this group of four combinations of allergies, utilizing the same covariates and parameters as the primary model. Additionally, there may be differences in outcomes depending upon the particular agent or class that is documented as an allergy among patients with BL allergies. As an extension of this secondary analysis, beta-lactam allergies were also broken out into four groups: penicillins, cephalosporins, carbapenems, and aztreonams (non-mutually exclusive). The primary analysis was repeated using this group of four groups of allergies, also using the same covariates and parameters as the primary model.

Next, the cohort used represents a unique opportunity to examine the ability of beta-lactam allergy status to act as a time-varying exposure. The cohort contained a number of patients whose beta-lactam allergy status changed during the follow-up period. For example, some patients who initially had a documented beta-lactam allergy ceased to have this allergy present later in the follow-up period, and vice-versa. The reason for this time-varying phenomenon has not been directly examined, but may be due to generally poor and inconsistent status of allergy documentation into electronic medical records.[213,214] The potential for beta-lactam allergies to act in a time-varying capacity has not been previously considered, but would be an important finding to emphasize the importance of accurate allergy evaluation at every healthcare encounter to minimize the potential for the re-introduction of erroneous penicillin allergies into patients' medical records.

The primary analysis was repeated, allowing beta-lactam allergy status to change as a time-varying variable at each encounter. More simply, a patient would be analyzed as allergic during each encounter period where a beta-lactam allergy was present and would be analyzed as non-allergic at each encounter where a beta-lactam allergy was not present. The mixed-effect parametric survival models used allow for covariates to alter over time, while still providing accurate estimates of annualized hazard ratios. The fixed effects within each patient cluster would remain constant, and would not be affected by a change in their allergy status, providing the benefit of using a mixed-effect model. This analysis may more accurately reflect the management of beta-lactam allergies in practice by allowing for the removal of erroneous beta-lactam allergies and the introduction of new allergies into the medical record.

5.4 RESULTS

5.4.1 Cohort Characteristics

Baseline cohort characteristics and descriptive statistics for the cohort are shown in Table 5-3. Beta-lactam allergies, and antibiotic allergies in general have been shown to have a slight female predominance, and this was also seen in our cohort with almost 70% of BL-allergic patients being female.[215] Older patients and white patients were also more likely to report a BL allergy compared to other races, which is also consistent with previous epidemiologic studies.[216-218] Patients with BL allergies were much more likely to report additional antibiotic allergies, as well as chronic pulmonary disorders such as asthma, which is more prevalent in patients with multiple drug allergies.[216] Patients with BL allergies had on average 1.9 more healthcare encounters over the study period than non-allergic patients, but the groups did not differ greatly in the baseline clinical markers of baseline SCr and Elixhauser Comorbidity scores.

Table 5-3: Patient Demographics and Baseline Characteristics

Characteristic	Non-beta-lactam-Allergic (N = 15881)	Beta-lactam-allergic (N = 4211)	P Value
Age*	62.6 (19.9)	64.2 (19.0)	<0.001
Sex:			<0.001
Male	6561 (41.3)	1300 (30.9)	
Female	9320 (58.7)	2911 (69.1)	
Race:			<0.001
White	12026 (75.7)	3332 (79.1)	
Black	2849 (17.9)	664 (15.8)	
Other	1006 (6.3)	215 (5.1)	
Total encounters	168327	52607	N/A
Number of healthcare encounters over follow-up period	10.6 (20.5)	12.5 (20.9)	<0.001
Baseline SCr	1.7 (1.8)	1.7 (1.7)	0.71
Baseline EGFR	54.8 (28.6)	52.6 (26.2)	<0.001
Encounter type:			0.621
Elective	40293 (24.3)	12825 (24.4)	
Emergency	115409 (68.6)	36072 (68.6)	
Urgent	10283 (6.1)	3194 (6.1)	
Trauma	1459 (0.9)	440 (0.8)	
Other	253 (0.20)	76 (0.1)	
Antibiotic Allergies:			
Beta-lactam	0 (0)	4211 (100)	N/A
Penicillin	0 (0)	3828 (90.9)	N/A
Cephalosporin	0 (0)	689 (16.4)	N/A
Carbapenem	0 (0)	26 (0.6)	N/A
Aztreonam	0 (0)	21 (0.5)	N/A
Glycopeptide	119 (0.8)	128 (3.0)	<0.001
Lincosamide	25 (0.2)	63 (1.5)	<0.001
Macrolide	200 (1.8)	335 (8.0)	<0.001
Furan	70 (0.4)	58 (1.4)	<0.001
Peptide	18 (0.1)	13 (0.3)	0.004
Quinolone	379 (2.4)	399 (9.5)	<0.001

Table 5-3 (Continued)

Tetracycline	130 (0.8)	158 (3.8)	<0.001
Misc antibiotic allergy	209 (1.3)	73 (1.7)	0.041
Elixhauser weighted summary Score*	9.8 (9.9)	9.8 (9.6)	0.99
Congestive heart failure	3490 (22.0)	1028 (24.4)	<0.001
Cardiac arrhythmias	4417 (27.8)	1193 (28.3)	0.51
Valvular disease	1828 (11.5)	546 (13.0)	0.009
Pulmonary circulation disorders	1282 (8.1)	365 (8.7)	0.21
Peripheral vascular disorders	1231 (7.8)	349 (8.3)	0.25
Hypertension, uncomplicated	6169 (38.8)	1734 (41.2)	0.006
Paralysis	385 (2.4)	99 (2.4)	0.78
Other neurological disorders	1835 (11.6)	494 (11.7)	0.75
Chronic pulmonary disease	4660 (29.3)	1503 (35.7)	<0.001
Diabetes, uncomplicated	3336 (21.0)	1016 (24.1)	<0.001
Diabetes, complicated	925 (5.8)	281 (6.7)	0.039
Hypothyroidism	2024 (12.7)	684 (16.2)	<0.001
Renal failure	2738 (17.2)	780 (18.5)	0.052
Liver disease	1649 (10.4)	413 (9.8)	0.27
Peptic ulcer disease excluding bleeding	239 (1.5)	76 (1.8)	0.16
AIDS/HIV	82 (0.5)	25 (0.6)	0.54
Lymphoma	282 (1.8)	77 (1.8)	0.82
Metastatic cancer	807 (5.1)	157 (3.7)	<0.001
Solid tumor without metastasis	1153 (7.3)	254 (6.0)	0.005
Rheumatoid arthritis/collagen vascular	637 (4.0)	247 (5.9)	<0.001
Coagulopathy	2105 (13.3)	558 (13.3)	0.99
Obesity	1043 (6.6)	379 (9.0)	<0.001
Weight loss	1571 (9.9)	379 (9.0)	0.082
Fluid and electrolyte Disorders	5712 (36.0)	1541 (36.6)	0.45
Blood loss anemia	321 (2.0)	85 (2.0)	0.99

5.4.2: Survival Table and Longitudinal Outcome Occurrence

The survival table for the analysis cohort for the years 2007-2018 is shown in Table 5-4. Cumulative survival during each year of the follow-up period remained relatively equal regardless of BL allergy status. The difference in cumulative survival between allergy groups never exceeded 2% during any year of follow-up. The mortality rate was higher during the first three years of follow-up compared to the remaining 9 years, and the overall rate of deaths tended to decrease with each ongoing year. There is a larger number of patients censored during the last year than any other year due to reaching the end of follow-up. In total, patients without BL allergies were observed for 77496 total patient-years (mean = 4.88 years), and BL-allergic patients for 20692 patient-years (mean = 4.91 years).

The unadjusted occurrence, as well as their longitudinal distributions throughout the follow-up period can be seen in Table 5-5. The rate of mortality was higher in the BL-allergic group (62.6% vs. 60.4%). With respect to resistant infections, MRSA (28.7% vs. 24.4%), and VRE (9.1% vs. 7.5%) were both more likely to occur in the BL-allergic group compared to the non-allergic group. CDiff occurred at roughly even rates between BL-allergic and non-allergic patients (9.2% vs. 8.8%) There did not appear to be any temporal relationship between the occurrence of resistant infections and allergy status after the index visit. The rate and severity of AKI did not change significantly between allergy groups, with stage 2/3 and stage 3 AKI occurring at similar rates regardless of BL allergy status.

Table 5-4: Survival Table

	Non-BL Allergic			BL-Allergic		
Date Range	**Number at Risk**	**Deaths**	**Censored**	**Number at Risk**	**Deaths**	**Censored**
Jan 2007 – Jun 2007	3865	549	99	1109	155	24
July 2007 – Dec 2007	7284	827	139	1915	212	26
Jan 2008 – Jun 2008	10225	975	150	2760	259	30
July 2008 – Dec 2008	13129	918	185	3504	236	38
2009	12039	1329	237	3231	397	52
2010	10473	1013	222	2782	268	51
2011	9238	815	198	2463	234	52
2012	8225	673	221	2177	187	48
2013	7331	563	284	1942	171	74
2014	6484	495	316	1697	146	63
2015	5673	459	419	1488	127	81
2016	4795	411	521	1280	95	126
2017	3863	349	874	1059	87	236
2018	2640	226	2414	736	61	675

Intervals include the full year unless month is noted (e.g. '2009' = Jan 1, 2009 – Dec 31, 2009). Number at risk defined as allergy status being present for any encounter at any time during the applicable time period. Deaths and Censored are counted according to the allergy status at the time of death/censoring. BLA → Non-BLA and Non-BLA → BLA defined as allergy status switching from Non-BL allergic or BL-allergic, or vice versa, during the applicable study period (each individual patient could only be counted as at risk once during each group/time period).

Table 5-5: Outcome Counts and Longitudinal Distributions

Characteristic	Non-beta-lactam-Allergic (n = 15881)	Beta-lactam-allergic (n = 4211)	P-value
All-cause mortality	9602 (60.5)	2635 (62.6)	0.013
Years to Death:			0.719
0 – 1	3622 (37.7)	966 (36.7)	
1 – 2	1026 (10.7)	295 (11.2)	
2 – 5	2453 (25.6)	687 (26.1)	
5 - 10	2501 (26.1)	687 (26.1)	
MRSA infection	3870 (24.4)	1208 (28.7)	<0.001
Years to first MRSA infection:			0.577
0 – 1	2412 (62.3)	756 (62.6)	
1 – 2	375 (9.7)	128 (10.6)	
2 – 5	612 (15.8)	192 (15.9)	
5 - 10	471 (12.2)	132 (10.9)	
C-difficle infection	1393 (8.8)	388 (9.2)	0.372
Years to first C-Difficile infection:			0.132
0 – 1	835 (60.0)	207 (52.4)	
1 – 2	116 (8.3)	38 (9.8)	
2 – 5	231 (16.6)	72 (18.6)	
5 - 10	211 (15.2)	71 (18.3)	
VRE Infection	1189 (7.5)	385 (9.1)	<0.001
Years to first VRE Infection:			0.353
0 – 1	784 (65.9)	239 (62.1)	
1 – 2	100 (8.4)	34 (8.8)	
2 – 5	192 (16.2)	64 (16.6)	
5 - 10	113 (9.5)	48 (12.5)	
Any Resistant Infection	5215 (32.8)	1549 (36.8)	<0.001
Years to First Resistant Infection			0.711
0 – 1	3427 (65.7)	1023 (66.0)	
1 – 2	450 (8.6)	141 (9.1)	
2 – 5	752 (14.4)	226 (14.6)	
5 - 10	586 (11.2)	159 (10.3)	

Table 5-5 (Continued)

Stage 2/3 AKI	**4375 (27.6)**	**1161 (27.6)**	**0.977**
Years to first stage 2/3 AKI:			0.052
0 – 1	3173 (72.5)	799 (68.8)	
1 – 2	254 (5.8)	87 (7.5)	
2 – 5	489 (11.2)	143 (12.3)	
5 - 10	459 (10.5)	132 (11.4)	
Stage 3 AKI	3164 (25.6)	843 (25.5)	0.931
Years to first stage 3 AKI:			0.042
0 – 1	2282 (72.1)	574 (68.1)	
1 – 2	191 (6.0)	71 (8.4)	
2 – 5	351 (11.1)	103 (12.2)	
5 - 10	340 (10.8)	95 (11.3)	

5.4.3. Primary Analysis

The results from the multivariate mixed-effect parametric survival models can be seen in Table 5-6. In all models, the likelihood ratio test comparing the goodness of fit of the model including the patient-level mixed effect model to a model without the mixed effects was highly significant, favoring the robustness of the mixed-effects model over a standard parametric survival model not containing the patient-level mixed effects. BL allergies were not associated with all-cause mortality (HR1.01; 95%CI 0.96 – 1.07). The occurrence and severity of AKI remained non-significant regardless of BL allergy status. The rate of MRSA (HR 1.50; 95%CI 1.34 – 1.68) and VRE (HR 1.23; 95%CI 1.07 – 1.42) were both significantly increased with the presence of a BL allergy.

Survival curves for the primary analysis can be found in Figure Set 5-3. It is important to note that these curves do not show true population effects, but instead show a single patient's

survival curve who was estimated to be the most ‘average’ patient in each allergy group, so the shown hazard rates will not necessarily align with the population hazards. There is not a visual difference in the hazard of mortality (Figure 5-3-1). The proportional hazards assumption was tested visually by comparing the hazard functions of BL-allergic and non-allergic patients, and the hazard for these two groups being parallel supports that the proportional hazards function is not violated (Figure 5-3-2). MRSA showed a significantly increased hazard in the BL-allergic group (Figure 5-3-3). Cdiff also did not differ greatly between allergy groups. The result seen may be underpowered with respect to statistical significance and may benefit from a longer follow-up period or a large cohort of patients (Figure 5-3-4). The survival curves for VRE were almost identical, with virtually no difference between the allergy groups (Figure 5-3-5). The survival curve for the pooled occurrence of any resistant infection is similar to the curve for VRE (Figure 5-3-6). The hazard of AKI severity and occurrence were also not appreciably different between allergy groups (Figure 5-3-7 & 5-3-8).

Table 5-6: Results of Mixed-effect Multivariate Survival Models

	MULTIVARIATE MODEL HR (95% CI)	P-VALUE	LRT COEF.†	LRT. P-VALUE†
ALL-CAUSE MORTALITY	1.01 (0.96 – 1.07)	0.700	533.08	<0.001
STAGE 2 OR 3 AKI	0.99 (0.90 – 1.10)	0.985	251.09	<0.001
STAGE 3 AKI	1.02 (0.91 – 1.13)	0.763	299.49	<0.001
MRSA**	1.50 (1.34 – 1.68)	<0.001	337.19	<0.001
C. DIFFICILE	1.05 (0.87 – 1.26)	0.635	108.66	<0.001
VRE	1.23 (1.07 – 1.42)	0.003	70.01	<0.001
ANY RESISTANT INFECTION*	1.32 (1.20 – 1.46)	<0.001	420.98	<0.001

Figure Set 5-3: Survival Curves for Primary Analysis

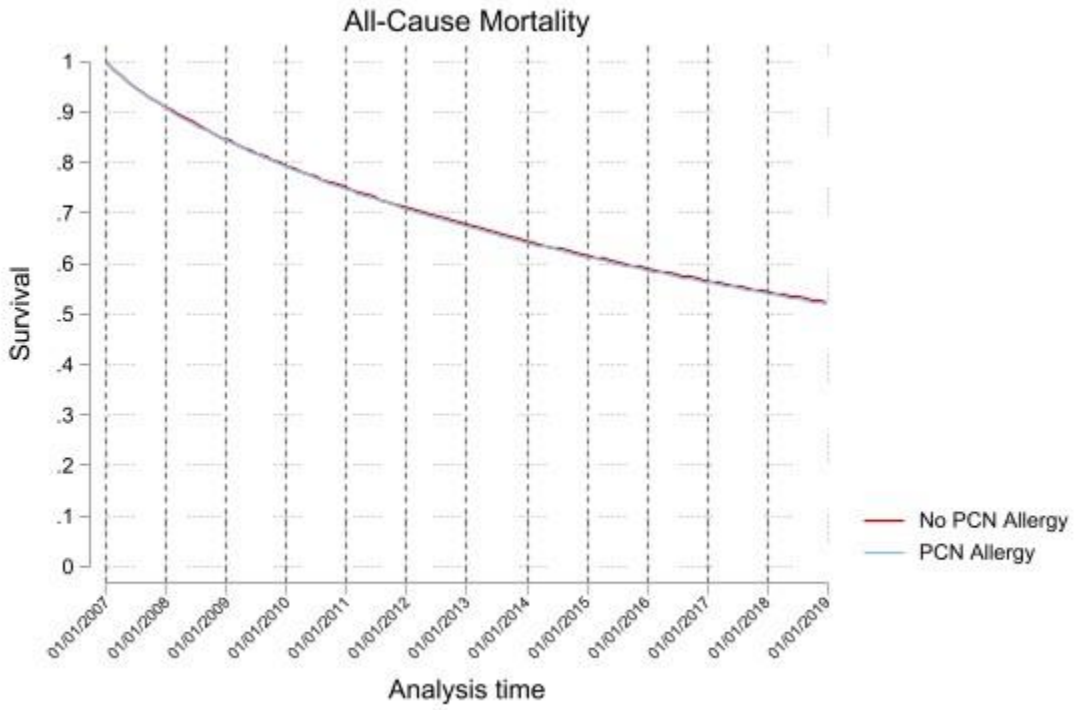


Figure 5-3-1: Long-Term All-Cause Mortality Associated with BL Allergies

Results from parametric mixed-effects survival models for all-cause mortality

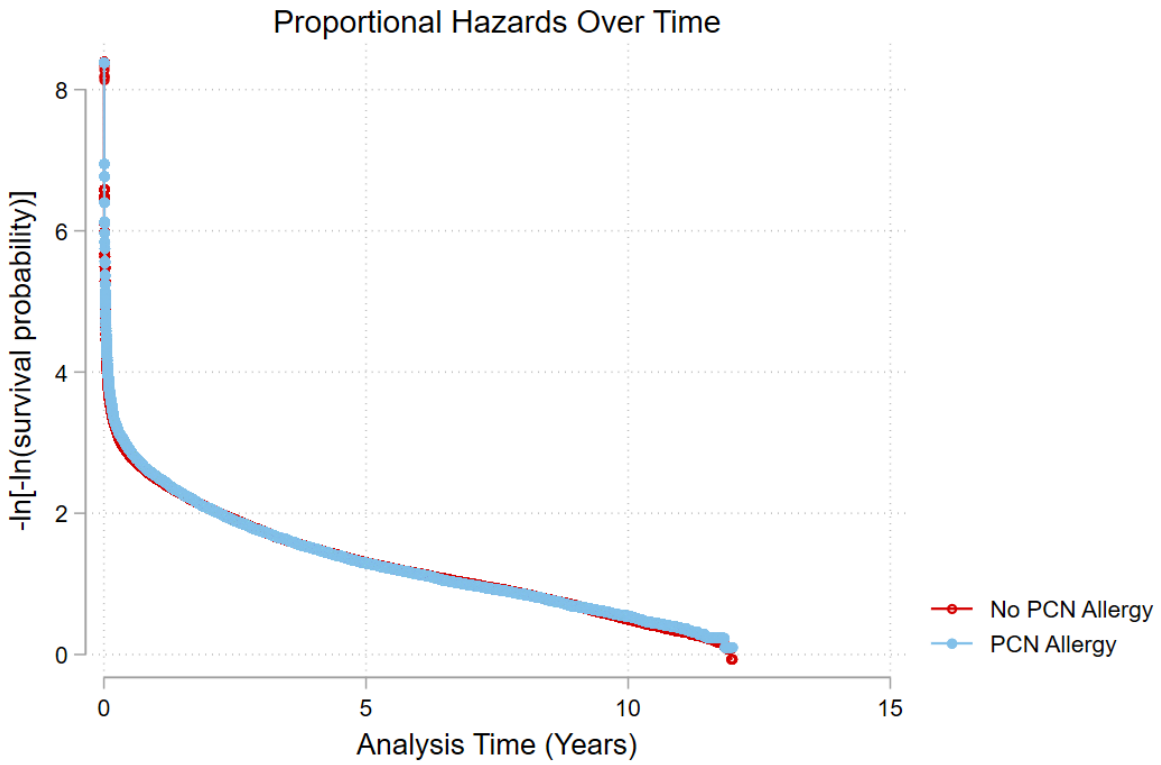


Figure 5-3-2: Proportional Hazards of All-cause Mortality by BL Allergy Group

Proportional Hazards adjusted at each group mean for the following covariates: age, race, sex, baseline Scr, Elixhauser Comorbidity Score, number of healthcare encounters, hemodialysis use, intensive care admissions.

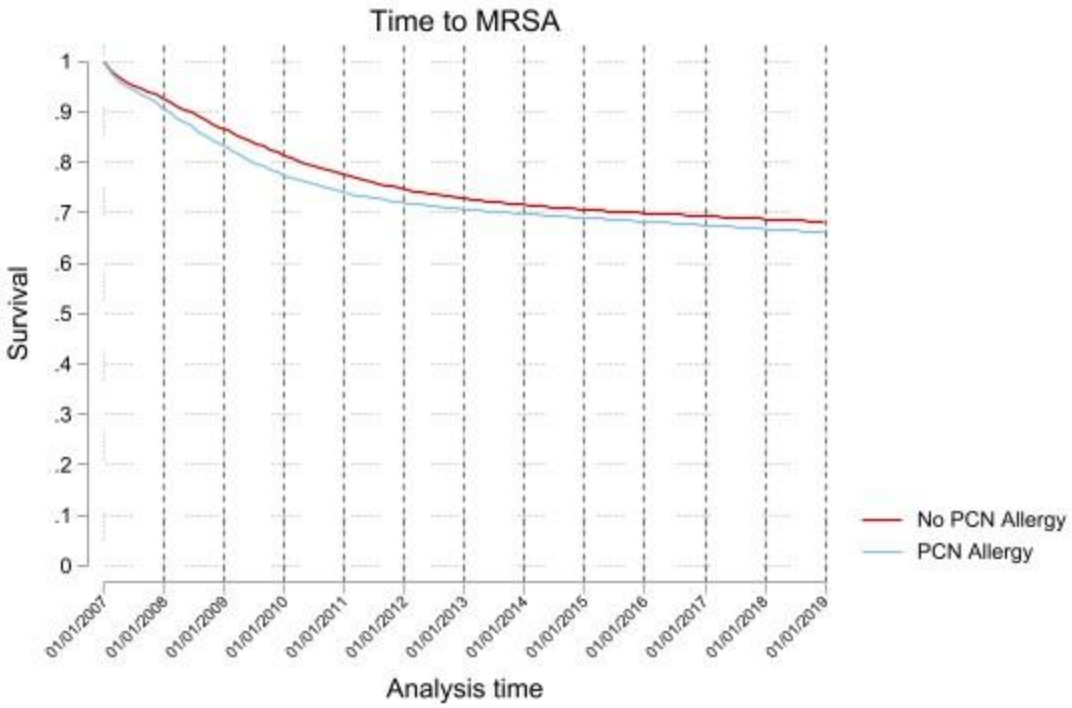


Figure 5-3-3: MRSA Occurance Associated with BL Allergies

Results from parametric mixed-effects survival models for MRSA

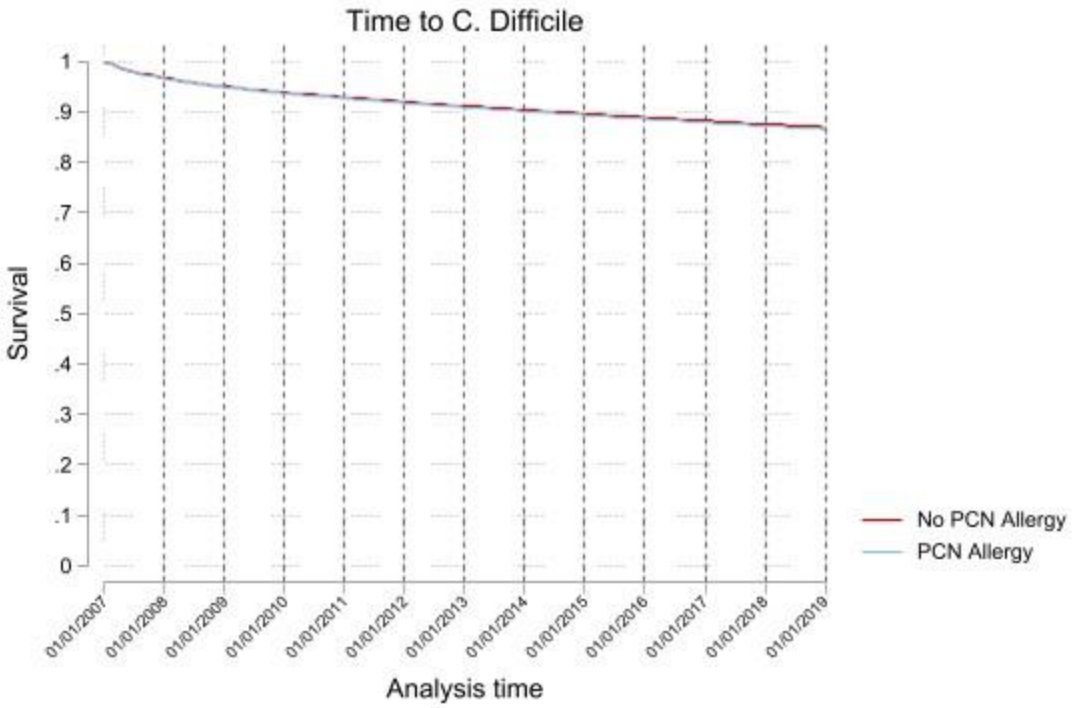


Figure 5-3-4: CDiff Occurance Associated with BL Allergies

Results from parametric mixed-effects survival models for CDiff

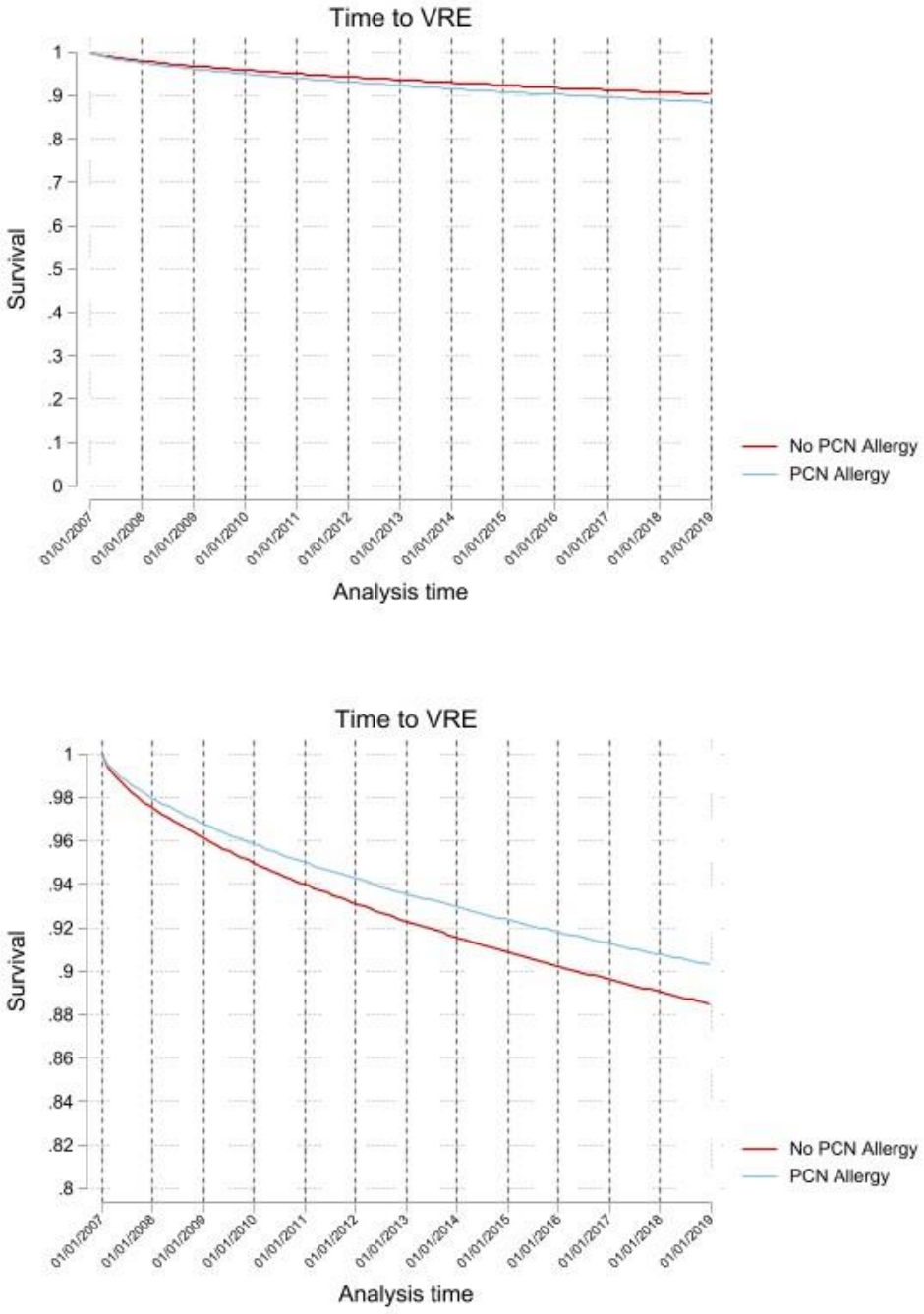


Figure 5-3-5: VRE Occurance Associated with BL Allergies

Note Scale: Figures display the same graph

Results from parametric mixed-effects survival models for VRE

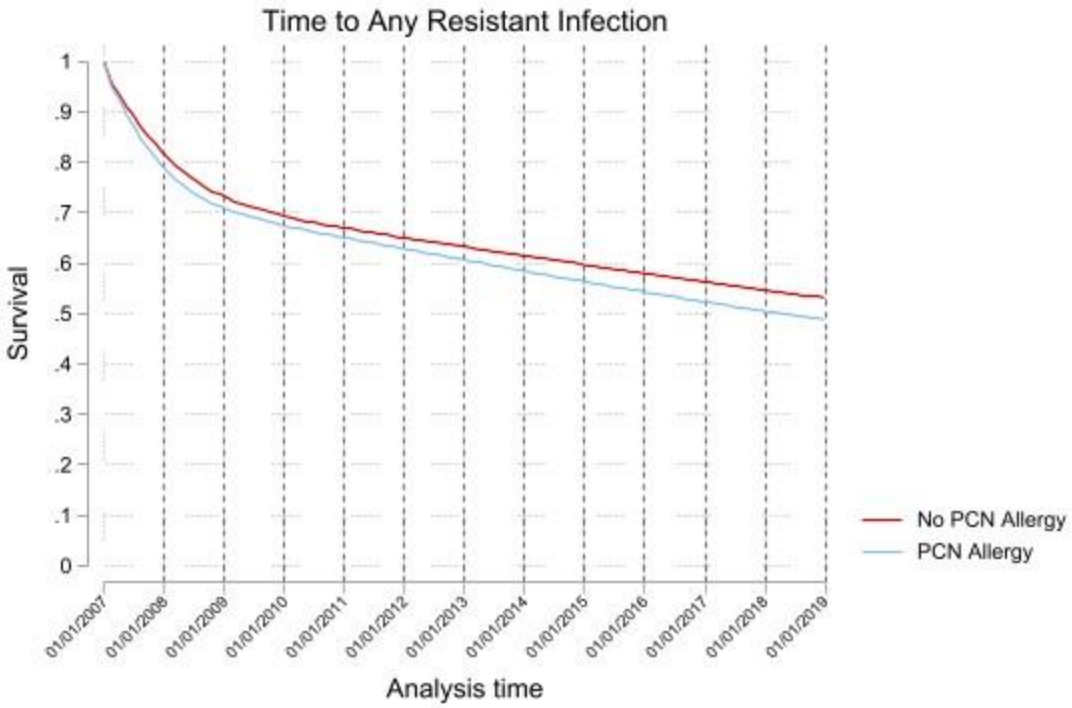


Figure 5-3-6: Any Resistant Infection Occurance Associated with BL Allergies

Results from parametric mixed-effects survival models for pooled occurrence of MRSA, CDiff., or VRE.

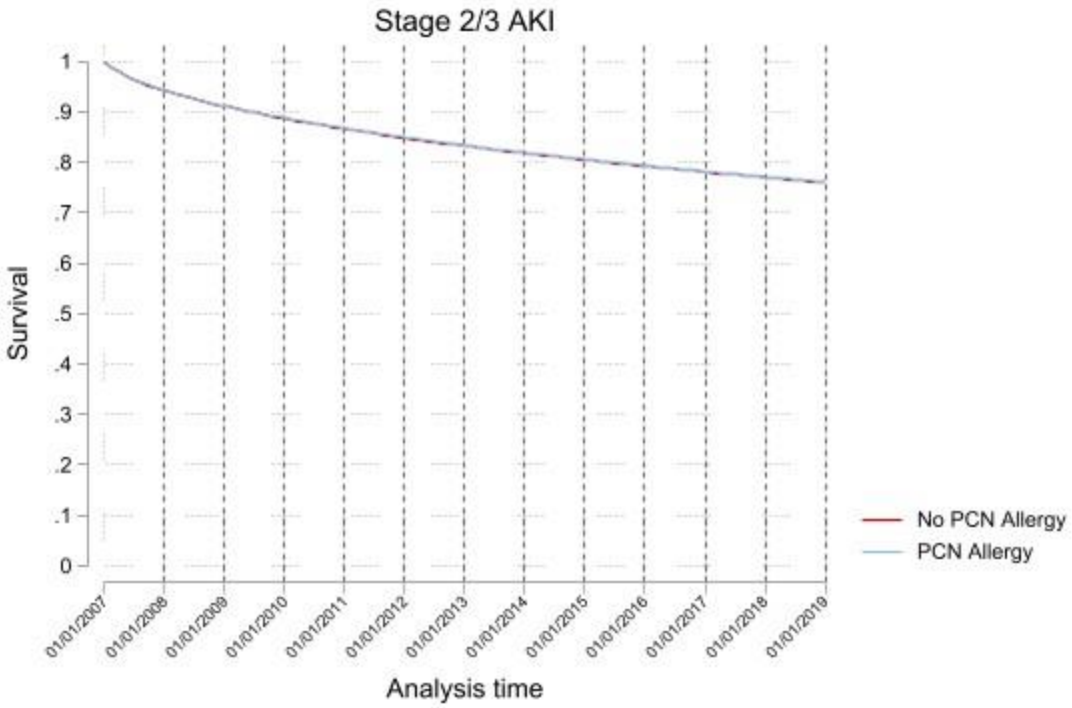


Figure 5-3-7: Stage 2/3 AKI Occurrence Associated with BL Allergies

Results from parametric mixed-effects survival models for stage 2/3 AKI

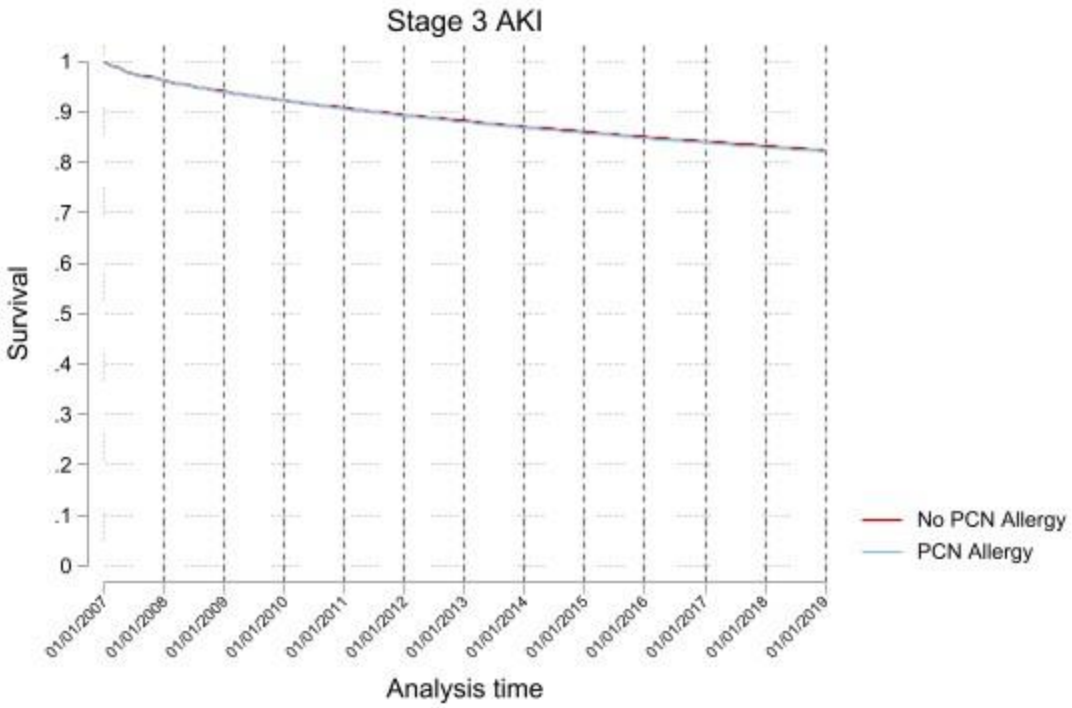


Figure 5-3-8: Stage 3 AKI Occurrence Associated with BL Allergies

Results from parametric mixed-effects survival models for stage 3 AKI

5.4.4. Sensitivity Analysis

The primary analysis was repeated using Cox Proportional Hazard Models with shared frailty to test the robustness of our initial survival model (Table 5-7). This analysis was conducted using R due to matrix size limits within Stata SE.[219] The largest difference in results observed between this approach and our primary model is that the Cox Proportional Hazard Models provides a higher estimate for the effect of BL allergies on mortality, which was statistically significant, but all other results are largely similar to the estimates provided by the mixed-effect parametric survival models. All-cause mortality, AKI occurrence and severity, and VRE occurrence did not violate the proportional hazards assumption; however, MRSA, CDiff, and pooled resistant infection occurrence outcomes did violate the assumption. These violations may indicate that our primary results for MRSA, CDiff, and pooled resistant infections do not consistently apply over all time points of the full twelve years analyzed, but likely still do reflect accurate estimations of the covariate effects.

The primary analysis used an intent-to-treat approach to allergy status to handle patients who had their BL allergy status modified throughout the follow-up period. The primary analysis design may have introduced some bias by constraining patients into having a consistent allergy status since allergy status documentation may have changed over time second to unobserved factors such as delabeling efforts or new allergy exposure. Excluding the patients whose allergy status changed during follow-up instead of carrying forward their initial allergy status did not change the results appreciably (Table 5-8), supporting the robustness of the primary analysis. MRSA, VRE, and pooled resistant infections occurrence remained statistically significantly associated with BL allergies, while other outcomes remained insignificant.

A final sensitivity analysis was used to examine whether the effect of a BL allergy on the outcomes would differ when comparing patients with higher or lower baseline morbidity (Table Set 5-9). The effects of a BL tended to be slightly higher in patients within the highest 30% of baseline morbidity compared to

those in the lowest 30% of baseline morbidity (as measured through the first available Elixhauser score). The higher baseline morbidity score had increased rates of stage 2/3 AKI (HR 1.10 vs. 0.86), stage 3 AKI (HR 1.05 vs. 0.95), and MRSA (HR 1.48 vs. 1.31), but had lower rates of VRE (HR 1.10 vs. 1.58). Interestingly, the rate of mortality associated with BL allergies did not differ much between morbidity groups despite the differences in resistant infections and AKI. The rate of CDiff between these two groups could not be compared due to the higher baseline morbidity group failing required maximization parameters, likely secondary to low sample sizes.

Table 5-7: Outcome Results – Beta-lactam-Allergic Patients Compared to Non-Beta-Lactam-Allergic Patients using Cox Proportional Hazard Models with Shared Frailty

	MULTIVARIATE MODEL HR (95% CI)	P-VALUE	SCHOENFELD RESIDUAL COEFFICIENT*	SCHOENFELD RESIDUAL P-VALUE*
ALL-CAUSE MORTALITY	1.38 (1.05 – 1.81)	0.019	0.052	0.436
STAGE 2 OR 3 AKI	1.05 (0.73 – 1.13)	0.26	1.46	0.226
STAGE 3 AKI	1.07 (0.98 – 1.17)	0.13	2.13	0.144
MRSA	1.49 (1.33 – 1.67)	<0.001	6.09	0.003
C. DIFFICILE	1.03 (0.87 – 1.19)	0.79	5.36	0.007
VRE	1.24 (1.05 – 1.46)	0.010	0.178	0.410
ANY RESISTANT INFECTION**	1.37 (1.24 – 1.51)	<0.001	8.77	<0.001

Controlled for: Age, Race, Sex, baseline Scr, number of healthcare encounters, Elixhauser, Hemodialysis during visit, ICU admission during visit

*Coefficients presented in terms of a one-sided test of significance using a Chi-Squared distribution

**Any Resistant Infection corresponds to pooled occurrence of MRSA, C. Difficile, and VRE

Table 5-8: Outcome Results – Beta-lactam-Allergic Patients Compared to Non-Beta-Lactam-Allergic Patients using Mixed Effect Survival Models Excluding Patients with Inconsistent Allergy Status

	MULTIVARIATE MODEL HR (95% CI)	P-VALUE
ALL-CAUSE MORTALITY	1.00 (0.95 – 1.07)	0.819
STAGE 2 OR 3 AKI	1.00 (0.91 – 1.11)	0.932
STAGE 3 AKI	1.02 (0.91 – 1.14)	0.720
MRSA	1.47 (1.30 – 1.65)	<0.001
C. DIFFICILE	1.02 (0.85 – 1.24)	0.803
VRE	1.24 (1.07 – 1.43)	0.003
ANY RESISTANT INFECTION*	1.31 (1.18 – 1.45)	<0.001

Controlled for: Age, Race, Sex, baseline Scr, number of healthcare encounters, Elixhauser, Hemodialysis during visit, ICU admission during visit

*Any Resistant Infection corresponds to pooled occurrence of MRSA, C. Difficile, and VRE

Table Set 5-9: Sensitivity Analysis Results for Patients with Increased and Decreased Baseline Morbidity

Table 5-9-1: Patients with Baseline Elixhauser of 13 or Greater:

BL-Allergic (n=1460) vs. non-Bl-allergic (n=5572)

	MULTIVARIATE MODEL HR (95% CI)	P-VALUE
ALL-CAUSE MORTALITY	0.99 (0.87 – 1.13)	0.903
STAGE 2 OR 3 AKI*	1.10 (0.95 – 1.26)	0.194
STAGE 3 AKI	1.05 (0.92 – 1.21)	0.479
MRSA	1.48 (1.22 – 1.78)	<0.001
C. DIFFICILE	***	
VRE*	1.10 (0.88 – 1.38)	0.414
ANY RESISTANT INFECTION	1.20 (1.02 – 1.41)	0.027

*Convergence not achieved

***Failed maximization parameters

Table 5-9-2: Patients with Baseline Elixhauser of 3 or Lower:

BL-Allergic (n=1385) vs. non-Bl-allergic (n=5451)

	MULTIVARIATE MODEL HR (95% CI)	P-VALUE
ALL-CAUSE MORTALITY	0.94 (0.84 – 1.06)	0.315
STAGE 2 OR 3 AKI	0.86 (0.68 – 1.09)	0.215
STAGE 3 AKI	0.95 (0.71 – 1.25)	0.698
MRSA	1.31 (1.26 – 1.52)	<0.001
C. DIFFICILE	1.07 (0.80 – 1.43)	0.659
VRE	1.58 (1.61 – 2.14)	0.004
ANY RESISTANT INFECTION*	1.26 (1.08 – 1.47)	0.003

*Convergence not achieved

Controlled for: Age, Race, Sex, baseline Scr, number of healthcare encounters, Elixhauser, Hemodialysis during visit, ICU admission during visit

5.4.5. Mediation Analysis

The results from the mediation analysis conducted for the causal pathway between BL allergy status (Exposure) through the number of healthcare encounters (Mediator) to the outcome of all-cause mortality are shown in Table 5-10. The controlled direct effect is roughly identical to the natural direct effect, indicating that there is likely not an interaction between the number of healthcare encounters and BL-allergy status on the risk of all-cause mortality. This interpretation can be drawn because the natural indirect effect is the estimate of the effect of a BL allergy when the mediator is set to particular value (e.g. Number of healthcare encounters = 10), and the natural direct effect is the estimate of a BL-allergy when the mediator is observed at its naturally occurring state. The difference between these two effects can be interpreted as BL allergies providing the same estimate regardless of controlling for the mediator, and since the difference between these two effects would be close to zero, there is not strong evidence of an interaction between the number of healthcare encounters and BL-allergy status. Since the natural indirect effect is significant, there is evidence that the total number of healthcare encounters is a significant predictor of all-cause mortality, which makes logical sense. However, since there is not evidence that the effect of the number of healthcare encounters changes at different levels of BL allergy status, it is reasonable to include the number of healthcare encounters as a covariate in the analysis.

Table 5-10: Mediation Analysis Results for the Relationship Between Beta-Lactam Allergy Status and Healthcare Utilization

MEDIATOR	CONTROLLED DIRECT EFFECT (COEFF, 95% CI)	NATURAL DIRECT EFFECT (COEFF, 95% CI)	NATURAL INDIRECT EFFECT (COEFF, 95% CI)	MARGINAL TOTAL EFFECT (COEFF, 95% CI)
NUMBER OF HEALTHCARE ENCOUNTERS	1.08 (0.97 – 1.20)	1.09 (0.99 – 1.19)	0.98 (0.97 – 0.99)	1.07 (0.98 – 1.17)

Estimates are bias-corrected using bootstrapped errors

5.4.6. Secondary Analysis

When using a time-varying form of BL allergy status, there was a moderate number of patients in each allergy group whose allergy status changed over time, from BL-allergic to non-allergic, and vice-versa (Table 5-11). The proportion of patients in each allergy group switching allergy statuses remained relatively constant, with roughly three times as many patients being newly labeled with BL allergies compared to those with allergies having their allergies removed, which is generally proportional to the non-BL-allergic group being three times as large as the BL-allergic group. Repeating the primary model using this time-varying allergy status produced an increased estimated hazard of mortality associated with a BL allergy label relative to the use of an intent-to-treat definition that carried forward the initial BL allergy status (Table 5-12). Notably, this difference was now statistically significant, with mortality being significantly associated with BL allergies (HR 1.08; 95%CI 1.02-1.14). Overall, the direction of all other clinical outcomes remained consistent, with an increase in the hazard of MRSA, (HR 1.46; 95%CI 1.31 – 1.63), VRE (HR 1.32; 95%CI 1.15 – 1.51), and pooled resistant infections (HR 1.39; 95%CI 1.26 – 1.53) all of which were significantly associated with the presence of a BL allergy.

Within the BL allergy group, there were differences in clinical outcomes depending upon if the patient had a documented penicillin, cephalosporin, carbapenem, or aztreonam allergy (Table 5-13). While penicillin allergies alone were not significantly associated with all-cause mortality, patients with allergies to cephalosporins (HR 1.26; 95%CI 1.14 – 1.41), carbapenems (HR 2.78; 95%CI 1.80 – 4.30), or aztreonam (HR 1.83; 95%CI 1.07– 3.13) all did have significantly increased hazards of mortality compared to non-allergic patients. In general,

penicillin allergies mirrored the results of the primary analysis, with MRSA, VRE, and pooled resistant infections all significantly increased in the presence of a penicillin allergy. Cephalosporins showed similar results, but also with an increase in the hazards of CDiff (HR 1.60; 95%CI 1.15 – 2.22). Patients with carbapenem or aztreonam allergies were also associated with resistant infections, but the confidence intervals for these groups are very wide due to their small sample sizes (26 and 21 total patients, respectively), and are likely not highly reliable estimates.

When comparing BL allergies to non-BL allergies and patients with at least one BL allergy and one non-BL allergy, there were notable differences in outcomes (Table 5-14). The presence of a non-BL allergy was not associated with differences in all-cause mortality, but was associated with increased rates of MRSA, (HR 1.36; 95%CI 1.16 – 1.60), and VRE (HR 1.60; 95%CI 1.30 – 1.96) which is similar to the results seen with BL allergies, but also with a significantly increased hazard of CDiff (HR 1.51; 95%CI 1.19 – 1.91). The group with both BL and non-BL allergies showed similar trends, but did show significant results for an increase in the adjusted hazards of all-cause mortality (HR 1.21; 95%CI 1.10 – 1.33), as well as MRSA(HR 1.55; 95% CI 1.29 – 1.86), MRSA (HR 1.55; 95%CI 1.29 – 1.86) and VRE (HR 1.38; 95%CI 1.09 – 1.78).

Table 5-11: Survival Table - Time-varying Allergy Status

	Non-BL Allergic				BL-Allergic			
Date Range	**Number at Risk**	**Deaths**	**Censored**	**BLA → Non-BLA**	**Number at Risk**	**Deaths**	**Censored**	**Non-BLA → BLA**
Jan 2007 – Jun 2007	3929	541	99	8	1324	154	23	10
July 2007 – Dec 2007	7386	843	141	14	2340	214	27	35
Jan 2008 – Jun 2008	10362	973	146	19	3359	267	32	41
July 2008 – Dec 2008	13297	928	187	16	4263	244	37	53
2009	12203	1308	234	32	3985	446	59	110
2010	10629	1003	219	32	3475	295	59	112
2011	9389	815	198	39	3118	265	55	95
2012	8365	671	218	28	2789	233	55	85
2013	7456	555	284	21	2497	211	86	91
2014	6597	499	312	9	2194	116	77	57
2015	5775	464	416	10	1940	161	104	32
2016	4885	419	521	15	1672	120	151	40
2017	3935	349	873	19	1398	111	289	56
2018	2690	223	2416	20	990	84	885	53

Intervals include the full year unless month is noted (e.g. '2009' = Jan 1, 2009 – Dec 31, 2009). Number at risk defined as allergy status being present for any encounter at any time during the applicable time period. Deaths and Censored are counted according to the allergy status at the time of death/censoring. BLA → Non-BLA and Non-BLA → BLA defined as allergy status switching from Non-BL allergic or BL-allergic, or vice versa, during the applicable study period (each individual patient could only be counted as at risk once during each group/time period).

Table 5-12: Secondary Analysis Results Using Mixed Effect Survival Models with Time-Varying Beta-Lactam Allergy Status

	MULTIVARIATE MODEL HR (95% CI)	P-VALUE
ALL-CAUSE MORTALITY	1.08 (1.02 – 1.14)	0.006
STAGE 2 OR 3 AKI	1.00 (0.91 – 1.11)	0.903
STAGE 3 AKI	1.03 (0.92 – 1.14)	0.610
MRSA	1.46 (1.31 – 1.63)	<0.001
C. DIFFICILE*	1.18 (0.99 – 1.41)	0.063
VRE	1.32 (1.15 – 1.51)	<0.001
ANY RESISTANT INFECTION**	1.39 (1.26 – 1.53)	<0.001

Controlled for: Age, Race, Sex, baseline Scr, number of healthcare encounters, Elixhauser, Hemodialysis during visit, ICU admission during visit

*Convergence not achieved

**Any Resistant Infection corresponds to pooled occurrence of MRSA, C. Difficile, and VRE

Table 5-13: Secondary Analysis Results Comparing the Outcomes of BL Allergy Groups

	PENICILLIN ALLERGY, HR (95% CI) [P-VALUE] (N = 3828)	CEPHALOSPORIN ALLERGY, HR (95% CI) [P-VALUE] (N = 689)	CARBAPENEM ALLERGY HR (95% CI) [P-VALUE] (N = 26)	AZTREONAM ALLERGY, HR (95% CI) [P-VALUE] (N = 21)
ALL-CAUSE MORTALITY	1.06 (1.00 – 1.12) [0.047]	1.26 (1.14 – 1.41) [<0.001]	2.78 (1.80 – 4.30) [<0.001]	1.83 (1.07 – 3.13) [0.029]
STAGE 2 OR 3 AKI	1.00 (0.90 – 1.10) [0.952]	1.11 (0.91 – 1.35) [0.313]	2.37 (1.08 – 5.24) [0.032]	0.95 (0.30 – 3.03) [0.928]
STAGE 3 AKI	1.04 (0.93 – 1.16) [0.499]	1.06 (0.84 – 1.32) [0.588]	1.69 (0.66 – 4.32) [0.271]	1.30 (0.40 – 4.26) [0.660]
MRSA	1.42 (1.27 – 1.59) [<0.001]	Failed maximization parameters	Failed maximization parameters	5.49 (1.84 – 16.43) [0.002]
C. DIFFICILE	1.08 (0.90 – 1.30) [0.420]	1.60 (1.15 – 2.22) [0.006]	3.90 (1.01 – 15.00) [0.048]	0.98 (0.13 – 7.38) [0.988]
VRE	1.24 (1.08 – 1.43) [0.003]	1.41 (1.09 – 1.83) [0.009]	7.52 (3.38 – 16.76) [<0.001]	2.09 (0.61 – 7.18) [0.240]
ANY RESISTANT INFECTION*	1.30 (1.18 – 1.43) [<0.001]	1.64 (1.35 – 1.98) [<0.001]	10.94 (4.90 – 24.46) [<0.001]	3.01 (1.10 – 8.27) [0.032]

All outcomes expressed as hazard ratios. Models controlled for with age, race, sex, baseline serum creatinine, Elixhauser, number of total healthcare encounters in follow-up period and AKI during each healthcare encounter

*Any Resistant Infection corresponds to pooled occurrence of MRSA, C. Difficile, and VRE

Table 5-14: Secondary Analysis Results for the Relationship Between Beta-Lactam Allergies and Non-Beta-Lactam Allergies

	BL ALLERGY ONLY HR (95% CI)	P-VALUE	NON-BL-ALLERGY ONLY HR (95%CI)	P-VALUE	BOTH BL AND NON-BL ALLERGY HR (95% CI)	P-VALUE
ALL-CAUSE MORTALITY	0.97 (0.91 – 1.03)	0.260	1.01 (0.93 – 1.11)	0.698	1.21 (1.10 – 1.33)	<0.001
STAGE 2 OR 3 AKI	1.01 (0.91 – 1.13)	0.801	1.00 (0.85 – 1.18)	0.979	0.94 (0.78 – 1.14)	0.545
STAGE 3 AKI	1.33 (1.19 – 1.49)	<0.001	1.36 (1.16 – 1.60)	<0.001	1.55 (1.29 – 1.86)	<0.001
MRSA	1.33 (1.19 – 1.49)	<0.001	1.36 (1.16 – 1.60)	<0.001	1.55 (1.29 – 1.86)	<0.001
C. DIFFICILE	1.00 (0.83 – 1.20)	0.997	1.51 (1.19 – 1.91)	0.001	1.40 (1.06 – 1.85)	0.016
VRE	1.27 (1.08 – 1.48)	0.003	1.60 (1.30 – 1.96)	<0.001	1.38 (1.09 – 1.76)	0.009
ANY RESISTANT INFECTION*	1.21 (1.10 – 1.33)	<0.001	1.37 (1.19 – 1.57)	<0.001	1.44 (1.24 – 1.69)	<0.001

All outcomes expressed as hazard ratios. Models controlled for with age, race, sex, baseline serum creatinine, Elixhauser, number of total healthcare encounters in follow-up period and AKI during each healthcare encounter

*Any Resistant Infection corresponds to pooled occurrence of MRSA, C. Difficile, and VRE

Figure Set 5-4: Survival Curves for Secondary Analysis with Expanded Allergy Groups

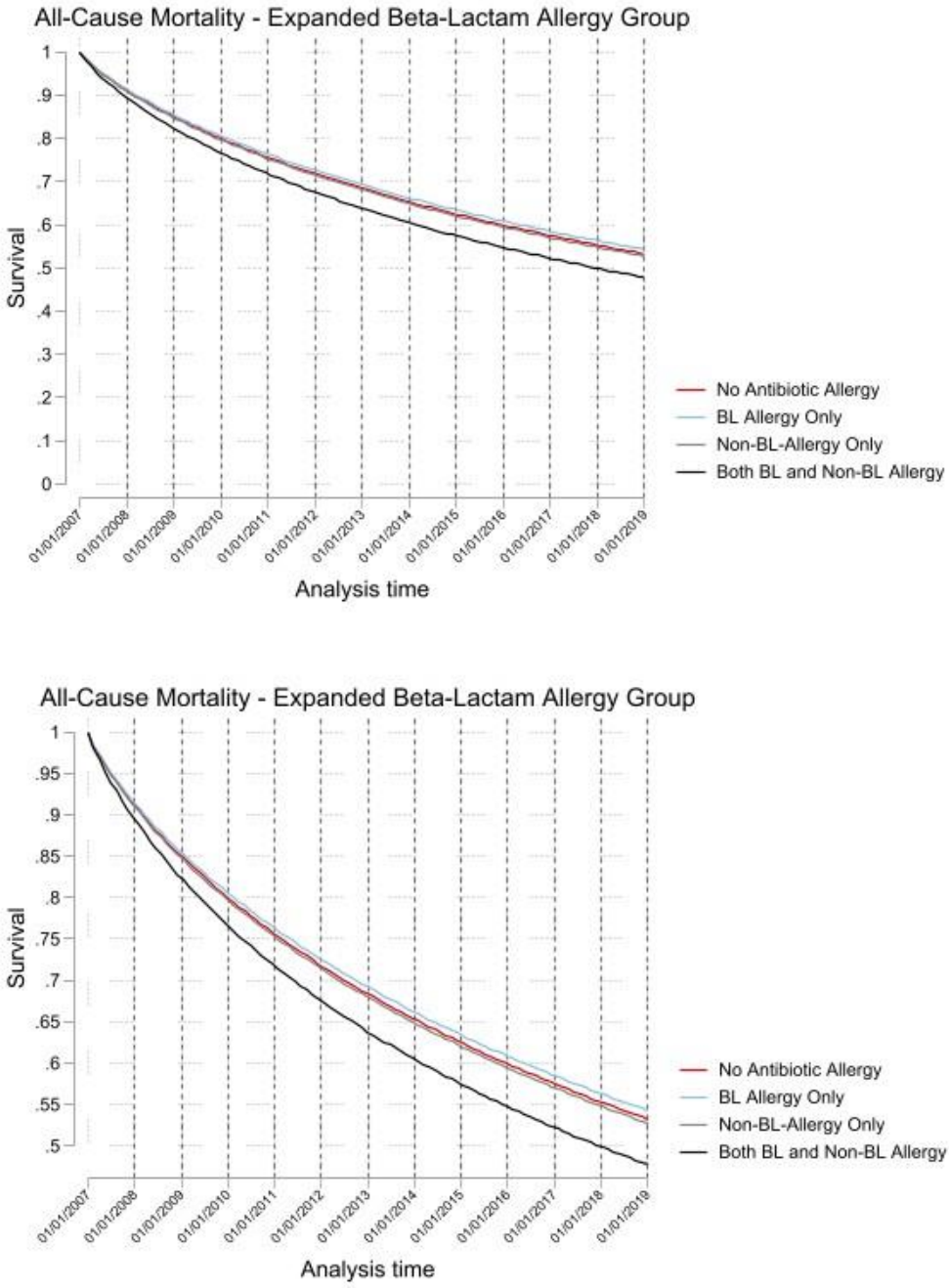


Figure 5-4-1: Mortality Rate with Expanded Allergy Groups

Note Scale: Figures display the same graph.

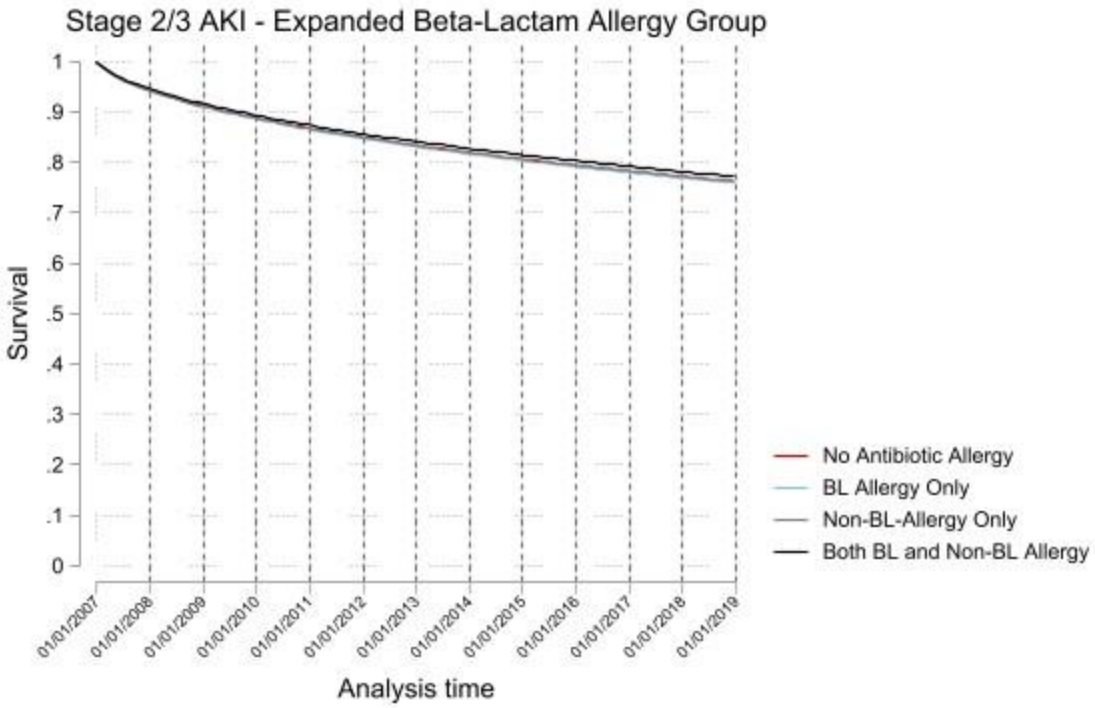


Figure 5-4-2: Stage 2/3 AKI Rate with Expanded Allergy Groups

Results for parametric mixed-effects survival models for stage 2/3 AKI using expanded allergy groups.

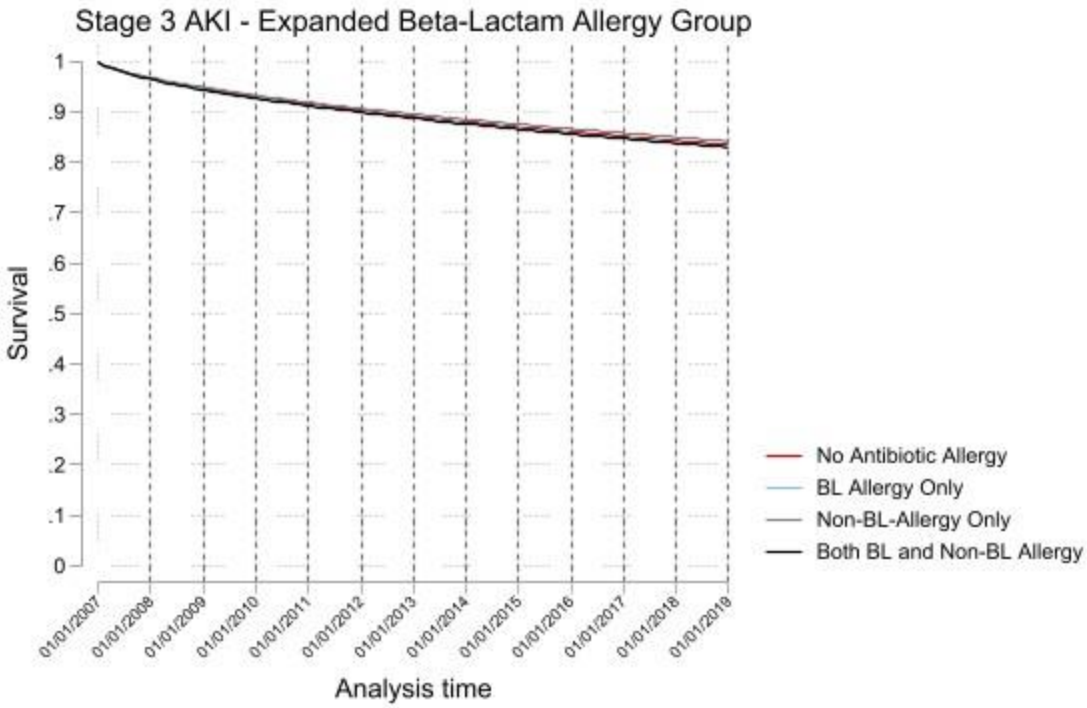


Figure 5-4-3: Stage 3 AKI Rate with Expanded Allergy Groups

Results for parametric mixed-effects survival models for stage 3 AKI using expanded allergy groups.

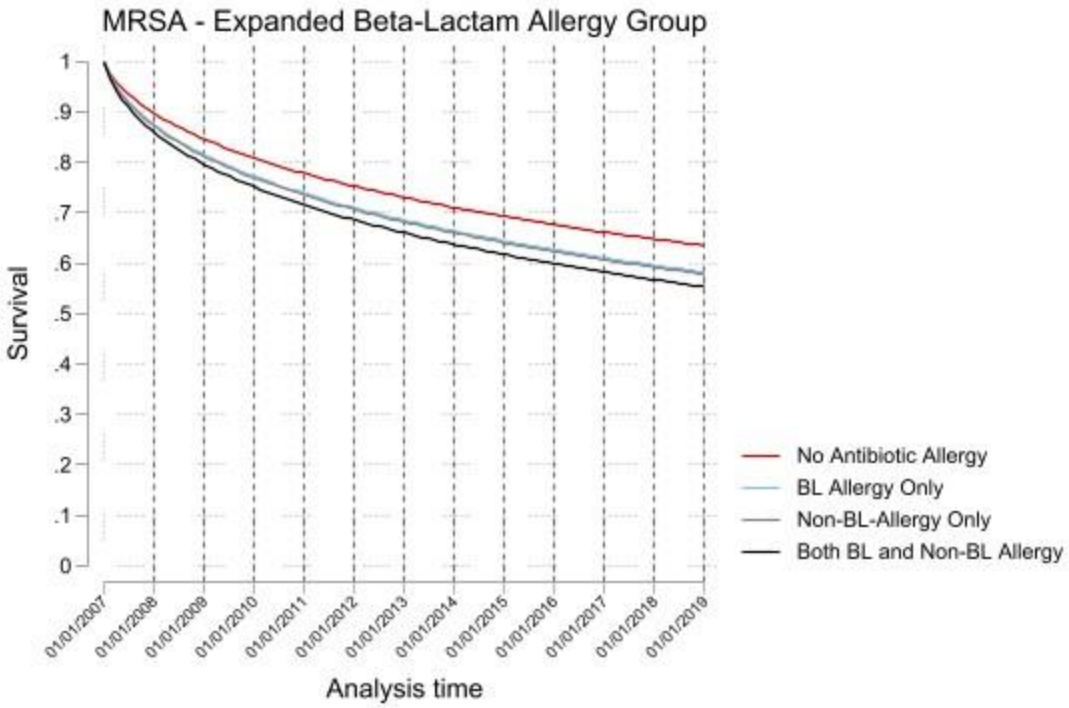


Figure 5-4-4: MRSA Rate with Expanded Allergy Groups

Results for parametric mixed-effects survival models for MRSA using expanded allergy groups.

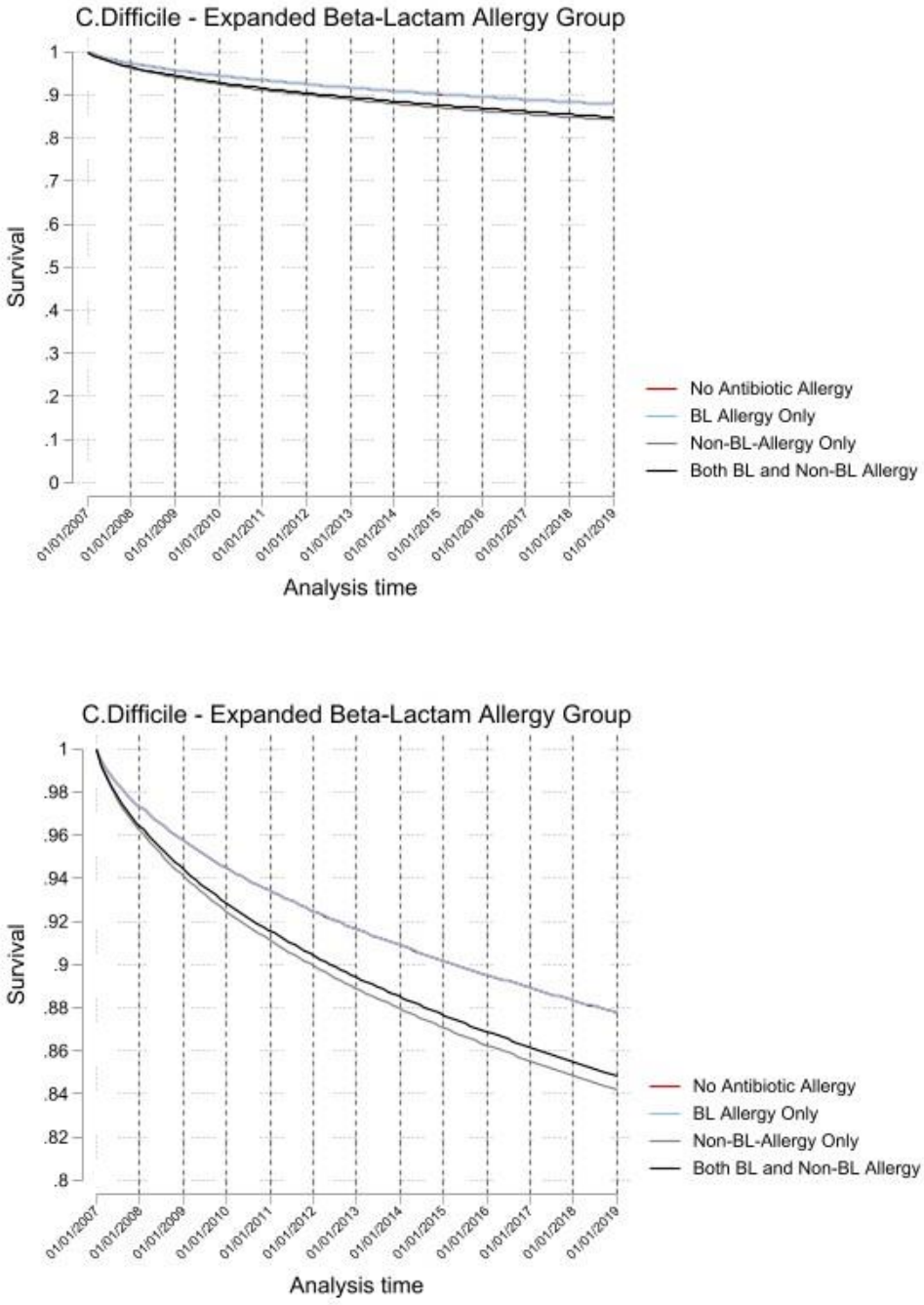


Figure 5-4-5: C. Diff Rate with Expanded Allergy Groups

Note Scale: Figures display the same graph

Results for parametric mixed-effects survival models for CDiff using expanded allergy groups.

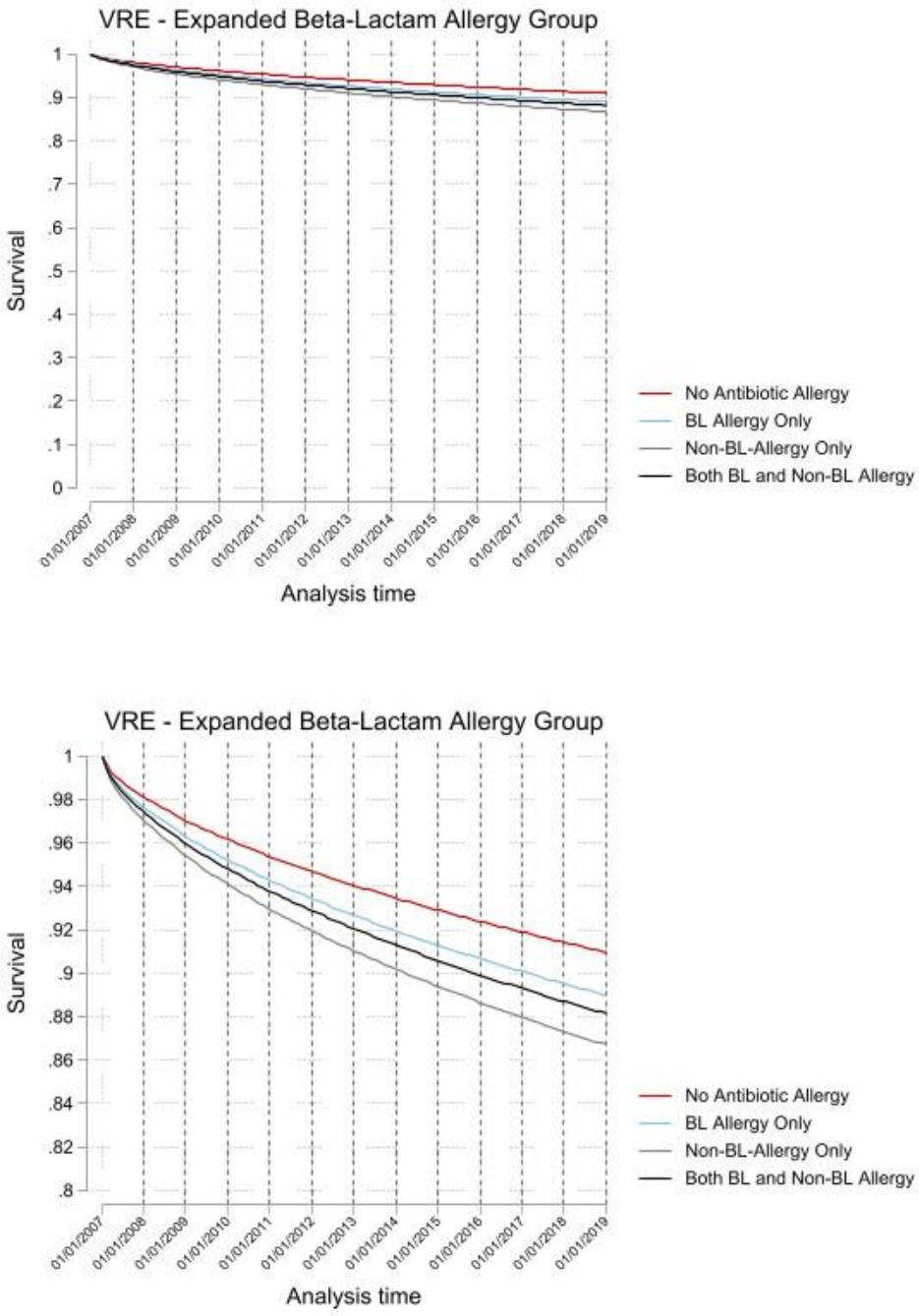


Figure 5-4-6: VRE Rate with Expanded Allergy Groups

Note Scale: Figures display the same graph

Results for parametric mixed-effects survival models for VRE using expanded allergy groups.

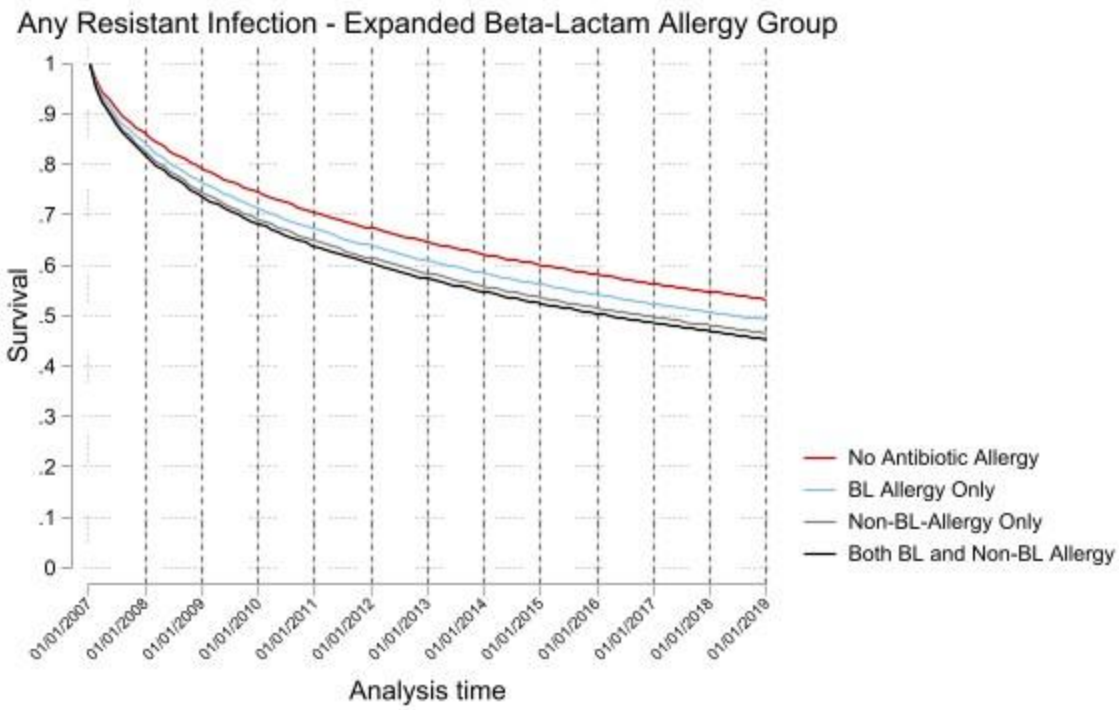


Figure 5-4-7: Any Resistant Infection Rate with Expanded Allergy Groups

Results for parametric mixed-effects survival models for pooled MRSA, C. difficile, and VRE hazards using expanded allergy groups.

5.5 DISCUSSION

This study is the first to use a mixed-effect time-to-event analysis in BL-allergic patients over an extended time span to determine the effect of BL allergies on clinical outcomes. This study shows that the presence of a BL allergy in a patient's medical record is associated with a statistically significant increase in rates of infection with MRSA or VRE and may be associated with an increase in all-cause mortality.

There has only been one previous examination of the long-term (>5 years total follow-up) outcomes associated with BL allergies, which found a 14% increase in all-cause mortality and an increase in both MRSA and CDiff.[10,65] Our study extends on the previous results by Blumenthal et al. in a number of ways. First, our study utilized patient-level mixed-effects survival models in order to minimize residual confounding. As noted in their study, residual confounding is particularly concerning when studying such a complex outcome as all-cause mortality in such a diverse population. Despite controlling for known clinical factors related to BL allergy status and mortality, such as female sex, there will always remain unmeasured confounders that affect mortality which cannot be included in a model. By utilizing mixed-effects in our model, we can theoretically estimate and control for this unmeasured confounding by assuming that this unmeasured confounding is associated with the patient identifier, and the inclusion of this patient identifier in the mixed effects model can and minimize the potential for unmeasured confounding to a level that cannot be achieved using more traditional cohort study techniques. However, the pseudo R-squared values estimated during the model validation step showed low overall predictive value, so it is likely that some residual confounding remains. Second our study analyzed additional clinical endpoints such as AKI and a pooled risk of resistant infections. BL allergies have been previously associated with an increased risk of AKI and resistant infections, and it is important to understand how this effect may translate to an extended follow-up period.[220,221] Our study design was uniquely positioned to analyze these secondary endpoints and

to provide this needed analysis. Also, our study accounted for changes in allergy status that may have happened over time in a sensitivity analysis, which the previous study did not. Finally, our analysis included an examination of non-BL antimicrobial allergies, which receive less attention than their BL counterparts but can pose similar risks.[222-225] Our study considered these patients in a secondary analysis, and also allows for a direct comparison of the long-term risks of BL to non-BL allergies, as well as multi-allergic patients.

Our results display an inconsistent trend between the relationship between BL allergies and long-term all-cause mortality. Shorter-term studies have also found mixed results on the impact of BL allergies on mortality.[194,226] However, longer-term cohort studies such as the twelve-year span analyzed in our study should be able to minimize the short-term variation that may be influencing previous studies, and provide more accurate estimates of the true long-term effect of BL allergies on mortality while taking into account clinical covariates to minimize the risk for confounding. Relative to the previous examination of all-cause mortality which found a 14% increase in annual hazards found almost no difference in the long-term all-cause mortality in our primary model, but did find a roughly 8% increase in all-cause mortality (patient-specific) when modeling BL allergies as a time-varying variable, which is more consistent with prior short-term studies..[56] The time-varying modeling of penicillin allergies may more accurately model the effect of BL allergies over time by taking changes in allergy documentation into account. Additionally, there may be a varying level of risk associated with certain BL allergies that is causing this incongruity, such as more severe allergies (e.g., anaphylaxis) leading to more harm due to complete BL avoidance, but less severe allergies (e.g., rash) sometimes being bypassed and being associated with less BL avoidance and less harm. This hypothesis would support recent delabeling efforts which risk stratify the severity of patient allergies according to reaction and timing characteristics, and should be a direction for future research to determine if allergic reactions which necessitate complete avoidance pose a greater risk than more mild reactions such as rash.[19]

Our study suggests a significantly increased hazard for MRSA and VRE infection associated with BL allergies, but no difference in the hazards of Cdiff. Short-term studies have also found increased rates of resistant infections associated with BL allergies, although there are some conflicting results, particularly concerning Cdiff infection rate.[227,228] Overall, the increased rate of MRSA is consistent with previous literature.[66] Avoiding particular first-line antibiotics appears to predispose the BL-allergic patients to more MRSA infections, with possible secondary effects on increasing the risk for Cdiff and VRE, but the specific antibiotics which are most influential in this pathway are not well described. Future efforts should relate the altered prescribing pathways which BL-allergic patients go through, and the associated risk of each antibiotic with resistant infections to implement targeted review and oversight to reduce the unnecessary use of these predisposing antibiotics.

When comparing BL to non-BL allergies, non-BL-allergies appear to show similar or even slightly more significant results than BL allergies alone. Despite it being understood that non-BL allergies can pose clinical risks for the same reasons as BL allergies, direct comparison between the two groups of allergies is rare.[229] However, the group of patients who had both BL and non-BL allergies showed the greatest risk across all outcomes. Patients who had at least one BL allergy and one non-BL allergy documented showed the highest increase in the hazards for death, and resistant infections. Patients with one antimicrobial allergy are at increased risk for hypersensitivity to other classes, and this can quickly narrow prescribing options and force the use second-line or even third-line antibiotics with worse antimicrobial coverage and greater toxicity.[230,231] Our study also found that there may be differences in outcomes among patients with BL allergies depending upon the specific agent that is reported as the allergy. Patients with cephalosporin allergies experienced higher rates of all-cause mortality and resistant infections compared to patients with penicillin allergies. It is possible that since cephalosporins are a larger class, that a cephalosporin allergy is leading to higher rates of avoidance of first-line agents and more difficulty in finding suitable alternatives

when compared to penicillin allergies.[1] Our study shows that while BL allergies are most often emphasized due to their overwhelming prevalence, all antimicrobial allergies can pose a differing risk and should be considered individually. Patients with multiple allergies are at the greatest risk and should receive the greatest scrutiny in allergy evaluation. Such multi-allergic patients should be particularly targeted for BL allergy testing where appropriate since the risk with a non-BL allergy alone was much less than patients with both BL and non-BL antimicrobial allergies.

Our study found an inconsistent relationship between BL allergies and increased all-cause mortality. It is likely that this risk is not the same for all patients, and patients who have serious allergic reactions documented such as anaphylaxis or hives which cause near to complete avoidance of BL-containing products incur the greatest risk, while the risk may be lower for those with minor reactions. In general, our study finds that any antimicrobial allergy can lead to averse clinical outcomes, whether it be an allergy to BL-containing products or another class such as macrolides. We also conducted sensitivity analysis comparing patients with the highest and lowest baseline morbidity, which showed that the detrimental impact of BL allergies, particularly on increasing the risk for resistant infections, was highest among patients with the highest baseline morbidity. These findings are consistent with previous findings that BL allergy delabeling generates the most value when performed in high-risk patients such as those with a history of resistant infections or a high likelihood to receive ongoing antimicrobial therapy. A challenge presented by this pattern is that the high-risk patients with increased baseline morbidity who would likely benefit the most from BL allergy evaluation and delabeling may also be more likely to have their allergy status overlooked as low-priority as a result of this increased baseline morbidity.[79] When implementing BL evaluation and delabeling initiatives, health systems should focus their efforts on those with the highest antimicrobial utilization to maximize the benefit that is produced from each allergy that is delabeled.

Our study has some notable limitations. First, although we used mixed-effect models to minimize the risk for residual confounding, there is still a remaining risk for unmeasured confounding due to the broad range of patients that report BL allergies. Additionally, the use of a mixed-effect model limits the interpretation of some of the results since each patient has their own specific covariate effects, and generalization to a broader population is difficult. Second, we included patients into the study cohort through the use of an index encounter with one of three specific infectious disease diagnoses in a two-year span. These infections were chosen because each has a high likelihood to include a BL product within the first or second lines of treatment, and would be affected by the presence of a BL allergy. Limiting to these indications and timeline reduced the risk for immortal time bias and indication bias but limited the generalizability of our results when applied to a broad ambulatory population and may have greatly reduced our statistical power as a result. Our cohort was also constrained to a single regional health system in western Pennsylvania, which limits its external validity in other populations. The cohort design which was used necessitated that the last observed healthcare encounter be used as the censoring date for each patient, but this may introduce selection bias due to excluding periods where patients were 'healthy' and were not experiencing observable healthcare encounters. Our results indicate that BL allergies may have variable effects depending upon factors such as the baseline morbidity of the patient. However, another important factor includes the severity of the allergic reaction, which we were not able to analyze due to data limitations. Finally, the use of EHR data involves the acceptance of some risk for data inaccuracies and inconsistencies. We attempted to standardize the definitions and variables used to the best of our ability possible through the use of published methods and system-level dictionaries, but there remains a risk for information and misclassification bias.

6.0 NATURAL-LANGUAGE PROCESSING OF CLINICAL NOTES TO PROMOTE THE USE OF PREVIOUSLY TOLERATED BETA-LACTAM PRODUCTS IN BETA-LACTAM-ALLERGIC PATIENTS

6.1 ABSTRACT

Most documented beta-lactam (BL) allergies are erroneous in nature and do not represent true hypersensitivity reactions, and patient outcomes would be improved if these erroneous allergies were removed from patient records. To determine which patients are most likely to have BL allergies that can safely be delabeled, allergies are often risk stratified using factors such as the severity of the allergic reaction, the historical timing of the reaction, whether treatment was required, and if the patient has ever received BL antimicrobials since the reaction occurred.

We aimed to use natural language processing (NLP) of clinical notes to automate the risk stratification process and calculate a PEN-FAST score for patients with documented BL allergies. However, the information contained in general clinical notes was not amenable to calculating a PEN-FAST because the time when the reaction last occurred and whether treatment was required for the reaction, which combined represent 60% of the PEN-FAST, was identified in only 1 of 550 clinical notes that were reviewed. As a result, our focus shifted to identification of antimicrobial products that patients with BL allergies have previously tolerated since many treatment algorithms promote the use of previously tolerated products despite documented allergies. Using a sample of 189,847 clinical notes, we used a dictionary-based NLP pipeline to identify entities corresponding to BL-containing products and phrases indicating medication usage. We then used a rule-based system implemented in SQL to relate the relative location of

these entities to determine prior usage of BL antimicrobials (e.g. BL product within 100 characters of a use phrase). Finally, we created simulated CDS alerts including the NLP-derived information and surveyed clinician feedback on the utility of including this historical BL usage information in CDS alerts.

Three Rules were created: Rule 1 (F1 score = 0.975) identified BL use in 9.7% of notes by identifying BL entities in medication lists, Rule 2 (F1 score = 0.946) identified BL use in 24.3% of notes by identifying singular sentences containing both BL and use phrase entities, and Rule 3 (F1 scores = 0.946, 0.935, 0.883) identified BL use in 25.2%, 28.7%, and 30.6% by identifying BL entities within 50, 100, and 150 characters of use phrases, respectively. Among notes for patients who had documented BL allergies at the time the note was written, 3.5% of notes identified through Rule 1 contained BL use, and between 21% – 28.3% contained BL use using rules 2 or 3. Roughly 2-4% of notes from BL-allergic patients were identified to contain BL use were from patients who had no history of receiving BL containing products using structured medication dispensing history, meaning this BL use information was only contained in the clinical notes. We surveyed 9 clinicians on the clinical utility of including the NLP-derived allergy information in CDS allergy alerts. Overall, clinician confidence in using BL-containing products in BL-allergic patients was always higher when using CDS alerts which included the BL use history information.

This is the first attempt to include BL usage history in CDS allergy alerts for patients with BL allergies. We created an NLP pipeline that had performance characteristics in identifying prior BL usage from clinical notes that can be used in a broader workflow to include historical BL usage information in CDS allergy alerts. Additionally, we showed that some allergy information is only contained in clinical notes, and inclusion of this information may lead to more comprehensive models than using structured medication usage information alone. Finally, simulated CDS alerts containing information about historic BL usage from our NLP allergy alert pipeline increased clinician confidence in using BL products in patients with documented BL allergies.

6.2 INTRODUCTION

Although most reported BL allergies are erroneous in nature and what constitutes a true hypersensitivity reaction is commonly misunderstood by patients, there is a significant percentage of the population that do show severe reactions such as angioedema, anaphylaxis, or severe cutaneous reactions which preclude the use of some or all BL antimicrobials.[18] Risk stratification is a process which can be used to quickly identify the allergies that are amenable to delabeling by using standardized questions or clinical history to quickly estimate the likelihood that a particular patient is reporting a true hypersensitivity to BL-containing products.[18,112,118,175,232,233] One such risk stratification method that has been highly validated is the PEN-FAST, which is an algorithm that can be used to easily evaluate the legitimacy of a BL allergy using three criteria: 1) - (F) **F**ive years or less since the reaction occurred worth 2 points; 2) – (AS) **A**naphylaxis/angioedema, or **S**evere cutaneous reaction worth 2 points; 3) – (T) **T**reatment required for reaction worth 1 point; with a score of 0 corresponding to a <1% of a BL allergy being a true allergy, and an increasing score corresponding to an overall higher chance of a documented BL allergy representing a true allergy.[19] Methods such as the PEN-FAST can significantly decrease the costs and resources required to challenge a BL allergy and greatly enables delabeling efforts because risk stratification tools have high predictive accuracy which allow for the bypassing of more allergy evaluation intensive techniques such as skin testing and instead allows for direct challenge and observation.[19,97,104,234-238]

Risk stratification provides clinicians with an ideal starting point for identifying patients which could most successfully be targeted for BL allergy review and delabeling, but the risk stratification process itself can be time-consuming and requires patients to be knowledgeable enough about their own allergy history to be able to provide sufficient information, and these factors have been reported as reasons that clinicians may not evaluate potentially erroneous BL allergy labels.[16] One option to overcome these

limitations is to automate the risk-stratification process and provide an initial estimate of the patient's risk for a true BL allergy to the clinician through a clinical decision support (CDS) alert.[239] There have been previous attempts to use automation to standardize the documentation of allergy reactions and reduce the need for clinician interpretation of the severity of reactions.[240] Machine-learning models, and simpler key-word searches of allergy reactions can achieve reliability in distinguishing true hypersensitivity reactions from less serious reactions.[124] This is a promising approach for improving the documentation of BL allergies, however, allergies cannot be standardized through this manner if the allergy reaction is not recorded in the EHR, which is the case for over 36% of documented BL allergies.[241] The process of utilizing CDS alert information also almost always still requires the clinician to confirm the results of the risk assessment with allergy information from the patient or family regardless of whether or not this initial process is automated, and this confirmation step can be highly limiting when information from patients or family is unavailable or unreliable.[16]

We sought to improve upon the process of automated BL risk-stratification with the goal of overcoming these previous limitations by using natural-language processing to calculate a PEN-FAST score for patients with documented BL allergies from information documented in clinical notes. This process would have additional utility over methods which rely solely on the allergy and reaction information by including more information about the history of the reaction and whether treatment was required when the reaction occurred, as well as allowing for a conservative score to be assigned to patients even when a reaction for the allergy is not available if this additional allergy history information was available in previous clinical notes. Additionally, we will make use of prior allergy evaluations which were conducted by clinicians and documented in clinical notes, enabling more productive and informed conversations with patients and family regarding allergy histories and minimizing duplicative allergy evaluation.

Ultimately, since 60% of the information required to calculate a PEN-FAST was found in only 1/550 notes following a targeted review, our goal was shifted to focus on identifying previous use of BL-containing products using NLP of clinical notes. While this was different from our initial goal, the identification of previously tolerated BL products for use in CDS alerts would still overcome the stated limitations of automated risk stratification in a similar manner by informing clinician behavior when the BL allergy reaction is not available and would make use of previously occurring allergy evaluations.

6.3 METHODS

6.3.1 Study Design and Goals, Data Source & Review Board Approval

The goal of this study was to design a natural language processing-based process that would provide clinicians an initial estimate of the legitimacy of a BL drug allergy, which would expedite BL allergy evaluation and the delabeling of erroneous BL allergies, as well as promote the use of BL-containing products despite the documentation of a BL allergy. In doing so, our process would serve as a proof-of-concept for health systems to design and implement similar systems and reduce the impact of erroneous BL allergies in their respective patient populations. The data source for this project was a corpus of clinical notes generated from the cohort of patients used in the previously described longitudinal analysis (Aim 2). Patients were included in the analysis by having a healthcare encounter with a diagnosis of sepsis, pneumonia, or UTI between the years 2007-2008 and were then followed until death or the end of the year 2018. The following clinical note types were included: history and physicals, physician progress notes, emergency room notes, and discharge summaries. The de-identified clinical notes from each patient's index visit (N = 130844), as well as a random sub-set of follow-up notes occurring after 2008 (N = 59003) were

included in the analysis. This study was reviewed by the University of Pittsburgh's International Review Board and designated as exempt status.

6.3.2 Clinical Note Pre-processing & NLP Software

Clinical notes were formatted as de-identified, full-text documents with delimiter key phrases which identified the beginning and end of each individual note. The NLP pipeline required that the notes be structured as individual clinical notes, so a Python-based parser was used to split each note into its own independent file. During this process, necessary patient and date identifiers were also parsed from the header of each clinical note and were exported to a separate data table. The result of parsing the clinical notes produced a corpus containing 189,847 individual clinical notes.

The Clinical Language Annotation, Modeling, and Processing (CLAMP) toolkit version 1.66 was used for corpus annotation and NLP pipeline development.[242] CLAMP contains built-in functions that are useful for NLP pipeline development such as tokenization, sentence detection, section identification, chunking, concept mapping with common ontologies such as ULMS and RxNorm, and multiple frameworks for conducting NER. The visual graphics user interface version of CLAMP was used for model development and refinement, and the command-line version was to run the final NLP pipeline on the corpus of clinical notes.

6.3.3 Risk Stratification, Corpus Annotation, & Study Goal Refinement

We sought to identify pertinent information from clinical notes that could be used to quickly evaluate the legitimacy of a documented BL allergy. Initially, we planned to use an NLP pipeline to identify the information required in calculating the PEN-FAST as our basis for risk stratification. Using the PEN-

FAST as our model, we emphasized the recognition of severe BL-allergic reactions, the historic timing of documented BL allergies, and whether treatment was required for the reaction since these three components comprise the PEN-FAST calculation. After identifying these three criteria, our pipeline would be able to provide a 0-5 risk score to clinicians that would be able to quickly quantify the likelihood that a documented BL-allergy was legitimate. When a criterion required for the calculation could not be identified, the highest value for that score would be used to provide conservative estimates (e.g. if no information regarding treatment of the reaction was available, the patient would automatically be assigned 1 point for this criteria), which would allow for the calculation of an estimated score despite the allergy reaction not being documented.

A corpus of clinical notes was annotated to identify the three factors required for the PEN-FAST. A random sample of 300 notes was initially annotated to determine the viability of this approach. Through this review, it was determined that only 1 of the 300 notes contained information about the time since the allergy had occurred, and none of the 300 notes contained information needed to evaluate whether the allergic reaction required treatment. To increase the likelihood of identifying the required criteria in a given note, an additional 250 notes were reviewed from patients who had documented BL allergies, consisting of 50 discharge summaries, 50 ER notes, 50 history and physicals, and 100 clinical progress notes. From this set of 250 additional notes, there were no notes identified which contained information related to the historical timing of the allergy or whether treatment was required for the allergy. Instead, it was identified that often when allergies were discussed in the clinical notes, it focused on the reaction or previous tolerance of products, such as a tolerance to a cephalosporin despite a penicillin allergy. Due to the lack of success in identifying criteria which would be required for 60% of the PEN-FAST, our approach was then shifted to identifying previous tolerance of BL-containing products, since this would be able overcome the limitations

associated with systems focused on the documented reaction to the allergy and has not been previously examined.

6.3.4 NLP Pipeline Development

The updated goal of identifying previous tolerance of BL-containing products required the defining of new entities which would be identified through the named entity recognition (NER) process. Three entities were defined: 1) **Beta-lactam products** – all brand and generic names corresponding to BL-containing products. These were further subdivided by clinical class as: penicillins, generation 1 – 5 cephalosporins, aztreonam, or carbapenems. 2) **Current medication use phrases** – phrases such as "initiate" or "start on" which indicate current use of medications. 3) **Previous medication use phrases** – phrases such as "was given" or "treated with" which indicate previous use of medications. The BL products list was generated using a CLAMP-provided built-in list of medication names from RXnorm which was supplemented through a list previously used to identify BL-containing medications (Appendix 5-3). The phrases for current and previous medication use were developed by including phrases that occurred in the 550 previously annotated clinical notes. The complete dictionary of entity phrases can be seen in Appendix 6-1.

The NLP pipeline was developed using an iterative process with a sub-set of clinical notes to determine the ideal set of components and settings. The following component steps (in order) are included in the final pipeline: sentence detection, tokenization, part-of-speech tagging, section identification, and dictionary-based named entity recognition. During this stage, the dictionary of BL-products and medication use phrases was refined by adding additional phrases which were not initially included. The finished pipeline was then used to process the 189,847 clinical notes to identify previous use of BL containing products.

6.3.5 Structured Data Incorporation and Rule Development

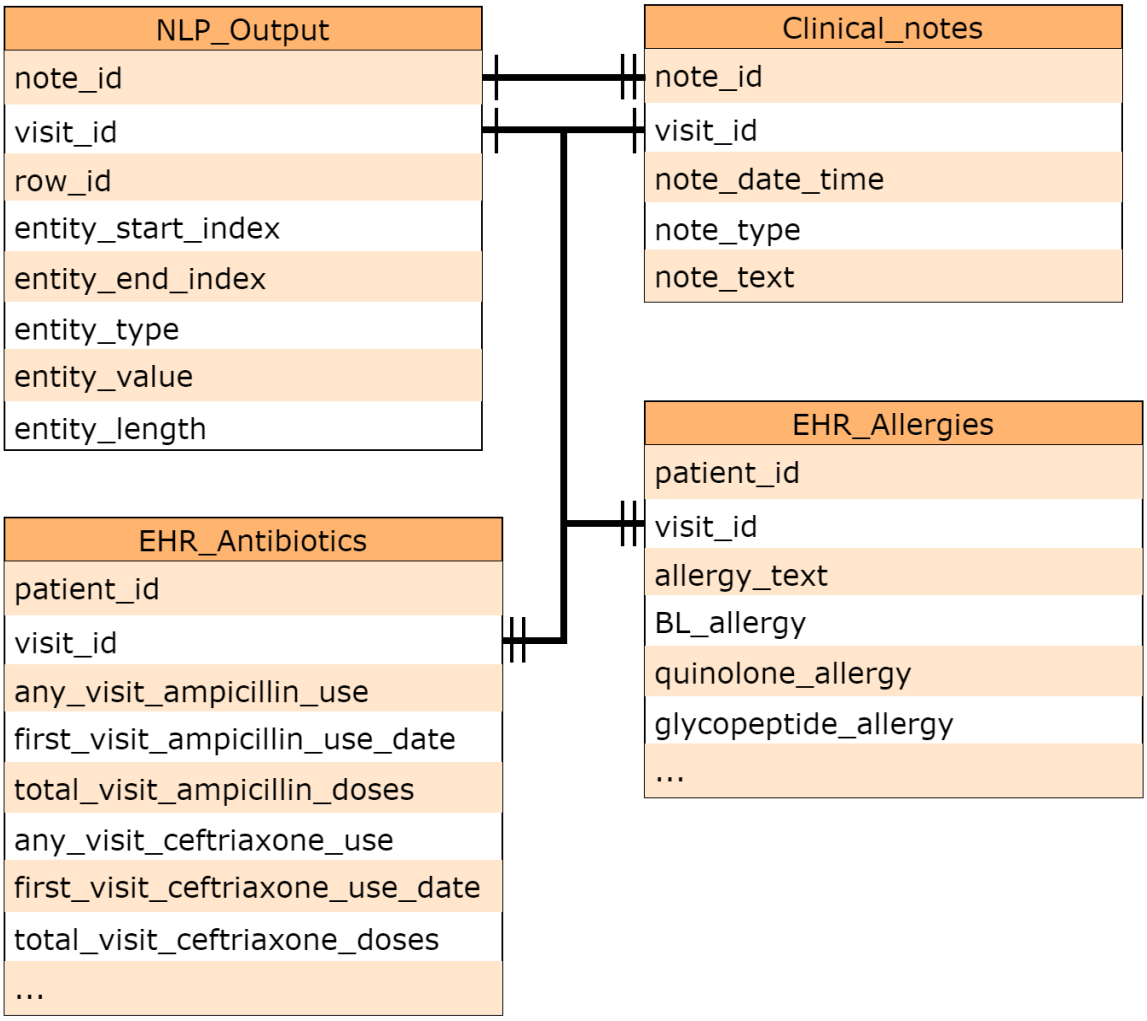


Figure 6-1. Entity-Relationship Diagram of Structured Clinical Data Incorporating NLP Pipeline Results

A Python script was created to aggregate the results from the individually processed clinical notes into a data table format. This data table of NLP results was then loaded into a relational database which also contained structured clinical EHR information for the same patients, including documented allergy status, admissions and discharge dates, and medication use. A separate data table that contained the full-text clinical notes was also loaded into the relational database. The result of this process was a fully cross-linked, readily queryable relational database which housed both the structured EHR clinical information related to BL allergy status and antibiotic use, as well as the NLP output and clinical note textual information (Figure 6-1).

A rule-based system was developed in structured query language (SQL) which incorporated both the NLP results and the structured EHR data to identify positive instances of historic BL product usage. Three Rules were defined and tested for their ability to positively identify instances of BL product usage:

Rule 1 – The listing of any BL-containing product within the medication list section of a patient's clinical note. Returns the suspected BL entity and full allergy section. **Rule 2** – The listing of any BL-containing product within the same sentence as a medication use phrase. Returns the suspected BL entity, target sentence, and previous and following sentence. **Rule 3** – The listing of any BL-containing product within 50/100/150 characters medication use phrase. Returns the suspected BL entity, target sentence (containing the BL entity), and previous and following sentence.

Rule 1 used the section identifier to define beginning and end indices of the medication sections. Rule 2 used the sentence detection algorithm to identify the beginning and end indices of individual sentences within the clinical note. Rule 3 was agnostic to punctuation or section location, and instead relied only upon the relative location of a BL entity and a use phrase entity, regardless of each phrase being in the same section or sentence. Importantly, when each Rule did positively identify BL usage, it also used entity start and end indices to query the corresponding clinical note text and return the context of the penicillin use phrase from the clinical note. For Rule 1, this process returns the full allergy section, and for Rules 2 and 3 the process returns the target sentence and the immediately preceding and following sentences.

6.3.6 Allergy Rule Evaluation and Clinical Utility

The performance characteristics of each Rule was evaluated. The output from 200 positive instances of each Rule were independently reviewed by two reviewers (MG, ND). Additionally, 200 negative instances where none of the three Rules positively identified BL usage were also independently reviewed to ensure that the Rules were identifying the majority of instances where BL usage was being discussed in clinical

notes. A third reviewer (BS) was then used to review an additional 50 positive instances of each Rule, and 50 negative instances, for a total of 250 instances of each Rule and negative controls being evaluated. Disagreement was resolved through discussion and consensus between the two reviewers (MG & ND, and MG & BS) following the initial review. The results of these reviews were used to calculate positive predictive value, negative predictive value, F1 scores, and percent agreement for each Rule. Recall was estimated by comparing the number of times each Rule positively identified BL usage during each encounter to the actual usage of BL usage throughout the encounter which was evaluated using the structured EHR data. Usage of BL products in the structured data was defined as the patient receiving at least two doses of BL-containing products during the healthcare encounter.

Finally, the clinical utility of the BL Rules was evaluated using information from the structured EHR datasets. First, we identified the number of clinical notes where each Rule identified suspected BL product usage while the patient had a documented BL allergy. Second, it was also considered that there may be a significant number of instances where patients had a history of BL usage or tolerance, but this information was only documented through clinical narratives captured in clinical notes and could not be otherwise identified using structured clinical information such as medication dispensing records. To quantify the number of instances where this occurred, we provide a count of the number of clinical notes which were positively identified through each allergy rule to contain suspected BL usage among patients with a documented BL allergy, but where the patient also did not receive any BL-containing products during the encounter during which the clinical note was written.

6.3.7 Simulated Clinical Decision Support Alerts and Feedback

Following the evaluation of the SQL allergy rules, we sought to design a framework to translate the information produced from the Rules into usable clinical decision support alerts (CDS). Figure 6-2 outlines

the flow of data through extraction from the EHR to creation of readable allergy alerts for clinician evaluation to inform treatment decisions involving a patient's BL allergy status. This process framework would serve as a proof-of-concept for other health systems to develop and implement similar systems to support BL allergy delabeling efforts. Three simulated CDS alerts were created using combined information produced by the SQL Rules and background clinical information from the structured EHR data such as patient allergy status and medication dispenses for BL antimicrobials. The alerts were designed to provide clinicians with the information required to determine if a particular patient had previously tolerated a BL product and allow the clinician to quickly compare this historical tolerance against the patient's allergy status to make informed treatment decisions regarding whether the use

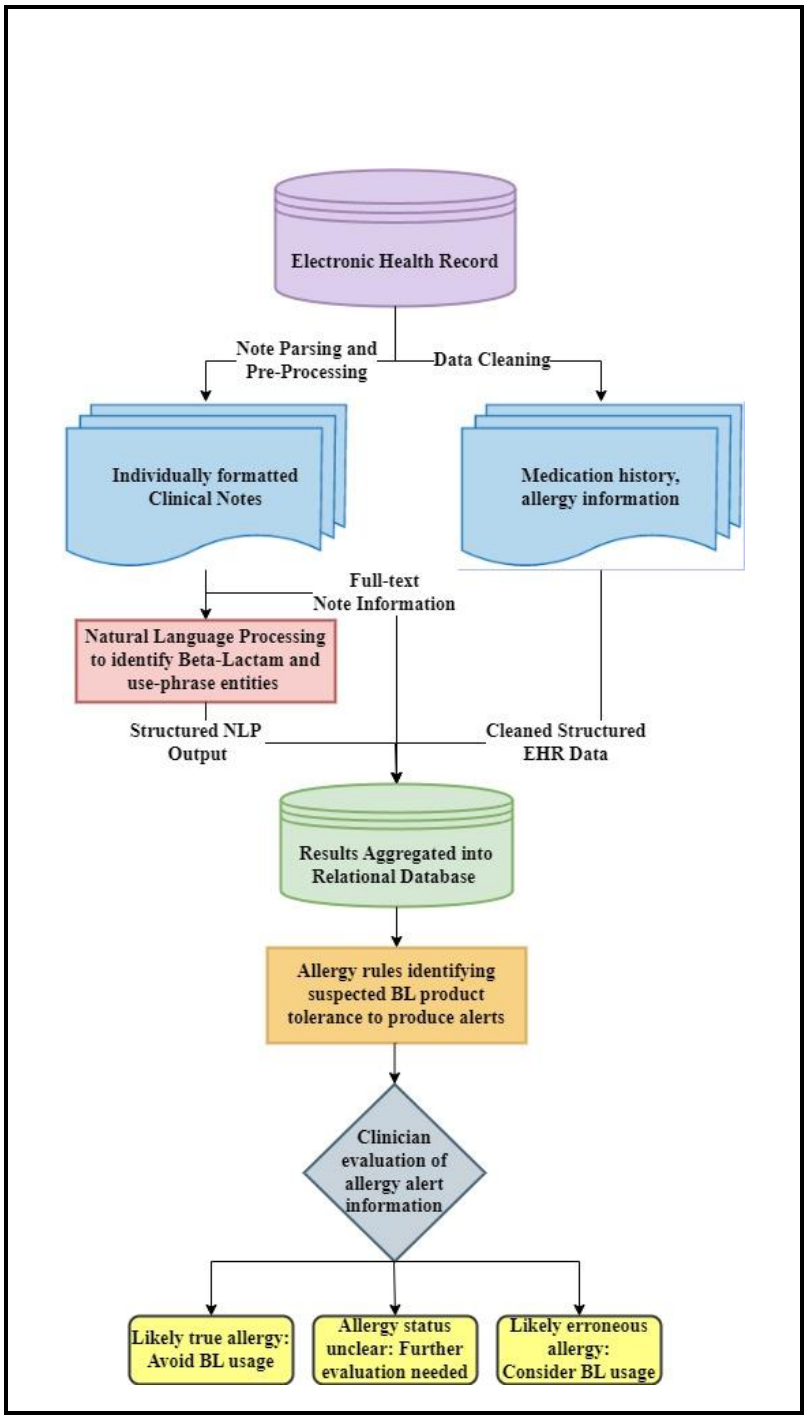


Figure 6-2: Flowchart of Information Resulting in Clinical Allergy Alerts

of a particular BL product may be appropriate. The simulated alerts were designed using actual results from positive instances of suspected BL usage identified through Rule 3 using a 100-character limit, with the exception of the allergic reaction, which was not available in the structured data, and was instead input using clinical judgement to simulate varying levels of risk in utilizing penicillin/cephalosporin products. Although both Rules 2 and 3 had highly similar performance characteristics (except at the 150-character limit), Rule 3 at the 100-character limit was selected as the test case because we sought to evaluate whether the text results produced by this Rule, which could include entities from different sentences, would still be clear and interpretable by clinicians for the purpose of allergy evaluation. The simulated alerts also contained BL usage information which was derived from the structured EHR information using net medication dispenses if the patient received a BL antimicrobial during the associated encounter. Comparison 'control' alerts were then created which contained only basic allergy information, such as the specified allergen and reaction to directly compare the value of the added NLP-derived information and historical BL usage information.

Following the creation of the simulated CDS alerts, we sought to evaluate the alerts' usefulness in assisting in practical BL allergy evaluation. An online survey was created using Qualtrics software to present the simulated alerts to practicing clinicians and receive feedback on the alert format and utility.[243] A cohort of clinicians which were previously interviewed by the study team about their attitudes when evaluating BL allergies in practice were contacted through email to participate in the anonymous survey. No compensation was offered for completion. Demographics for clinicians who completed the online survey were calculated from introductory survey questions. The 'control' alerts were presented first to clinicians, followed by the alerts containing the NLP-derived information, and clinicians were then asked to rank their confidence in prescribing/verifying particular BL products in patients with documented BL allergies when presented with each alert. Finally, the clinicians were then asked to provide feedback on the overall

usefulness of the alert in improving the care of their patients, reducing the time to evaluate BL allergies, and the format and presentation of the alert. The full survey is shown in Appendix 6-2.

6.4 RESULTS

6.4.1 Beta-Lactam Usage Rule Results and Comparison

The performance characteristics of each Rule were calculated to determine which Rule would be the most promising in accurately identifying previous BL usage (Table 6-1). Instead of evaluating 250 individually negative controls notes for each Rule, a single random sample of 250 notes which did not meet the criteria of any of the alerts was evaluated and used for all calculations (i.e. each Rule has the same calculated NPV). Each note was considered individually, such that two notes from the same patient or healthcare encounter would be counted as two separate positive notes if meeting the appropriate criteria.

Rule 1 achieved high levels of performance, with a positive predictive value (PPV) of 0.976, and the overall highest F1 score of 0.974, which is a method of jointly evaluating both precision and recall with 1.0 meaning perfect prediction.[244] However, Rule 1 also was positive on the least number of notes by a large margin, with only 9.7% of the total corpus of notes being positively identified to contain BL usage by using the medication list alone. This may indicate that this Rule is not identifying many instances of BL usage, since roughly 50% of hospitalized patients in the US receive an antimicrobial and BL products comprise over 40% of this use.[245] Rule 2 also performed well, with a PPV of 0.924 and an F1 score of 0.947. However, Rule 2 identified almost 2.5 times more positive notes than Rule 1. The performance of Rule 3 was similar to Rule 2 when using a range of 50 or 100 characters from the BL product to the use phrase but was less accurate when extending this range to 150 characters, where the PPV and F1 scores dropped to 0.836 and 0.897, respectively. The negative controls showed that the Rules were accurately identifying close to all instances of BL usage within clinical notes when combined, with a negative predictive value of 0.972.

The ability to utilize both the structured and unstructured datasets in a combined database allowed for the ability to compare the rate of actual BL usage to the rate at which the Rules were positively firing. Recall was calculated using this information by comparing the number of healthcare encounters that each Rule was present during and the frequency during these encounters where the patient received at least two doses of BL-containing antimicrobials (Table 6-2). All Rules had calculated recalls above 70%, and at least some portion of the encounters without evidence of inpatient BL use is likely due to the note containing information relevant to BL usage that did not occur during the present encounter.

Table 6-1: Performance Characteristics Three Rules in Accurately Identifying previous Beta-Lactam Antimicrobial Usage

	PPV	NPV	Sensitivity	Specificity	F1 Score	Percent Agreement (Reviewer 1 / 2)	Number of Total Notes Positive; N, (%) (Total N=189847)
Rule 1 – BL entity within allergy section (N = 250)	0.976	0.972	0.972	0.976	0.974	99.5% 98%	18464 (9.7%)
Rule 2 – BL entity in same sentence as use phrase (N = 250)	0.924	0.972	0.971	0.928	0.947	98.5% 98%	46142 (24.3%)
Rule 3 – BL entity within 50 characters of use phrase (N = 250)	0.932	0.972	0.97	0.935	0.951	98.5% 96%	47933 (25.2%)
Rule 3 – BL entity within 100 characters of use phrase (N=250)	0.896	0.972	0.97	0.903	0.931	97.5% 94%	54549 (28.7%)
Rule 3 – BL entity within 150 characters of use phrase (N = 250)	0.836	0.972	0.968	0.856	0.897	96.5% 96%	58188 (30.6%)
		NPV				**Percent Agreement (Reviewer 1 / 2)**	**Number of Total Notes Negative N, (%)**
Notes predicted to not contain BL use phrases (N=250)	---	0.972	---	---	---	99% 100%	125209 (66.0%

PPV = Positive Predictive Value; NPV = Negative Predictive Value. Percent agreement calculated as simple agreement between the two reviewers. Notes were considered at the individual level even if from the same patient or healthcare encounter

Table 6-2: Identification of Potential BL use through Allergy Rules Among BL-Allergic Patients

	Number of encounters with alert firing	Number of encounters with alert firings and evidence of inpatient BL usage during encounter	Percent of encounters with alert firing and evidence of inpatient BL usage during encounter (Recall)
Rule 1 – BL entity within allergy section	5592	4438	79.36%
Rule 2 – BL entity in same sentence as use phrase	10625	8014	75.43%
Rule 3 – BL entity within 50 characters of use phrase	10680	8028	75.17%
Rule 3 – BL entity within 100 characters of use phrase	11412	8252	72.31%
Rule 3 – BL entity within 150 characters of use phrase	11741	8359	71.19%

Number of encounters: The number of inpatient encounters were counted as a binary variable for whether the alert was present for any note during the healthcare encounter.

Evidence of inpatient BL usage: Evidence was defined as the patient receiving at least two inpatient doses of BL-class antimicrobials during the encounter

6.4.2 BL Allergy Rule Clinical Utility Analysis

The results of the clinical utility analysis for each Rule are shown in Table 6-3. Overall, there was a total of 28735 clinical notes which were processed for patients who had documented BL allergies during the encounter for which the clinical note was written. Rule 1 identified BL allergy usage in 1005 (3.5%) of the medication list sections from these notes. Using the broader methods, Rule 2 identified 6045 (21.0%) notes contained suspected BL usage, while Rule 3 identified 6194 (21.6%), 7465 (26.0%), and 8128 (28.3%) of clinical notes contained suspected BL usage using a range of 50, 100, and 150 characters from BL product to use phrase, respectively. Among each of these positive instances of suspected BL usage, the Rules were then further analyzed by patients who received BL products during the associated healthcare encounter for the clinical note using net medication dispenses (n = 1369 notes). Rule 1 identified 77 (5.6%) of instances where the structured information did not contain evidence of usage that was possibly identified through the NLP model. Again, the broader rules identified even higher rates, with Rule 2 identifying 605 (44.2%) of such instances, and Rule 3 identifying 635 (46.4%), 1059 (77.4%), and 1337 (97.7%) of instances using the 50, 100, and 150 character ranges, respectively. Finally, Table 6-3 provides some examples of outputs from the Rules which would identify suspected BL usage that was not identified through the structured medication usage data. However, it should be noted that each note positively identified does not guarantee that the note truly contains wording which would sufficiently indicate prior BL usage, and false positives were possible.

Table 6-3: Identification of Potential BL use through Allergy Rules Among BL-Allergic Patients

	Number of Clinical Notes (Total N=28735), N (%)	Number of Clinical Notes Containing BL Usage without Inpatient Use of a BL Product (Total N=1369), N (%)	Example Text Output
Rule 1 – BL entity within allergy section	1005 (3.5%)	77 (5.6%)	"1. Vicodin. 2. Allopurinol. 3. Keflex. 4. Rocephin. 5. Oral contraceptive. 6. Oxycodone. 7. Morphine."
Rule 2 – BL entity in same sentence as use phrase	6045 (21.0%)	605 (44.2%)	"The patient received outpatient Rocephin on last Thursday, Friday, and Monday."
Rule 3 – BL entity within 50 characters of use phrase	6194 (21.6%)	635 (46.4%)	"He has tolerated amoxicillin, however."
Rule 3 – BL entity within 100 characters of use phrase	7465 (26.0%)	1059 (77.4%)	"Recently completed a 10 day course of Augmentin for cellulitis"
Rule 3 – BL entity within 150 characters of use phrase	8128 (28.3%)	1337 (97.7%)	"She was given amoxicillin by her dentist and developed epigastric pain and chest pain."

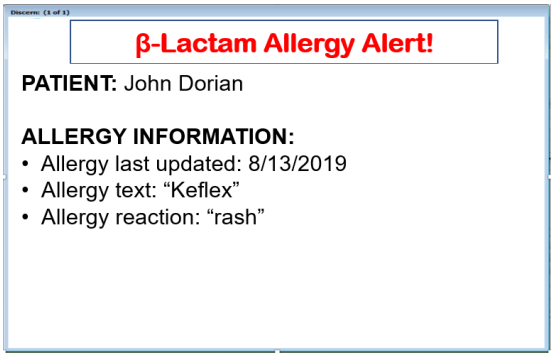
Number of Clinical Notes: the number of clinical notes where each BL-allergy rule positively indicated suspected BL use among patients with a documented BL allergy.

Number of Clinical Notes Containing BL Usage without Inpatient Use of a BL product: The number of clinical notes where each BL-allergy rule positively indicated suspected BL use among patients with a documented BL allergy and who did not receive at least one BL-containing product during the encounter**.**

6.4.3 Simulated Clinical Decision Support Alert using NLP-Derived Information and Clinician Feedback

Figure 6-3-1 shows a comparison between the 'control' clinical decision support alert that uses only structured clinical data such as the patient's allergy status and associated reaction information when compared to an alert containing the same information, but that also contains information attained from the output of the NLP-based allergy rules. A total of three alerts were designed and are shown in Figure Set 6-3. In addition to each simulated alert, Figure Set 6-3 also shows the results of clinician confidence in using particular BL products in patients with documented BL allergies based on the information presented in the alert which was gathered through the online survey. Overall, confidence in using a BL product in a patient with a BL allergy was always higher when presented with the additional context provided by the NLP-based allergy rules. The difference in confidence levels was highest when the associated alert text indicated strongly that the patient previously tolerated the antimicrobial which was being considered for use or when there was direct evidence of prior tolerance from dispensing records, such as in Alert 1 where confidence in using cefazolin increases from 6.78/10 to 9.33/10. The added information did not have much effect in serious allergic reactions where the alert text and dispensing records did not indicate direct usage of the product being considered for use, such as in Alert 2 where confidence in using piperacillin/tazobactam (3.22/10 with the basic alert vs 3.38/10 with the NLP-derived information) in the setting of an anaphylactic penicillin allergy did not change despite evidence of tolerating a cephalosporin.

Figure Set 6-3: Clinician Confidence Comparison in Utilizing Beta-Lactams in Patients with Beta-Lactam Allergies with



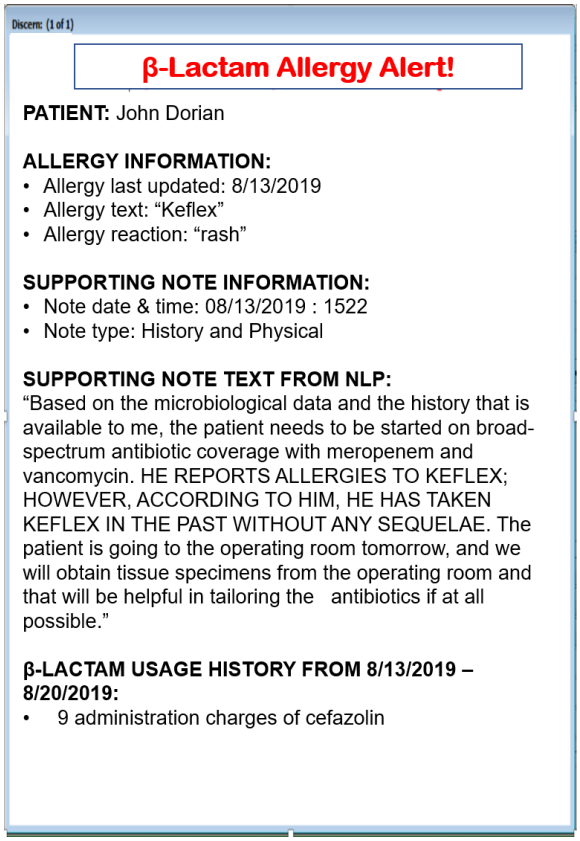


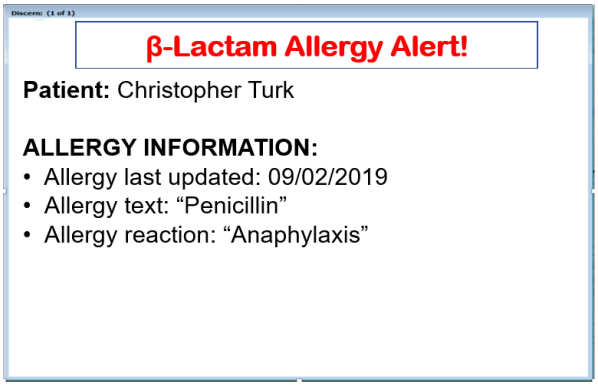
Figure 6-3-1: Simulated Alert #1:

Simulated CDS Alerts

Beta-Lactam Antimicrobial	Confidence in Prescribing/Verifying if indicated: Range 1 (lowest confidence) – 10 (highest confidence)
Cefazolin	6.78
Ceftriaxone	7.89

Beta-Lactam Antimicrobial	Confidence in Prescribing/Verifying if indicated: Range 1 (lowest confidence) – 10 (highest confidence)
Cefazolin	9.33
Ceftriaxone	9.33

Legend: Simulated CDS alerts created using information from SQL rule-based alerts system including (Right) and not including (Left) the NLP-derived BL usage information. Patient names were fabricated to simulate a realistic format. Dates were modified to protect identifiability, but each date's relative occurrence remained the same. Respondents were asked to use only the information within the alert (as well as a link to a beta-lactam cross-reactivity chart) to provide their responses in assigning confidence for each product.



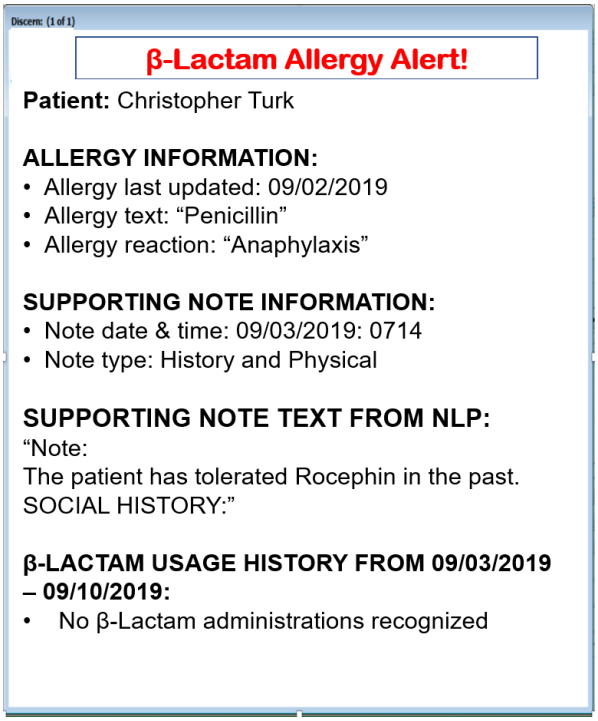


Figure 6-3-2: Simulated Alert #2:

Beta-Lactam Antimicrobial	Confidence in Prescribing/Verifying if indicated: Range 1 (lowest confidence) – 10 (highest confidence)
Cefepime	6.22
Piperacillin/ Tazobactam	3.22

Beta-Lactam Antimicrobial	Confidence in Prescribing/Verifying if indicated: Range 1 (lowest confidence) – 10 (highest confidence)
Cefepime	8.56
Piperacillin/ Tazobactam	3.38

Legend: Simulated CDS alerts created using information from SQL rule-based alerts system including (Right) and not including (Left) the NLP-derived BL usage information. Patient names were fabricated to simulate a realistic format. Dates were modified to protect identifiability, but each date's relative occurrence remained the same. Respondents were asked to use only the information within the alert (as well as a link to a beta-lactam cross-reactivity chart) to provide their responses in assigning confidence for each product.

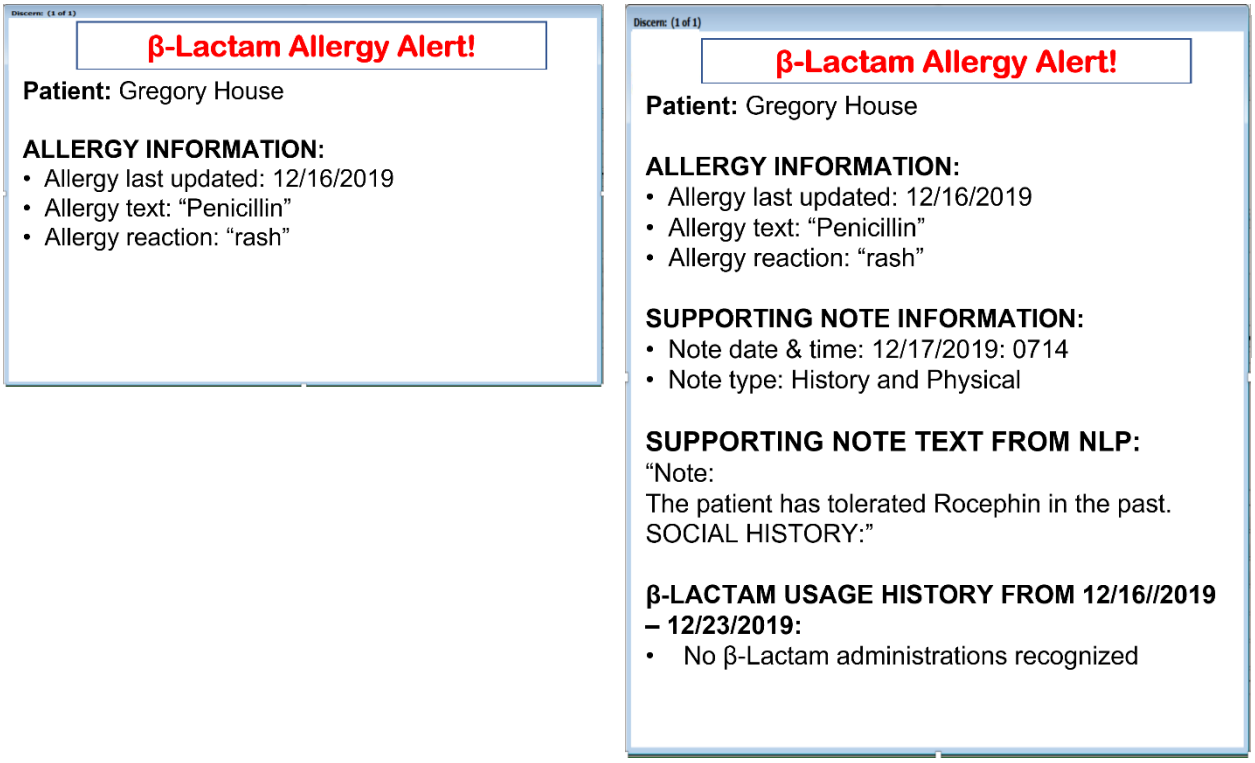


Figure 6-3-3: Simulated Alert #3:

Legend: Simulated CDS alerts created using information from SQL rule-based alerts system including (Right) and not including (Left) the NLP-derived BL usage information. Patient names were fabricated to simulate a realistic format. Dates were modified to protect identifiability, but each date's relative occurrence remained the same. Respondents were asked to use only the information within the alert (as well as a link to a beta-lactam cross-reactivity chart) to provide their responses in assigning confidence for each product.

6.4.4 Online Survey Demographics and Summary Results on BL Allergy Rule Alert Utility

There was a total of 9 surveys which were completed to provide feedback on the clinical utility of the simulated CDS alerts which included the NLP-derived BL usage information. The group of clinicians completing the survey included 4 physicians, 3 pharmacists, and 2 nurses / advanced practice providers. There was a relatively even split in clinical specialties, with 3 clinicians reporting a background in critical care, 3 in emergency medicine, 1 in infectious disease / infection prevention, and 2 which did not specify a specialty. All surveys that were submitted were fully completed, and while the study design did not specify the exclusion partial surveys, no consideration of partial surveys was required.

Clinicians reported a high level of usefulness in the utility of including the NLP-derived BL usage information in evaluating the legitimacy of a BL allergy, with clinicians rating the usefulness of this information at a mean of 4.44 / 5. There were lower ratings provided for the format and content understandability of the alert, with mean ratings of 3.67 / 4 and 3.56 / 4, respectively. The lowest provided rating was for the understandability of where the NLP-derived information was being attained from, at a rating of 2.89 / 4, and which was the only category receiving scoring instances of the minimum rating score allowable. The clinicians reported particularly high scores in the potential benefits to clinical care that could result through including the NLP-derived allergy information in CDS allergy alerts, including the alert's potential to reduce the time required to evaluate BL allergies (mean rating 3.56 / 4), usefulness in the clinician's individual care setting (mean rating 3.56 / 4), and an overall improvement in the care of their patients (mean rating 3.67 / 4).

Table 6-3: Respondent Demographics for Survey Evaluating the Utility of Simulated CDS Alerts Including NLP-derived BL Usage Information

Respondents Profession	Number, % (N = 9)
Physicians	4 (44%)
Pharmacists	3 (33%)
Nurse / APP	2 (22%)
Clinical Specialty	
Emergency Medicine	3 (33%)
Critical Care	3 (33%)
Infectious Disease / Infection Prevention	1 (11%)
Other / Not Reported	2 (22%)

Legend: Professional background and clinical specialty of respondents completing the online survey. All respondents completed the entire survey, and no partial responses were recorded.

Table 6-4: Summary Responses of Survey Evaluating the Utility of Simulated CDS Alerts Including NLP-derived BL Usage Information

Category Evaluated	**Responses** (n = 9)						
Rating Scale	**0 = Not useful at all**					**5 = Extremely useful**	
Rating Score	**0**	**1**	**2**	**3**	**4**	**5**	**Mean**
Usefulness in determining the legitimacy of a beta-lactam allergy	0	0	0	1	3	5	4.44
Rating Scale	**Strongly Disagree**	**Disagree**	**Neutral**	**Agree**	**Strongly Agree**		**Mean**
Rating Score	**0**	**1**	**2**	**3**	**4**		
The format of the alert is understandable	0	0	0	3	6		3.67
The content of the alert is understandable	0	0	0	4	5		3.56
I know where in the electronic health record the alert information was obtained	0	2	1	2	4		2.89
This alert would reduce the time required to evaluate Beta-lactam allergies	0	0	0	4	5		3.56
This alert would be useful for my care setting	0	0	0	4	5		3.56
This alert would improve the care of my patients	0	0	0	3	6		3.67

Legend: Responses provided by clinicians when presented with Alert 1 (Figure 6-4-1). Responses were recorded on a slider and required whole number answers.

6.5 DISCUSSION

We used natural-language processing with a dictionary-based NER pipeline to identify instances where patients with documented BL allergies have previously tolerated BL antimicrobials, and created example CDS alerts which serve as a proof-of-concept for health systems to implement similar alert systems. Although identification of prior BL use was not the initial goal of our study, management algorithms for evaluation and treatment of patients with BL allergies recommend considering prior tolerance of BL containing products to inform current treatment decisions, and this information can allow for bypassing of evaluation methods such as skin testing in a similar manner to risk stratification.[18,87,246,247] Identification of previous tolerance of BL products would be of high value to clinicians in quickly determining whether a particular antimicrobial can be safely administered to a patient, particularly if the patient has a history of tolerating the same product or a product in the same class.

Our results show that NLP of clinical notes can be used to build an evaluation pipeline which identified patients who previously received beta-lactam products with a high positive predictive value. Furthermore, the NLP of clinical notes showed clinical utility which can supplement the use of structured inpatient medication usage information alone, since there was some allergy evaluation information which was not documented through inpatient medication usage history and was found only in the clinical notes, such as outpatient tolerance or first-hand discussions that were conducted with the patients and family. Finally, our results show that CDS allergy alerts which include both antimicrobial usage history and context from corresponding clinical notes increased clinician confidence in using BL antimicrobials in patients with a documented BL allergy.

Our pipeline used an approach consisting of three different Rules to identify previous usage of BL antimicrobials, and the ideal implementation of a combination of these three rules will largely be influenced

by the individual use-case of each environment. For example, if minimizing false-positives is of the highest importance, then stricter approaches such as Rule 1 could be implemented along with EHR dispensing history, and this approach may lead to a lower rate of allergy alerts being bypassed, which is currently a major issue affecting uptake of delabeling efforts.[125] However, if a higher level of uncertainty is acceptable, then the more general approaches offered by Rules 2 and 3 can also achieve generally high levels of performance. The rule-based allergy system developed for our study achieved F scores of roughly 0.95, indicating excellent predictive value. The Rules positively identified BL usage in roughly one-quarter of clinical notes, and between 71-79% of the corresponding encounters for these notes contained evidence of BL usage from structured EHR data. Our positive results are similar to previous efforts of automated risk stratification of BL allergies which focused on using the allergy reaction to stratify the severity of the allergy, and add to the growing body of evidence that automated risk stratification is a promising first-step to helping clinicians perform targeted BL allergy review and delabeling.[124,175,240] It is important to note that both approaches are not mutually exclusive, and that picklists and algorithms which standardize allergy reactions could be implemented within the same pipeline as methods which use NLP and structured medical history to identify previous tolerance of BL antimicrobials, and that the combination of both processes would likely lead to superior results in informing clinician decision making than either process individually.

The current state of allergy CDS alerts is not meeting the needs of physicians, and changes such as including additional reaction information and including class information in alerts could increase the relevance of the alert and reduce the time that is required to evaluate BL allergies.[78] Applications have been developed which assist non-specialists in the real-time evaluation of BL allergies and direct the clinician towards the most appropriate prescribing decisions, and use of these applications lead to a 25% increase in appropriate antimicrobial prescribing decisions in BL-allergic patients.[119,248] However, these systems still

heavily rely on clinician time and training in order to succeed. Our NLP-based allergy alert system is positioned to supplement these approaches and could greatly reduce the amount of time required for allergy evaluation since our pipeline runs entirely on existing information, so a minimal amount of additional time investment is required. Additionally, to the best of our knowledge, this is the first attempt to incorporate BL usage history using NLP into CDS alerts, and the first attempt to relate this knowledge with BL usage history derived from structured medication dispensing history for the purpose of informing BL-allergy evaluation. Our CDS pipeline also allows for a unique opportunity to incorporate cross-reactivity information into allergy alerts. Differing BL allergies could be evaluated and standardized to agent or class-level allergies during the NLP process, and this information would be useful for evaluating cross-reactivity of ordered agents against documented allergies. Figure 6-5 shows an outline of how differing BL allergies could be evaluated against a theoretically ordered BL product to determine the likelihood of cross-reactivity.

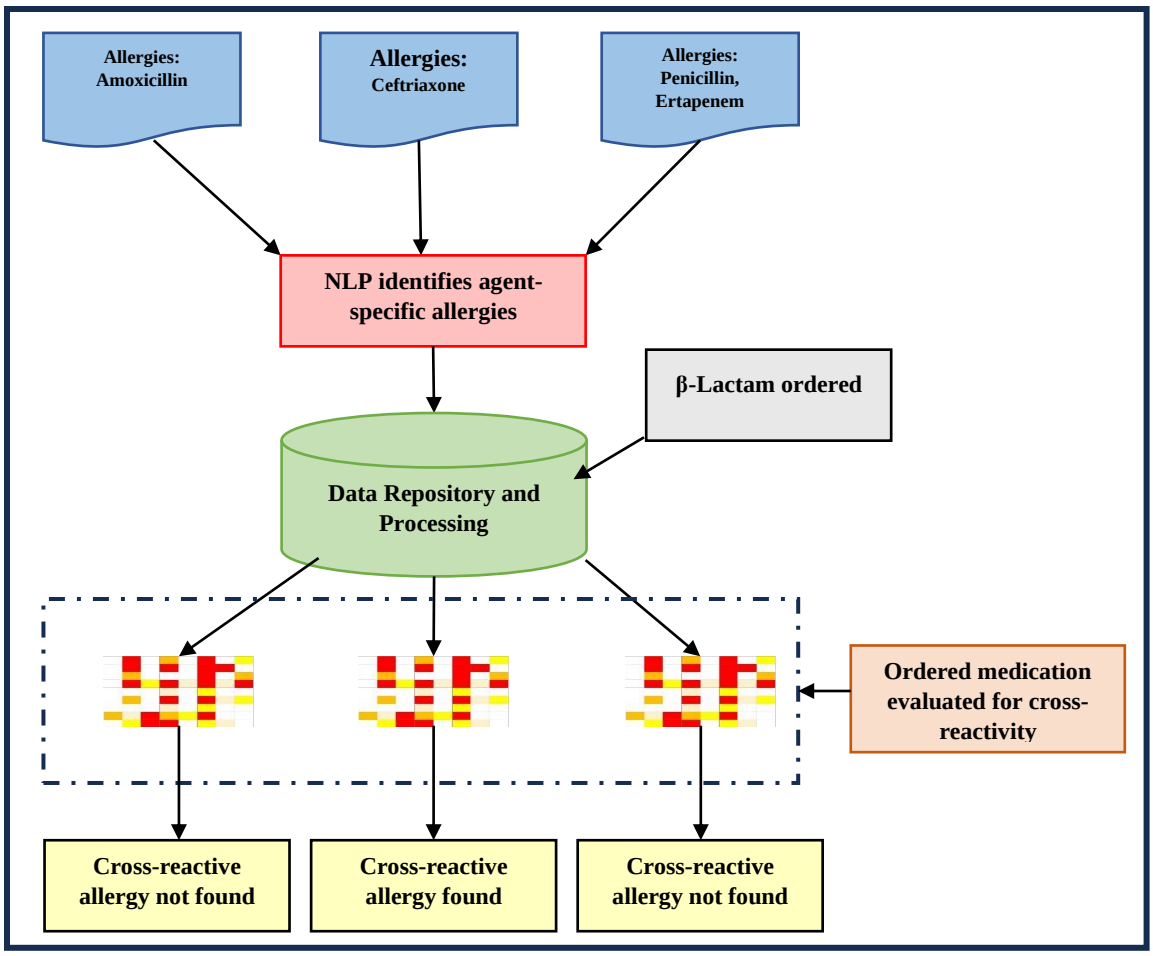


Figure 6-5: Potential for Incorporation of BL Cross-Reactivity Evaluation in NLP-based Allergy Evaluation Process

Another unique aspect to our study is the inclusion of selected textual output from NLP into CDS alerts for clinician evaluation. By providing this context and background information from the note that it was derived from, such as when the note was written and by whom, it can expedite a targeted review of the patient's medical chart to interrogate for further required information or confirm the information in the alert. Our general process of identifying medication use history which contradicts documented allergy status, as well as providing textual context from clinical notes could also be extended to other medication allergies such as contrast dye and is not limited to the particular use-case of BL usage and tolerance.[249]

While we formatted our results as an active CDS alert which would provide information potentially at the time of prescribing or allergy documentation, there are other theoretical implementations of our

pipeline into clinical workflows. One such implementation would be a batch-review system for situations such as surgical prophylaxis, which has become an area of focus for proper use of BL antimicrobials in patients with documented BL allergies.[250,251] Our process could be used to create a report of information for surgical teams to review ahead of surgery to help guide prophylaxis decisions despite BL allergies, and can overcome barriers involving patient acceptance since previously tolerated antimicrobials can often be administered without the need for additional testing as long as the product was tolerated after the allergic reaction had last occurred.[251] Since the onus of entering and documenting allergies often falls to nurses and non-specialist clinicians, it is important that allergy alert information be easily interpretable regardless of expertise in BL allergy evaluation. The results of our allergy alerts were designed to align with this goal and are highly interpretable, as evidenced by one of the two independent reviewers (reviewer 1) who helped to calculate the performance characteristics being a first-year pharmacy student with limited experience in allergy evaluation and infectious disease, and a high level of inter-rater reliability was achieved despite comparing this student's results with the results from a licensed pharmacist with direct clinical experience.

Our study represents an important step in improving the usefulness of CDS allergy alerts and a novel mechanism for including clinical note information in these alerts, but there remain limitations which should be addressed in future studies. We achieved high predictive value with the allergy alerts, but each Rule was only evaluated using 250 positive test cases and 250 negative test cases from a single regionally based health system, and we also only received 9 responses on the online survey evaluating the initial CDS alert utility and format. While this is a small and limited sample size, the goal of this initial evaluation was not to thoroughly refine our processes through a systematic evaluation, but instead was to confirm the overarching utility of enriching allergy CDS alerts through an NLP pipeline and rule-based process, and to evaluate this process as a proof-of-concept while gauging the overall format of the alert and potentially necessary information which could be added. When considering this goal, a large, representative cohort was

not necessary, but further surveys and study efforts should expand upon more specific aspects of the alert and its presentation to maximize the utility in increasing clinician confidence in BL allergy evaluation and decreasing the time that the evaluation takes. The dictionary used for identifying BL and usage entities is not exhaustive and will require updates over time. More sophisticated NLP methods may also be able to identify historical BL usage more accurately without the need for static a dictionary-based system. Finally, there was feedback provided through the online survey that the alerts may provide too much non-related information through including the full section of text from the clinical notes, so further refinement is required to balance the utility of including context from clinical notes with the ability of clinicians to quickly evaluate the information from the alert.

6.6 CONCLUSION

Our results are the first to translate historical use of BL antimicrobials in patients with documented BL allergies for inclusion in CDS alerts. Our pipeline reliably identified patients who have previously tolerated BL antimicrobials with a low proportion of false positives and showed that there is value in both using NLP of clinical notes and using structured medication history for this goal. In doing so, we produced a framework for implementation by health systems to create more informative CDS allergy alerts and facilitate delabeling of erroneous BL allergies by alleviating some of the time constraints involved in manually researching prior BL use in patients with BL allergies. Future efforts could improve upon the general framework proposed by our results by implementing more sophisticated NLP methods and refinement of CDS alert output.

7.0 CONCLUSIONS AND FUTURE DIRECTIONS

7.1 SUMMARY AND CONCLUSIONS

Through the use of a broad mixed-methods approach including both qualitative and quantitative analyses, we expanded the understanding of the outcomes of patients with BL allergies, identified barriers in practice which are currently impeding delabeling efforts, and developed an automated process to improve the management of patients with BL allergies. We found that the documentation of a BL allergy in a patient's medical record was associated with an increase in resistant infections, and may be associated with all-cause mortality. This finding highlights the importance for health systems to implement successful delabeling programs to remove erroneous BL allergies. We further identified that interventions including the promotion of pharmacists in the evaluation process and a rework of how EHR systems manage documentation of allergy information may increase the likelihood of a delabeling program's success. Finally, delabeling programs will likely be more successful when supported by tools which make use of advancements in risk stratification research. We developed an automated process to identify prior usage of BL products using an NLP pipeline which is a novel approach to supplement risk stratification efforts and could help alleviate the time constraints associated with BL evaluation. These results were all designed to address current gaps in the literature on BL evaluation and delabeling, and this dissertation represents a significant contribution to the field of improving the care of patients with documented BL allergies.

The long-term outcomes of patients with BL allergies are an under-explored area compared to the large number of studies conducted which have historically focused on how the presence of a BL allergy affects the care in patients with specific indications or in a specific population. Our results (Chapter 5) are in

agreement with the few studies which have examined BL-allergic patients over a time period of more than 5 years which have found an increased risk of resistant infections that was associated with the presence of a BL allergy. However, we did not find an association between BL allergy status and AKI. In a secondary analysis which analyzed allergy status as a time-changing covariate, which may more accurately model how BL allergy status occurs in practice due to poor allergy documentation and the high rate of relabeling, BL allergies were associated with an increase in all-cause mortality, as well as higher resistant infections compared to analyzing BL allergy status as a static indicator variable.

In a qualitative analysis (Chapter 4) of clinician attitudes and perspectives when evaluating BL allergies in practice, we identified important barriers which may be hindering the implementation and sustainability of delabeling programs. Among these barriers included beliefs that evaluating BL allergies was too time-consuming, that there was a lack of clear policies and protocols for evaluation, and that the documentation of BL allergies is often confusing or missing, often secondary to the unreliability of allergy information being provided by patients or family members. We translated these beliefs into two targeted intervention functions using the Behaviour Change Wheel for potential implementation by health systems: First – health systems should promote the use of pharmacists in BL allergy evaluation and design clear policies which outline responsibilities throughout the evaluation process; Second – the processes for documenting and accessing allergy information with EHR systems should be reworked to support unambiguous reaction documentation and encourage the use of picklists instead of free-text reactions.

Finally, we used a corpus of clinical notes to develop an NLP-based pipeline for identifying instances where patients have previously used BL products. We achieved this goal with high rates of positive predictions and low rates of false negatives, meaning that NLP of clinical notes can be a reliable method to identify prior BL usage, particularly when used in conjunction with structured medication usage data obtained from the EHR. Additionally, our process did identify a number of instances of BL use which

could only be derived from the clinical notes, and there may be unique value to a mixed implementation which maximizes the value that can be derived from both structured and unstructured data pipelines for the use of BL evaluation. We then created simulated CDS alerts which had high clinical utility and increased clinician confidence in using BL products relative to alerts without the BL usage information based on a preliminary online survey completed by clinicians.

7.2 IMPLICATIONS

Effective methods for BL allergy delabeling are well-established, but one of the remaining steps which need to be further examined is effective methods of implementation, and for health system leadership to champion programmatic efforts which prioritize BL allergy delabeling.[170] Because of this, we consider health systems to be the primary target and scope of our results. The results of this dissertation contain important implications that should be strongly considered by health systems in designing and implementing programs for BL evaluation and delabeling.

Our results showed a statistically significant increase in the long-term hazards of resistant infections which were associated with the presence of BL allergies. This adds to the already large body of evidence that the removal of erroneous BL allergies would improve clinical outcomes and our study also provides one of the longest follow-up periods which examined this effect to date. BL allergy delabeling has been shown to be cost-effective even in short-term analyses, and the cost savings and clinical benefit to patients could be even greater when extending this benefit to the long-term through efforts which emphasize delabeling and prevent relabeling.[60] In summary, health systems should consider the long-term benefits of delabeling efforts when considering the initial cost of implementing these programs, since the long-term benefit may provide an even greater return on their investment.

Our qualitative analysis of clinician interviews provides theory-informed recommendations for health systems. We presented the first US-based qualitative analysis of clinician perspectives and attitudes when evaluating BL allergies. The recommendations supported by this analysis include the promotion of pharmacists in the evaluation of BL allergies and a rework of the EHR process for documenting and accessing allergy information. Our results are not the first to produce either of these two recommendations, and previous efforts have shown that both interventions can be highly successful in enabling BL allergy delabeling efforts. Pharmacists were recognized in our interviews as the expert on medications and were consistently identified as the most equipped professional on the care team to undertake the role of BL allergy evaluation. While considering this in conjunction with the lack of clear policies and protocols, health systems have a highly promising opportunity to clarify clinician-specific roles throughout the BL allergy evaluation process through new policies, and to promote the use of pharmacists as a leader in this process when amenable. Further, health systems should prioritize implementing recent advances in picklists and CDS alerts while reworking the EHR process for documenting and accessing allergy information, as the current state of allergy documentation was a consistent source of frustration and failure reported by clinicians in our interviews.

Another opportunity for health systems while considering BL allergy related improvements includes EHR reworks and CDS improvements that automate aspects of the BL allergy evaluation process. Our results created a proof-of-concept framework for improvements in CDS allergy alerts that incorporates historical use of BL products despite the presence of a BL allergy. These alerts used a novel process that incorporated both structured medication use information and unstructured textual information derived through an NLP pipeline of clinical notes. CDS allergy alerts can have a striking impact on improving the rate of using first-line antimicrobials such as penicillins and early-generation cephalosporins in patients with documented BL allergies, and health systems should consider including our framework for providing

historical BL use information along with previously published improvements of suppressing penicillin-cephalosporin cross-reactivity alerts and advising clinicians on proper steps in the allergy evaluation process.[125,127]

7.3 STRENGTHS AND LIMITATIONS

As each of our aims used different forms of analysis and study designs, there are some limitations that should be considered that apply to each aim. First, the long-term analysis of patients with BL allergies is limited by factors inherent to an observational study design, such as misclassification bias due to the unreliable nature of some EHR data. Misclassification in this study may come in two forms, first - by a lack of ability to reliably determine BL allergy status using the free-text nature of allergy documentation, and second – by the inability to know whether or not the patient's allergy status as documented actually corresponded to the treatment decisions that were made. Also, the repeated-measures mixed effect model used limits some generalizability of the results from this analysis due to the inclusion of patient-level random effects.

We used a qualitative approach for one of our studies which also carries inherent limitations. There is bias introduced through the inductive and deductive analysis process, although we did use two reviewers and a standardized framework to attempt to minimize this bias. We only interviewed 2 clinicians in each clinician-specialty group, and a larger sample size may lead to a larger set of beliefs being identified. There was particular difficulty in recruiting emergency care nurses, and our recommendations therefore may not apply as strongly to the emergency care setting as a result.

Finally, our NLP pipeline did not achieve its initial goal of producing a fully automated risk-stratification process, and is the second such attempt which was unable to achieve this goal.[128] However, we

were able to succeed in automating another aspect of BL evaluation which can be considered an alternative form of risk stratification. The NLP process that was used is relatively basic in nature, and uses a static dictionary, and this process could likely be improved and refined through more sophisticated models. Additionally, the implementation of this information into CDS alerts needs further explored beyond our limited convenience sample survey of nine clinicians.

Our overall approach has several strengths. First, each aim was independently designed to target current gaps in the literature and the results of each study largely were not reliant upon the completion of another study. The independence of each aim is also beneficial because there is no single study which would have been able to effectively address all of these topics simultaneously, and we instead were able to design studies that were targeted to address the particular aspects of each area. However, despite the independence of the aims, this dissertation is able to provide evidence-based and logically-connected recommendations which are all targeted to the same scope of care directed at the health-system level. Next, there are aim-specific strengths to consider. The qualitative analysis is the first of its kind conducted using a US-based population and used a structured framework to reduce the subjective interpretation of recommendations. Our 12-year analysis of BL allergy outcomes one of the longest follow-up periods used for an analysis these clinical effects, and the repeated measured mixed-effect model used is well-suited to minimizing unmeasured bias inherent to long-term observational study designs. Finally, our novel approach to utilizing both structured and unstructured information to inform CDS alerts has a large amount of potential to be applied to other areas of care and lead to more generalized improvements of CDS alert systems.

7.4 FUTURE DIRECTIONS

There are some natural extensions of this dissertation that should be targeted in the future. Follow-up studies which implement the recommendations of the qualitative analysis should be conducted which measure both quantitative and qualitative outcomes associated with each intervention. Such studies should include an analysis of whether the recommendations lead to measurable improvements in BL allergy delabeling and the use of first-line antimicrobials, as well as follow-up interviews with clinicians to ensure that the interventions are meaningful, sustainable, and are addressing the barrier which were identified through our initial interviews.

The long-term outcomes of our studies should be extended to include an analysis of the long-term economic aspects of care associated with BL allergies. Health systems may be better able to prioritize BL evaluation if they can assign a specific economic benefit to such programs, and compare this economic and clinical benefit relative to other programs that are being considered. Also, future analyses should consider how the effects of BL allergies compare to the long-term effects of other drug allergies beyond BL class antimicrobials, and to multi-allergic patients. Analyzing these patients was a secondary goal of our study, but future projects which are primarily designed with this goal could better determine whether or not BL allergies represent a unique clinical risk, or whether they are simply the most commonly experienced risk in the area of antimicrobial allergies.

Finally, there are many future goals for the inclusion of our NLP pipeline and CDS alerts into actual patient care workflows. The CDS design should be further refined to maximize the value that it provides in informing clinical decision making, and further surveys with clinicians could achieve this goal. Next, studies examining the implementation of these improved alerts into ppractice should be conducted to determine whether the improved CDS alerts lead to measurable improvements in BL evaluation and delabeling. Such

implementation studies should continually evaluate feedback from clinicians through surveys on the format and the content value of the alerts so that the process can be further refined.

APPENDIX

Appendix 4-1: Semi-Structured Interview Guide

Interview / Topic Guide

Investigation of barriers to healthcare practitioners evaluating the legitimacy of beta-lactam allergies listed in electronic medical records

Introduction:

Read the following verbatim:

- Hello, my name is <researcher name>. I am a <researcher role> from the University of Pittsburgh School of Pharmacy.

- Thank you for agreeing to participate in this interview. The goal of this study is to interview practitioners to generate an understanding of the current practices, procedures, and attitudes when providing care for patients with beta-lactam drug allergies. The results will be used to improve the management of these patients by improving the recognition of erroneous penicillin allergies. The interview should last approximately <estimate duration>.

- Participation is voluntary, and there is no compensation as a result of participating. Any responses you provide will be de-identified following the interview, and will only be shared with the research team members. Your decision to participate, as well as your identity and responses will not be disclosed to your supervisor, co-workers, or employer. It is asked that you respond as honestly as possible in order to develop a realistic understanding of current practices and procedures. However, you may decline to answer any question or stop the interview at any time and for any reason.

- Study protocol requires that all interviews be audio recorded. Recordings will not be shared outside of the study team. Do you have any questions about what I have just explained? Do I have your permission to begin recording and proceed with the interview?

Ensure that you have begun recording:

Definitions: In the following questions we will be asking about practices and attitudes regarding beta-lactam allergies. For our purposes, we are considering a 'beta lactam allergy' to be defined as having any penicillin, cephalosporin, carbapenem, or aztreonam listed as an allergy in a patients' electronic medical record.

We will also be referring to the 'legitimacy' of beta-lactam allergies. By this, we are referring to the likelihood that a particular beta-lactam allergy is a true allergic reaction or not. For example, a patient who experiences anaphylaxis would be considered to have a true allergic reaction, but one who only had acute GI upset would not.

Lastly, we want to make the scope of our interview clear. We will ask a couple questions on the process of evaluating a beta-lactam allergy, however; the focus of this project is on the decision-making process that you as the clinician use to determine whether or not you will further investigate the legitimacy of a beta-lactam allergy. For example: imagine a situation where you were just presented with a new patient that you will provide care for, and notice the patient has a beta-lactam allergy. We are primarily interested in examining when you look further into this allergy to determine if it is a legitimate allergy, when you would not, and what motivates this decision.

Practice setting / specialty:

a. What is your current job title?

b. Do you have a clinical specialty that you work within?

    i. If yes: What is that specialty?

Current practices and procedures:

a. What is the current protocol/procedure for determining whether or not the legitimacy of a beta lactam allergy should be investigated?
    i. Is this a formal or informal policy?
b. What is the current protocol/procedure for evaluating the legitimacy of a beta-lactam allergy?
    i. Is this a formal or informal policy?

Hypothetical: Imagine the situation that was described previously: You have just been presented with a new patient that you will provide care for, and notice the patient has a beta-lactam allergy. What are your next steps?

A. Knowledge

a. What knowledge is most important in determining whether or not you will investigate the legitimacy of a particular beta-lactam allergy?
    i. Prompt: Knowledge related to the patient or the allergy being reported?
    ii. Prompt: How do external factors, such how busy you are or the time of day, influence this decision?

b. What is the most important knowledge for a <*insert practitioner role*> to have when evaluating a beta-lactam allergy to determine if it is a legitimate allergy?

i. **Prompt:** Knowledge related to the patient?
    1. Knowledge related to the reported allergy itself?
    2. Preferences or reports directly from the patient or caregivers?
ii. **Prompt:** Knowledge related to the process for investigation?
    1. What is the current process for evaluating beta-lactam allergies? Is this a formal process or an informal one?
    2. If there is more than one: Which investigation process is appropriate for the patient?
    3. How to conduct an investigation to determine the legitimacy of a beta-lactam allergy?
iii. **Prompt:** Previous experience or personal knowledge?
    1. How does your previous experience affect how you perform these investigations?

B. Skills

a. What skills do you use when determining whether or not to investigate the legitimacy of a beta-lactam allergy?

i. Prompt: Skills that help you understand information about the patient?

ii. Prompt: Skills that help you understand the allergy?

b. What skills have you learned through your experiences in evaluating the legitimacy of beta-lactam allergies? How long did it take you to develop these skills?

i. **Prompt**: Skills that help you decide whether or not to investigate the legitimacy of an allergy?

ii. **Prompt**: Skills that help you perform the actual investigation?

C. Social / Professional Role and Identity

a. Who's job is it to investigate the legitimacy of a beta-lactam allergy?

i. **Follow-up**: Who's job should it be and why?

b. Who is the most equipped to investigate the legitimacy of a beta lactam allergy?

i. **Follow-up**: Why them and not <*other clinician*>

D. Beliefs about Capabilities

a. In what circumstances do you feel confident in your decision about whether you do or do not investigate the legitimacy of a beta-lactam allergy?

   i. **Prompt:** Can you describe some situations where you would, and some where you would not?

   ii. **Follow-up:** In what circumstances do you not feel confident in this decision?

b. On a scale from 1 to 10, with 10 being the highest; How confident are you in your ability to determine the legitimacy of a beta-lactam allergy?

   i. **Follow-up:** Once this determination is made; how confident are you in updating a patient's electronic medical record to reflect this outcome? (i.e. removing the allergy from a patient's record)

E. **Beliefs about Consequences**

a. What do you expect to happen when you decide to investigate the legitimacy of a beta-lactam allergy?

   i. **Prompt:** What will happen to the patient or their care?

   ii. **Prompt:** What will happen to you or other staff?

iii. **Follow-up:** What will happen if you don't investigate an allergy?

b. How much confidence do you have that the current procedures/policies for evaluating the legitimacy of beta-lactam allergies leads to the correct result?

i. **Prompt:** in what circumstances are you confident in this process, and when are you not?

F. Optimism

a. How optimistic are you that a patient's true allergy status related to beta-lactam products can be determined?

i. **Prompt:** How optimistic are you that you will have the tools and resources available to make this determination?

b. When are you not optimistic that a patient's allergy status related to beta lactam allergies can be determined?

G. Reinforcement

a. How are you rewarded or recognized for evaluating the legitimacy of a beta-lactam allergy?

i. **Prompt:** Recognition by superiors or peers? Recognition for going 'above and beyond'?

ii. **Follow-up:** How might you be reprimanded for not evaluating the legitimacy of a beta-lactam allergy, if at all?

b. What could be changed to encourage you to investigate the legitimacy of beta-lactam allergies?

i. **Prompt:** To investigate them more often than you currently do?

ii. **Prompt:** To investigate them to a greater depth than you currently do?

H. Intentions

a. What are the most important factors in determining whether or not you investigate the legitimacy of a beta-lactam allergy?

i. **Prompt:** What patient factors are most important?

ii. **Prompt:** What environment factors?

iii. **Prompt:** What personal factors?

I. Goals

a. What is your goal when evaluating the legitimacy of a beta-lactam allergy?

i. **Prompt:** Goals for the patient?

ii. **Prompt:** Goals for you personally?

b. On a scale from 1 – 10, with 10 being the highest; How highly would you rate the priority of investigating the legitimacy of beta-lactam allergies?

i. **Prompt:** Higher priority than most tasks? Much lower?

ii. **Prompt:** In what circumstances does it become a very high or low priority?

J. Memory, Attention, and Decision Processes

a. In what circumstances would you forget to investigate the legitimacy of a beta-lactam allergy, if any?

i. **Follow-up:** When would you remember?

ii. **Follow-up:** When you forget to, what procedures are in place that may help you to remember or to return to complete the investigation later?

b. Relative to other procedures you may complete at the same time; how much more or less difficult is evaluating the legitimacy of a beta-lactam allergy?

i. **Prompt:** Difficulty in relation to other allergies? Difficulty in relation to other patient work-up / admission procedures?

ii. **Follow-up:** What makes it more/less difficult?

iii. **Follow-up:** How much more or less time consuming is it?

K. Environmental Context and Resources

a. How confident are you in the resources / tools that are used to assist you in evaluating the legitimacy of a beta-lactam allergy? (For example: If the patient's EMR lists a penicillin allergy with a reaction of rash; how confident are you that the information is accurate?)

i. **Prompt:** Confidence in the EMR or other technologies?

ii. **Prompt:** Confidence in the patient or family members to provide information?

iii. **Prompt:** Confidence in other members of the care team that may assist in this process?

b. What additional resources would enable your ability or likelihood to investigate the legitimacy of beta-lactam allergies?

i. **Prompt:** Additional technology, information, or time with the patient?

ii. **Follow-up:** What is currently impeding your ability or likelihood to investigate the legitimacy of beta-lactam allergies?

L. Social Influences

a. Who influences your decision to investigate or not investigate the legitimacy of a beta-lactam allergy?

   i. **Prompt:** Patients or family? Colleagues and peers? Managers or administrators?

   ii. **Follow-up:** How does this influence occur and how does it influence your decision?

b. How important does your employer or supervisor believe it is to investigate the legitimacy of beta-lactam allergies?

   i. **Prompt:** More or less than you?

   ii. **Follow-up** How much more or less important do your peers or colleagues believe it is?

c. How does your practice of evaluating beta-lactam allergies differ from your peers or colleagues?

   i. **Prompt:** Do they do it more/less often? More/less thoroughly?

   ii. **Prompt:** Same or different procedures used by everyone?

M. Emotion

a. On a scale from 0 to 10, with 10 being the most stressful; How stressful is deciding to investigate a beta-lactam allergy?

i. **Prompt:** Is it more or less difficult than deciding whether or not to complete other tasks?

ii. **Follow-up**: How stressful is completing the investigation?

N. Behavioral Regulation

a. After completing an investigation of the legitimacy of a beta-lactam allergy, what are your next steps? (i.e. after the allergy was decided to be legitimate / illegitimate; what do you do next?)

i. **Prompt:** Who do you contact?

ii. **Prompt**: What medication or other changes do you make in the care the patient receives?

iii. **Prompt:** What additional information do you often need to gather?

Ending the Interview:

- **We have now reached the end of the interview.**
- *Thank the interviewee for their time and honest answers.*
- Do you have any further comments that you would like to add about anything we have just discussed?

- We want to give interviewees an opportunity to read the results by providing a copy of the manuscript by email once it has been published. If you would like this copy, what is your preferred email?

  Document email: _____

- Do you have any final questions about how this interview will be used?

Appendix 5-1: Definition of Pneumonia and Sepsis ICD-9 Codes

ICD-9 Codes Indicating Pneumonia	480.0, 480.1, 480.2, 480.3, 480.8, 480.9, 481, 482.0, 482.1, 482.2, 482.30, 482.31, 482.32, 482.39, 482.40, 482.41, 482.49, 482.81, 482.82, 482.83, 482.84, 482.89, 482.9, 483.0, 483.1, 483.8, 484.1, 484.3, 484.5, 484.6, 484.7, 484.8, 485, 486, 487.0

ICD-9 codes indicating infection

Code stem	Included codes	Code stem meaning
001	001.0, 001.1, 001.9	Cholera
002	002.0, 002.1, 002.2, 002.3, 002.9	Typhoid/paratyphoid fever
003	003.0, 003.1, 003.20, 003.21, 003.22, 003.23, 003.24, 003.29, 003.8, 003.9	Other salmonella infection
004	004.0, 004.1, 004.2, 004.3, 004.8, 004.9	Shigellosis
005	005.0, 005.1, 005.2, 005.3, 005.4, 005.81, 005.89, 005.9	Other food poisoning
008	008.00, 008.01, 008.02, 008.03, 008.04, 008.09, 008.1, 008.2, 008.3, 008.41, 008.42, 008.43, 008.44, 008.45, 008.46, 008.47, 008.49, 008.5, 008.61, 008.62, 008.63, 008.64, 008.65, 008.66, 008.67, 008.69, 008.8	Intestinal infection not otherwise classified
009	009.0, 009.1, 009.2, 009.3	Ill-defined intestinal infection
010	010.00, 010.01, 010.02, 010.03, 010.04, 010.05, 010.06, 010.10, 010.11, 010.12, 010.13, 010.14, 010.15, 010.16, 010.80, 010.81, 010.82, 010.83, 010.84, 010.85, 010.86, 010.90, 010.91, 010.92, 010.93, 010.94, 010.95, 010.96	Primary tuberculosis infection
011	011.00, 011.01, 011.02, 011.03, 011.04, 011.05, 011.06, 011.10, 011.11, 011.12, 011.13, 011.14, 011.15, 011.16, 011.20, 011.21, 011.22, 011.23, 011.24, 011.25, 011.26, 011.30, 011.31, 011.32, 011.33, 011.34, 011.35, 011.36, 011.40, 011.41, 011.42, 011.43, 011.44, 011.45, 011.46, 011.50, 011.51, 011.52, 011.53, 011.54, 011.55, 011.56, 011.60, 011.61, 011.62, 011.63, 011.64, 011.65, 011.66, 011.70, 011.71, 011.72, 011.73, 011.74, 011.75, 011.76, 011.80, 011.81, 011.82, 011.83, 011.84, 011.85, 011.86, 011.90, 011.91, 011.92, 011.93, 011.94, 011.95, 011.96	Pulmonary tuberculosis
012	012.00, 012.01, 012.02, 012.03, 012.04, 012.05, 012.06, 012.10, 012.11, 012.12, 012.13, 012.14, 012.15, 012.16, 012.20, 012.21, 012.22, 012.23, 012.24, 012.25, 012.26, 012.30, 012.31, 012.32, 012.33, 012.34, 012.35, 012.36, 012.80, 012.81, 012.82, 012.83, 012.84, 012.85, 012.86	Other respiratory tuberculosis

	013	013.00, 013.01, 013.02, 013.03, 013.04, 013.05, 013.06, 013.10, 013.11, 013.12, 013.13, 013.14, 013.15, 013.16, 013.20, 013.21, 013.22, 013.23, 013.24, 013.25, 013.26, 013.30, 013.31, 013.32, 013.33, 013.34, 013.35, 013.36, 013.40, 013.41, 013.42, 013.43, 013.44, 013.45, 013.46, 013.50, 013.51, 013.52, 013.53, 013.53, 013.54, 013.55, 013.56, 013.60, 013.61, 013.62, 013.63, 013.64, 013.65, 013.66, 013.80, 013.81, 013.82, 013.83, 013.84, 013.85, 013.86, 013.90, 013.91, 013.92, 013.93, 013.94, 013.95, 013.96	Central nervous system tuberculosis
	014	014.00, 014.01, 014.02, 014.03, 014.04, 014.05, 014.06, 014.80, 014.81, 014.82, 014.83, 014.84, 014.85, 014.86	Intestinal tuberculosis
	015	015.00, 015.01, 015.02, 015.03, 015.04, 015.05, 015.06, 015.10, 015.11, 015.12, 015.13, 015.14, 015.15, 015.16, 015.20, 015.21, 015.22, 015.23, 015.24, 015.25, 015.26, 015.50, 015.51, 015.52, 015.53, 015.54, 015.55, 015.56, 015.60, 015.61, 015.62, 015.63, 015.64, 015.65, 015.66, 015.70, 015.71, 015.72, 015.73, 015.74, 015.75, 015.76, 015.80, 015.81, 015.82, 015.83, 015.84, 015.85, 015.86, 015.90, 015.91, 015.92, 015.93, 015.94, 015.95, 015.96	Tuberculosis of bone and joint
	016	160.00, 016.01, 016.02, 016.03, 016.04, 016.05, 016.06, 016.10, 016.11, 016.12, 016.13, 016.14, 016.15, 016.16, 016.20, 016.21, 016.22, 016.23, 016.24, 016.25, 016.26, 016.30, 016.31, 016.32, 016.33, 016.34, 016.35, 016.36, 016.40, 016.41, 016.42, 016.42, 016.43, 016.44, 016.45, 016.46, 016.50, 016.51, 016.52, 016.53, 016.54, 016.55, 016.56, 016.60, 016.61, 016.62, 016.63, 016.64, 016.65, 016.66, 016.70, 016.71, 016.72, 016.73, 016.74, 016.75, 016.76, 016.90, 016.91, 016.92, 016.93, 016.94, 016.95, 016.96	Genitourinary tuberculosis
	017	017.00, 017.01, 017.02, 017.03, 017.04, 017.05, 017.06, 017.10, 017.11, 017.12, 017.13, 017.14, 017.15, 017.16, 017.20, 017.21, 017.22, 017.23, 017.24, 017.25, 017.26, 017.30, 017.31, 017.32, 017.33, 017.34, 017.35, 017.36, 017.40, 017.41, 017.42, 017.43, 017.44, 017.45, 017.46, 017.50, 017.51, 017.52, 017.53, 017.54, 017.55, 017.56, 017.60, 017.61, 017.62, 017.63, 017.64, 017.65, 017.66, 017.70, 017.71, 017.72, 017.73, 017.74, 017.75, 017.76, 017.80, 017.81, 017.82, 017.83, 017.84, 017.85, 017.86, 017.90, 017.91, 017.92, 017.93, 017.94, 017.95, 017.96	Tuberculosis not otherwise classified

018	018.00, 018.01, 018.02, 018.03, 018.04, 018.05, 018.06, 018.80, 018.81, 018.82, 018.83, 018.84, 018.85, 018.86, 018.90, 018.91, 018.92, 018.93, 018.94, 018.95, 018.96	Miliary tuberculosis
020	020.0, 020.1, 020.2, 020.3, 020.4, 020.5, 020.8, 020.9	Plague
021	021.0, 021.1, 021.2, 021.3, 021.8, 021.9	Tularemia
022	022.0, 022.1, 022.2, 022.3, 022.8, 022.9	Anthrax
023	023.0, 023.1, 023.2, 023.8, 023.9	Brucellosis
024	024	Glanders
025	025	Melioidosis
026	026.0, 026.1, 026.9	Rat-bite fever
027	027.0, 027.1, 027.2, 027.8, 027.9	Other bacterial zoonoses
030	030.0, 030.1, 030.2, 030.3, 030.8, 030.9	Leprosy
031	031.0, 031.1, 031.2, 031.8, 031.9	Other mycobacterial disease
032	032.0, 032.1, 032.3, 032.81, 032.82, 032.83, 032.84, 032.85, 032.89, 032.9	Diphtheria
033	033.0, 033.1, 033.8, 033.9	Whooping cough
034	034.0, 034.1	Streptococcal throat/scarlet fever
035	035	Erysipelas
036	036.0, 036.1, 036.2, 036.3, 036.40, 036.41, 036.42, 036.43, 036.81, 036.82, 036.89, 036.9	Meningococcal infection
037	037	Tetanus
038	038.0, 038.10, 038.11, 038.19, 038.2, 038.3, 038.40, 038.41, 038.42, 038.43, 038.44, 038.49, 038.8, 038.9	Septicemia
039	039.0, 039.1, 039.2, 039.3, 039.4, 039.8, 039.9	Actinomycotic infections
040	040.0, 040.1, 040.2, 040.3, 040.41, 040.42, 040.81, 040.82, 040.89	Other bacterial diseases
041	041.00, 041.01, 041.02, 041.03, 041.04, 041.05, 041.09, 041.10, 041.11, 041.19, 041.2, 041.3, 041.4, 041.5, 041.6, 041.7, 041.81, 041.82, 041.83, 041.84, 041.85, 041.86, 041.89, 041.9	Bacterial infection in other diseases not otherwise specified
090	090.0, 090.1, 090.2, 090.3, 090.40, 090.41, 090.42. 090.49, 090.5, 090.6, 090.7, 090.9	Congenital syphilis
091	091.0, 091.1, 091.2, 091.3, 091.4, 091.50, 091.51, 091.52, 091.61, 091.62, 091.69, 091.7, 091.81, 091.82, 091.89, 091.9	Early symptomatic syphilis
092	092.0, 092.9	Early syphilis latent
093	093.0, 093.1, 093.20, 093.21, 093.22, 093.23, 093.24, 093.81, 093.82, 093.89, 093.9	Cardiovascular syphilis
094	094.0, 094.1, 094.2, 094.3, 094.81, 094.82, 094.83, 094.84, 094.85, 094.86, 094.87, 094.89, 094.9	Neurosyphilis

	095	095.0, 095.1, 095.2, 095.3, 095.4, 095.5, 095.6, 095.7, 095.8, 095.9	Other late symptomatic syphilis
	096	096	Late syphilis latent
	097	097.0, 097.1, 097.9	Other and unspecified syphilis
	098	098.0, 098.10, 098.11, 098.12, 098.13, 098.14, 098.15, 098.16, 09.17, 098.19, 098.2, 098.30, 098.31, 098.32, 098.33, 098.34, 098.35, 098.36, 098.37, 098.39, 098.40, 098.41, 098.42, 098.43, 098.49, 098.50, 098.51, 098.52, 098.53, 098.59, 098.6, 098.7, 098.81, 098.82, 098.83, 098.84, 098.85, 098.86, 098.89	Gonococcal infections
	100	100.0, 100.81, 100.89, 100.9	Leptospirosis
	101	101	Vincent's angina
	102	102.0, 102.1, 102.2, 102.3, 102.4, 102.5, 102.6, 102.7, 102.8, 102.9	Yaws
	103	103.0, 103.1, 103.2, 103.3, 103.9	Pinta
	104	104.0, 104.8, 104.9	Other spirochetal infection
	110	110.0, 110.1, 110.2, 110.3, 110.4, 110.5, 110.6, 110.8, 110.9	Dermatophytosis
	111	111.0, 111.1, 111.2, 111.3, 111.8, 111.9	Dermatomycosis not otherwise classified or specified
	112	112.0, 112.1, 112.2, 112.3, 112.4, 112.5, 112.81, 112.82, 112.83, 112.84, 112.85, 112.89, 112.9	Candidiasis
	114	114.0, 114.1, 114.2, 114.3, 114.4, 114.5, 114.9	Coccidioidomycosis
	115	115.00, 115.01, 115.02, 115.03, 115.04, 115.05, 115.06, 115.10, 115.11, 115.12, 115.13, 115.14, 115.15, 115.19, 115.90, 115.91, 115.92, 115.93, 115.94, 115.95, 115.99	Histoplasmosis
	116	116.0, 116.1, 116.2	Blastomycotic infection
	117	117.0, 117.1, 117.2, 117.3, 117.4, 117.5, 117.6, 117.7, 117.8, 117.9	Other mycoses
	118	118	Opportunistic mycoses
	320	320.0, 320.1, 320.2, 320.3, 320.7, 320.81, 320.82, 320.89, 320.9	Bacterial meningitis
	322	322.0, 322.1, 322.2, 322.9	Meningitis
	324	324.0, 324.1, 324.9	Central nervous system abscess
	325	325	Phlebitis of intracranial sinus
	420	420.0, 420.90, 420.91, 420.99	Acute pericarditis
	421	421.0, 421.1, 421.9	Acute or subacute endocarditis
	451	451.0, 451.11, 451.19, 451.2, 451.81, 451.82, 451.83, 451.84, 451.89, 451.9	Thrombophlebitis
	461	461.0, 461.1, 461.2, 461.3, 461.8, 461.9	Acute sinusitis
	462	462	Acute pharyngitis
	463	463	Acute tonsillitis

	464	464.00, 464.01, 464.10, 464.11, 464.20, 464.21, 464.30, 464.31, 464.4, 464.50, 464.51	Acute laryngitis/tracheitis
	465	465.0, 465.8, 465.9	Acute upper respiratory infection of multiple sites/not otherwise specified
	481	481	Pneumococcal pneumonia
	482	482.0, 482.1, 482.30, 482.31, 482.32, 482.39, 482.40, 482.41, 482.49, 482.81, 482.82, 482.83, 482.84, 482.89, 482.9	Other bacterial pneumonia
	485	485	Bronchopneumonia with organism not otherwise specified
	486	486	Pneumonia
	491.21	491.21	Acute exacerbation of obstructive chronic bronchitis
	494	494.0, 494.1	Bronchiectasis
	510	510.0, 510.9	Empyema
	513	513.0, 513.1	Lung/mediastinum abscess
	540	540.0, 540.1, 540.9	Acute appendicitis
	541	541	Appendicitis not otherwise specified
	542	542	Other appendicitis
	562.01	562.01	Diverticulitis of small intestine without hemorrhage
	562.03	562.03	Diverticulitis of small intestine with hemorrhage
	562.11	562.11	Diverticulitis of colon without hemorrhage
	562.13	562.13	Diverticulitis of colon with hemorrhage
	566	566	Anal and rectal abscess
	567	567.0, 567.1, 567.21, 567.22, 567.23, 567.29, 567.31, 567.38, 567.39, 567.81, 567.82, 567.89, 567.9	Peritonitis
	569.5	569.5	Intestinal abscess
	569.83	569.83	Perforation of intestine
	572.0	572.0	Abscess of liver
	572.1	572.1	Portal pyemia
	575	575.0, 575.10, 575.11, 575.12, 575.2, 575.3, 575.4, 575.5, 575.6, 575.8, 575.9	Acute cholecystitis
	590	590.00, 590.01, 590.10, 590.11, 590.2, 590.3, 590.80, 590.81, 590.9	Kidney infection
	597	597.0, 597.80, 597.81, 597.89	Urethritis/ urethral syndrome
	599	599.0, 599.1, 599.2, 599.3, 599.4, 599.5, 599.60, 599.61, 599.7, 599.81, 599.82, 599.83, 599.84, 599.89, 599.9	Urinary tract infection not otherwise specified
	601	601.0, 601.1, 601.2, 601.3, 601.4, 601.8, 601.9	Prostatic inflammation
	614	614.0, 614.1, 614.2, 614.3, 614.4, 614.5, 614.6, 614.7, 614.8, 614.9	Female pelvic inflammation disease
	615	615.0, 615.1, 615.9	Uterine inflammatory disease

	616	616.0, 616.10, 616.11, 616.2, 616.3, 616.4, 616.50, 616.51, 616.81, 616.89, 616.9	Other female genital inflammation
	681	681.00, 681.01, 681.02, 681.10, 681.11, 681.9	Cellulitis
	682	682.0, 682.1, 682.2, 682.3, 682.4, 682.5, 682.6, 682.7, 682.8, 682.9	Other cellulitis or abscess
	683	683	Acute lymphadenitis
	686	686.00, 686.01, 686.09, 686.1, 686.8, 686.9	Other local skin infection
	711	711.00, 711.01, 711.02, 711.03, 711.04, 711.05, 711.06, 711.07, 711.08, 711.09, 711.10, 711.11, 711.12, 711.13, 711.14, 711.15, 711.16, 711.17, 711.18, 711.19, 711.20, 711.21, 711.22, 711.23, 711.24, 711.25, 711.26, 711.27, 711.28, 711.29, 711.30, 711.31, 711.32, 711.33, 711.34, 711.35, 711.36, 711.37 711.38, 711.39, 711.40, 711.41, 711.42, 711.43, 711.44, 711.45, 711.46, 711.47, 711.48, 711.49, 711.50, 711.51, 711.52, 711.53, 711.54, 711.55, 711.56, 711.57, 711.58, 711.59, 711.60, 711.61, 711.62, 711.63, 711.64, 711.65, 711.66, 711.67, 711.68, 711.69, 711.70, 711.71, 711.72, 711.73, 711.74, 711.75, 711.76, 711.77, 711.78, 711.79, 711.80, 711.81, 711.82, 711.83, 711.84, 711.85, 711.86, 711.87, 711.88, 711.89, 711.90, 711.91, 711.92, 711.93, 711.94, 711.95, 711.96, 711.97, 711.98, 711.99	Pyogenic arthritis
	730	730.00, 730.01, 730.02, 730.03, 730.04, 730.05, 730.06, 730.07, 730.08, 730.09, 730.10, 730.11, 730.12, 730.13, 730.14, 730.15, 730.16, 730.17, 730.18, 730.19, 730.20, 730.21, 730.22, 730.23, 730.24, 730.25, 730.26, 730.27, 730.28, 730.29, 730.30, 730.31, 730.32, 730.33, 730.34, 730.35, 730.36, 730.37, 730.38, 730.39, 730.70, 730.71, 730.72, 730.73, 730.74, 730.75, 730.76, 730.77, 730.78, 730.79, 730.80, 730.81, 730.82, 730.83, 730.84, 730.85, 730.86, 730.87, 730.88, 730.89, 730.90, 730.91, 730.92, 730.93, 730.94, 730.95, 730.96, 730.97, 730.98, 730.99	Osteomyelitis
	790.7	790.7	Bacteremia
	996.6	996.61, 996.62, 996.63, 996.64, 996.65, 996.66, 996.67, 996.68, 996.69	Infection or inflammation of device/graft
	998.5	998.51, 998.59	Postoperative infection
	999.3	999.31, 999.39	Infectious complication of medical care not otherwise classified.
ICD-9 codes indicating	785.5	785.50, 785.51, 785.52, 785.59	shock without trauma
	458	458.0, 458.1, 458.21, 458.29, 458.8, 458.9	hypotension

organ damage	348.3	348.30, 348.31, 348.39	encephalopathy
	293	293.0, 293.1, 293.81, 293.82, 293.83, 293.84, 293.89, 293.9	transient organic psychosis
	348.1	348.1	anoxic brain damage
	287.4	287.4	secondary thrombocytopenia
	287.5	287.5	thrombocytopenia, unspecified
	286.6	286.6	defibrination syndrome
	286.9	286.9	other/unspecified coagulation defect
	570	570	acute and subacute necrosis of liver
	573.4	573.4	hepatic infarction
	584	584.5, 584.6, 584.7, 584.8, 584.9	acute renal failure

Appendix 5-2: Earliest Available Date for Each UPMC Hospital Included in Analysis

UPMC Hospital	Earliest Date Available
Presbyterian	Jan 2007
Shadyside	Jan 2007
Saint Margaret	Jan 2007
Southside	Jan 2007
Magee Women's Hospital	July 2007
BMC	July 2008
Passavant	Jan 2009
Mercy	April 2009
McKeesport	Apr 2010
Horizon – Greenville	Nov 2010
Horizon – Shenango	Dec 2010
Northwest	April 2011
East	July 2012
Hamot	Sept 2012
Jameson	May 2017

Appendix 5-3: Antibiotic Allergy Classes (brand and generic names):

Beta-lactams	'pcn', penicillin, cloxacillin, dicloxacillin, flucloxacillin, methicillin, nafcillin, oxacillin, temocillin, amoxicillin, ampicillin, mecillinam, piperacillin, carbenicillin, ticarcillin, carbenicillin, ticarcillin, azlicollin, cefazolin, cephalexin, cephalosporin, cephalothin, cefapirin, cefaclor, cefamandole, cefuroxime, cefotetan, cefoxitin, cefixime, cefotaxime, cefpodoxime, ,ceftazidime, ceftriaxone, cefdininr, cefepime, cefpirome, ceftaroline, biapenem, dorpienem, ertapenem, faropenem, imipenem, meropenem, ,panipenem, razupenem, tebipenem, thienamycin, aztreonam, cloxapen, dycill, floxapen, invanz, doribax, primaxin, merrem, duricef, ancef, kefzol, keflex, distaclor, ceclor, raniclor, cefotetan, cefzil, ceftin, zinacef, cefspan, suprax, omnicef, cefdiel, spectracef, ,meiact, ,claforan, ,vantin, ,banadoz, ,fortaz, ,ceptaz, ,cedax, rocephin, maxipime, teflaro, zeftera, azactam,,amoxil, novamox, floxapen, staphcillin, mezlin, unipen, prostaphlin, pentids, veetids, piperacil,,pfizerpan, negaban, ticar, augmentin, unasyn, zosyn, timentin, cephalosporin, monobactam, carbapenem
Glycosamides	Teicoplanin, vancomycin telavancin, dalbavancin, oritavancin, 'glycopeptide', targocid, vancocin, vibatic, dalvance, orbactiv
Lincosamides	Clindamycin, cleocin, lincomycin, lincocin,' lincosamide'
Daptomycin	Daptomycin, cubicin, 'lipopeptide'
Macrolides	Azithromycin, Zithromax, sumamed, xithrone, clarithromycin, biaxin, erythromycin, erythocin, erythroped, roxithromycin, telithromycin, ketek, spiramycin, rovamycine, fidaxomicin, dificid, 'macrolide'
Furans	Furazolidone, furoxone, nitrofurantoin, macrodantin, macrobid, nitrofuran
Oxazoles	Linezolid, zyvox, posizolid, radezolid, torezolid, sivextro, oxazolidione
Peptides	Bacitracin, colistin, coly-mycin, colymicin, polymyxin, 'polypeptide'
Quinolones	Ciprofloxacin, cipro, enoxacin, penetrex, gatifloxacin, tequin, Gemifloxacin, factive, levofloxacin, Levaquin, lomefloxacin, maxaquin, moxifloxacin, avelox, nadifloxacin, nalidixic acid, neggram, norfloxacin, noroxin, ofloxacin, floxacin, ocuflox, trovafloxacin, trovan, grepafloxacin, raxar, sparfloxacin, zagam, temafloxacin, omniflox, 'quinolone'
Tetracyclines	Demeclocycline, declomycin, doxycycline, vibramycin, metacycline, minocycline, minocin, oxytetracycline, terramycin, tetracycline, sumycin, achromycin, steclin, 'tetracycline'
Other	Clofazimine, lamprene ,dapsone, avlosulfon, capreomycin, capastat, cycloserine, seromycin, ethambutol, myambutol, ethionamide, trecator, isoniazid, i.n.h., pyrazinamide, aldinamide, rifampicin, rifampin, rifadin, rimactane, rifabutin, mycobutin, rifapentine, priftin, streptomycin, arsphenamine, ,salvarsan, ,chloramphenicol, chloromycetin, fosfomycin, monurol, monuril, fusidic acid, fucidin, metronidazole, flagyl, mupirocin, bactroban, platensimycin, quinupristin, ,dalfopristin, synercid, thiamphenicol, tigecycline, tigacyl, tinidazole, tindamax, fasigyn, trimethoprim, proloprim, trimpex,

Appendix 5-4: Microbiology Codes Corresponding to Resistant Infection Diagnosis

*VRE Results excluded text results indicating colonization instead of active infection

Resistant Infection Diagnosis	Included UPMC Microbiology Codes
MRSA	“SAUR”, “MRSAIS”
CDiff	“CDFT” (excluding “XCDFT”), “CDFP”, “PCDNA”
VRE *	“VRE, “ENFC”, “ENFM” + “R” flag for Vancomycin

Appendix 5-5: RECORD Checklist

	Item No.	STROBE items	RECORD items	Location in manuscript where items are reported
Title and abstract				
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	1.1 Type of data and study design in abstract 1.2 Source of data and timing in abstract 1.3 No linkage required
Introduction				
Background rationale	2	Explain the scientific background and rationale for the investigation being reported		Section 5.2 Introduction – First three paragraphs
Objectives	3	State specific objectives, including any prespecified hypotheses		Section 5.2 Introduction – concluding paragraph

Methods				
Study Design	4	Present key elements of study design early in the paper		Section 5.3.1 – Study Design
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection		Section 5.3.1 – Data source
Participants	6	*(a) Cohort study* - Give the	RECORD 6.1: The methods of study	6.1: Section 5.3.2 and covered in detail in the supplement 6.2: Section 5.3.2 studies validating the search methods are provided 6.3: N/A

		eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria	population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases,	

		and the number of controls per case	consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	Sections: 5.3.2 for cohort definition. Sections 5.3.3 -5.3.6 contain all covariates and outcomes in depth including detailed processes
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group		Sections 5.3.6 – 5.3.7 Describes outcomes measurements and statistical processes

Bias	9	Describe any efforts to address potential sources of bias		Sections 5.3.7 – 5.3.10 describes how model reduces bias and sensitivity analysis to interrogate initial assumptions

Study size	10	Explain how the study size was arrived at		Section 5.3.2: sample size is result of cohort definitions
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why		Sections 5.3.7 – 5.3.10 describes statistical processes in depth including groups within each model
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses		Sections 5.3.7 – 5.3.10 all models are described in depth. Missingness is covered in 5.3.7 through MI.

Data access and cleaning methods		..	RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	12.1: Section 5.3.1 covers honest broker usage for data acquisition. 12.2: Sections 5.3.3 – 5.3.10 describe how all variables were derived and supplements provide all codes to repeat analysis
Linkage		..	RECORD 12.3: State whether the	N/A

			study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for nonparticipation at each stage. (c)	RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.*, study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	Flowchart shown in figure 5-1.

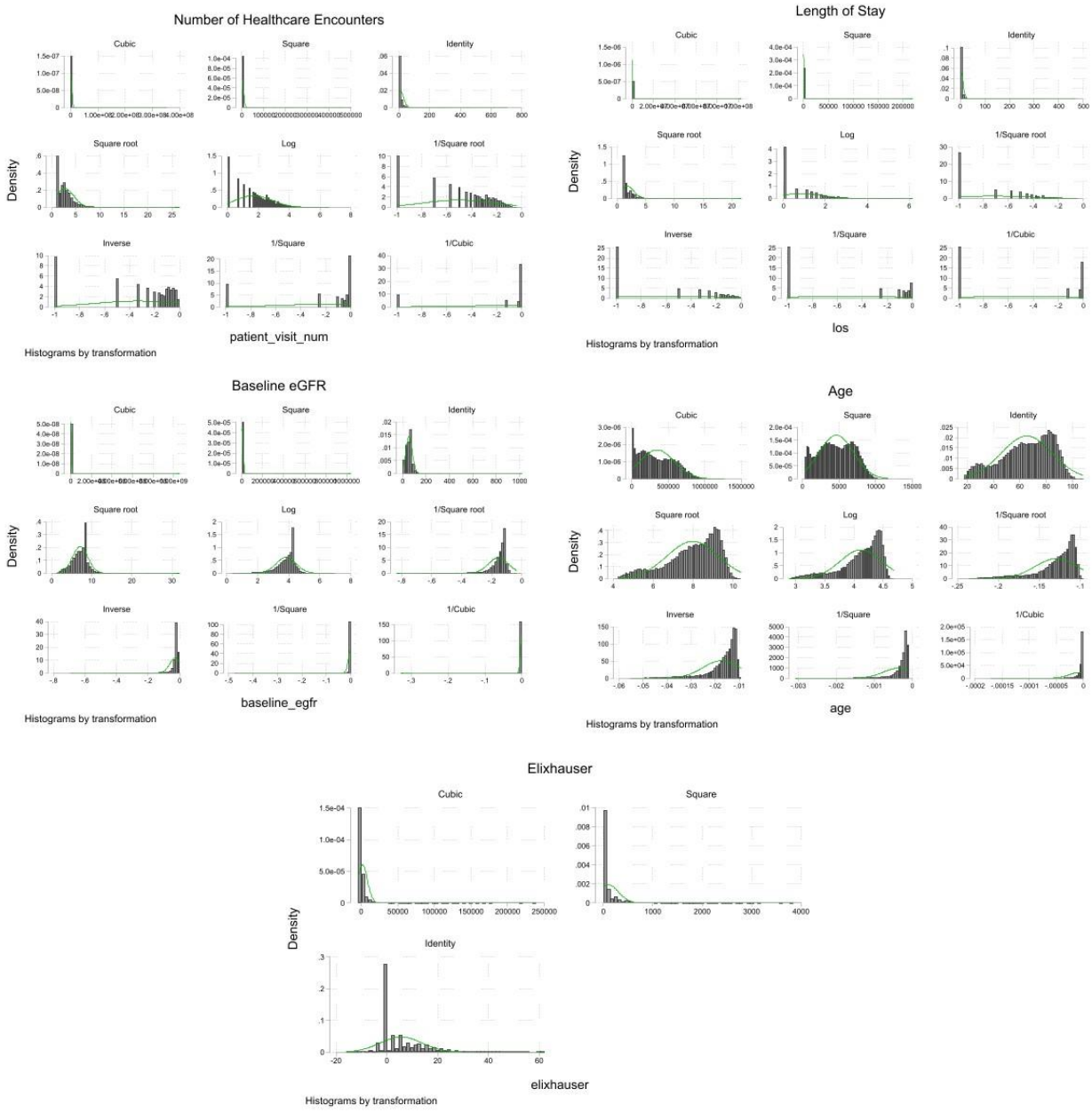
		Consider use of a flow diagram		
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)		Sections 5:4.1 and Table 5-2.
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures		Table 5-3: Shows outcomes over time

Main results	16	(a) Give unadjusted estimates and, if applicable, confounderadjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period		Table 5-3 shows unadjusted results. Table 5-4 shows primary results with legend to show confounders. Cis are provided
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses		Sections 5.4.4 to 5.4.6 show sensitivity and secondary analyses
Key results	18	Summarise key results with reference to study objectives		Section 5-5 First two paragraphs
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the	Section 5-5: final paragraph outlines limitations including the highlighted issues of misclassification, unmeasured confounding, and follow-up

			study being reported.	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence		Section 5-5: second, third, and fourth paragraphs
Generalisability	21	Discuss the generalisability (external validity) of the study results		Section 5-5: final paragraph in limitations covers limited external generalization due to cohort definition
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based		N/A No funding
Accessibility of protocol, raw data, and programming code		..	RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	N/A for dissertation – to be considered for future publications

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

Appendix 5-6: Continuous Covariate Normal Transformation Distributions



Appendix 6-1: Dictionary of Entities used for the Named-Entity Recognition Process

Phrase	Entity
aztreonam	AZTREONAM
aztreonam / dextrose	AZTREONAM
azactam	AZTREONAM
carbapenem rs - 533	CARBAPENEM
carbapenem rs 533	CARBAPENEM
cilastatin + imipenem	CARBAPENEM
cilastatin / imipenem	CARBAPENEM
doribax	CARBAPENEM
doripenem	CARBAPENEM
doripenem (product)	CARBAPENEM
doripenem (substance)	CARBAPENEM
ertapenem	CARBAPENEM
ertapenem sodium	CARBAPENEM
ertapenem sodium (substance)	CARBAPENEM
faropenem	CARBAPENEM
imipenem	CARBAPENEM
imipenem + cilastatin	CARBAPENEM
imipenem + cilastatin (product)	CARBAPENEM
imipenem + cilastatin (substance)	CARBAPENEM
imipenem + edta	CARBAPENEM
imipenem - cilastatin	CARBAPENEM
imipenem - cilastatin , sodium salt	CARBAPENEM
imipenem - cilastatin injection	CARBAPENEM
imipenem - cilastatin sodium	CARBAPENEM
imipenem / cilastatin sodium	CARBAPENEM
imipenem cilastatin sodium	CARBAPENEM
imipenem with cilastin sodium	CARBAPENEM
imipenem with cilastin sodium (substance)	CARBAPENEM
invanz	CARBAPENEM
merck brand of ertapenem sodium	CARBAPENEM
merck brand of imipenem - cilastatin , sodium salt	CARBAPENEM
merck frosst brand of imipenem - cilastatin , sodium salt	CARBAPENEM
merck sharp & dohme brand of imipenem - cilastatin , sodium salt	CARBAPENEM
meropenem	CARBAPENEM
meropenem , anhydrous	CARBAPENEM
meropenem anhydrous	CARBAPENEM
merrem	CARBAPENEM
merrem novaplus	CARBAPENEM
msd brand of ertapenem sodium	CARBAPENEM

panipenem	CARBAPENEM
primaxin	CARBAPENEM
primaxin im	CARBAPENEM
primaxin iv	CARBAPENEM
carbapenem	CARBAPENEM
carbapenems	CARBAPENEM
12 hr cefaclor	CEPHALOSPORIN
12 hr cefotiam	CEPHALOSPORIN
alti cefuroxime	CEPHALOSPORIN
ceftaroline -	CEPHFIVE
maxipime	CEPHFOUR
cefepime	CEPHFOUR
maxipime	CEPHFOUR
cefapime	CEPHFOUR
ambroxol / cefadroxil	CEPHONE
ambroxol / cephalexin	CEPHONE
ancef	CEPHONE
bromhexine / cephalexin	CEPHONE
cefadroxil	CEPHONE
cefadroxil hemihydrate	CEPHONE
cefadroxil hydrate	CEPHONE
cefadroxil hydrate @ @ powder (gm)	CEPHONE
cefadroxil hydrate powder (gm)	CEPHONE
cefadroxil monohydate	CEPHONE
cefadroxil monohydrate	CEPHONE
cefadroxil monohydrate @ @ powder (gm)	CEPHONE
cefadroxil monohydrate misc . powder (gm)	CEPHONE
cefadroxil monohydrate powder (gm)	CEPHONE
cefadyl	CEPHONE
cefalektin	CEPHONE
cefazolin	CEPHONE
cefazolin / dextrose	CEPHONE
cefazolin / sodium chloride	CEPHONE
cefazolin delta - 2 - methyl ester	CEPHONE
cefazolin delta - 3 - methyl ester	CEPHONE
cefazolin sodium	CEPHONE
cefazolin sodium @ @ powder (gm)	CEPHONE
cefazolin sodium misc . powder (gm)	CEPHONE
cefazolin sodium novaplus	CEPHONE
cefazolin sodium powder (gm)	CEPHONE
cephalexim	CEPHONE
cephalexin	CEPHONE
cephalexin (as monohydrate)	CEPHONE
cephalexin hcl	CEPHONE

cephalexin hydrochloride	CEPHONE
cephalexin monohydrate	CEPHONE
cephalexin monohydrate @ @ powder (gm)	CEPHONE
cephalexin monohydrate misc . powder (gm)	CEPHONE
cephalexin monohydrate powder (gm)	CEPHONE
cephalexin monohydrochloride , monohydrate	CEPHONE
cephalothin	CEPHONE
cephalothin / dextrose	CEPHONE
cephalothin sodium	CEPHONE
cephapirin	CEPHONE
cephapirin sodium	CEPHONE
duricef	CEPHONE
keflex	CEPHONE
keflex - c	CEPHONE
kefzol	CEPHONE
cephazolin	CEPHONE
cephalin	CEPHOTHER
cephaline	CEPHOTHER
cephaline (substance)	CEPHOTHER
cephalochromin	CEPHOTHER
cephalosporin agent	CEPHOTHER
cephalosporins & cephamycins	CEPHOTHER
cephalosporins & cephamycins (product)	CEPHOTHER
cephalosporins & cephamycins (substance)	CEPHOTHER
cephalosporium acremonium extract	CEPHOTHER
cephalosporium acremonium extract (product)	CEPHOTHER
cephalosporolide d	CEPHOTHER
cephalosporin	CEPHOTHER
cephalosporins	CEPHOTHER
cedax	CEPHTHREE
cefdinir	CEPHTHREE
cefixime	CEPHTHREE
cefixime @ @ granules ; powder - like , non - efervescent (gm)	CEPHTHREE
cefixime granules ; powder - like , non - efervescent (gm)	CEPHTHREE
cefotaxime	CEPHTHREE
cefotaxime sodium	CEPHTHREE
cefotaxime syn s - oxide	CEPHTHREE
cefotaxime syn s - oxide , (5 r - (5 alpha , 6 alpha , 7 beta (z))) - isomer	CEPHTHREE
cefotaxime.meningitis	CEPHTHREE
cefotaxime.meningitis & # 124 ; isolate	CEPHTHREE
cefpodoxime	CEPHTHREE
cefpodoxime proxetil	CEPHTHREE

ceftazidime	CEPHTHREE
ceftazidime (as l - arginine)	CEPHTHREE
ceftazidime / sodium chloride	CEPHTHREE
ceftazidime pentahydrate	CEPHTHREE
ceftazidime sodium	CEPHTHREE
ceftriaxone	CEPHTHREE
ceftriaxone / dextrose	CEPHTHREE
ceftriaxone / lidocaine	CEPHTHREE
ceftriaxone sodium	CEPHTHREE
ceftriaxone sodium 100 % ww	CEPHTHREE
ceftriaxone sodium @ @ powder (gm)	CEPHTHREE
ceftriaxone sodium misc . powder (gm)	CEPHTHREE
ceftriaxone sodium novaplus	CEPHTHREE
ceftriaxone sodium powder (gm)	CEPHTHREE
ceftriaxone.meningitis	CEPHTHREE
ceftriaxone.meningitis & # 124 ; isolate	CEPHTHREE
ceftrixone	CEPHTHREE
ceptaz	CEPHTHREE
claforan	CEPHTHREE
fortaz	CEPHTHREE
omnicef	CEPHTHREE
omnicef omni - pac	CEPHTHREE
rocephin	CEPHTHREE
rocephin im convenience kit	CEPHTHREE
rocephin im convenience kit (obsolete)	CEPHTHREE
spectracef	CEPHTHREE
suprax	CEPHTHREE
tazicef	CEPHTHREE
vantin	CEPHTHREE
ceclor	CEPHTWO
ceclor cd	CEPHTWO
ceclor pulvules	CEPHTWO
cefaclor	CEPHTWO
cefaclor @ @ powder (gm)	CEPHTWO
cefaclor ab.ige	CEPHTWO
cefaclor antibody.immunoglobulin e	CEPHTWO
cefaclor cd	CEPHTWO
cefaclor er	CEPHTWO
cefaclor extract	CEPHTWO
cefaclor extract (product)	CEPHTWO
cefaclor misc . powder (gm)	CEPHTWO
cefaclor monohydrate	CEPHTWO
cefaclor powder (gm)	CEPHTWO
cefamandole	CEPHTWO

cefamandole nafate	CEPHTWO
cefamandole naftate	CEPHTWO
cefamandole sodium	CEPHTWO
cefotetan	CEPHTWO
cefotetan disodium	CEPHTWO
cefoxitin	CEPHTWO
cefoxitin / dextrose	CEPHTWO
cefoxitin sodium	CEPHTWO
ceftin	CEPHTWO
cefuroxime	CEPHTWO
cefuroxime + metronidazole	CEPHTWO
cefuroxime + metronidazole (product)	CEPHTWO
cefuroxime + metronidazole (substance)	CEPHTWO
cefuroxime / dextrose	CEPHTWO
cefuroxime / sodium chloride	CEPHTWO
cefuroxime axetil	CEPHTWO
cefuroxime sodium	CEPHTWO
cefzil	CEPHTWO
oxacefamandole	CEPHTWO
oxacefamandole , (6 r - (6 alpha , 7 beta (r *))) - isomer	CEPHTWO
oxacefamandole , monosodium salt	CEPHTWO
oxacephem 6315 - s	CEPHTWO
zinacef	CEPHTWO
to treat with	crntuse
will treat with	crntuse
treat with	crntuse
treat him with	crntuse
treat her with	crntuse
treat the patient with	crntuse
initiate	crntuse
will initiate	crntuse
to initiate	crntuse
initiation of	crntuse
will need	crntuse
going to need	crntuse
current therapy includes	crntuse
includes	crntuse
with	crntuse
is taking	crntuse
is receiving	crntuse
requires	crntuse
start him on	crntuse
start her on	crntuse
to start on	crntuse

maintain on	crntuse
maintain him on	crntuse
maintain her on	crntuse
currently on	crntuse
I ordered	crntuse
have ordered	crntuse
current regimen of	crntuse
will give	crntuse
to be administered	crntuse
was ordered	crntuse
to cover with	crntuse
cover with	crntuse
will treat with	crntuse
add	crntuse
start	crntuse
continue on	crntuse
continue	crntuse
has been started on	crntuse
start the patient on	crntuse
start on	crntuse
to start on	crntuse
has been started on	crntuse
is on	crntuse
to be on	crntuse
will be started on	crntuse
on	crntuse
cont	crntuse
order	crntuse
will order	crntuse
ordered	crntuse
place him on	crntuse
place her on	crntuse
place on	crntuse
to place on	crntuse
will place one	crntuse
will get	crntuse
will take	crntuse
narrow to	crntuse
will narrow	crntuse
will switch	crntuse
switch	crntuse
is reasonable	crntuse
should be a reasonable agent	crntuse
should be reasonable	crntuse

may be reasonable	crntuse
is a reasonable agent	crntuse
to give	crntuse
1 ml penicillin g	PENICILLIN
1 ml penicillin g , benzathine	PENICILLIN
1 ml penicillin g , benzathine / penicillin g , procaine	PENICILLIN
1 ml penicillin g , procaine	PENICILLIN
12 hr amoxicillin / clavulanate	PENICILLIN
2 ml penicillin g , benzathine	PENICILLIN
2 ml penicillin g , benzathine / penicillin g , procaine	PENICILLIN
2 ml penicillin g , procaine	PENICILLIN
4 ml penicillin g	PENICILLIN
4 ml penicillin g , benzathine	PENICILLIN
4 ml penicillin g , benzathine / penicillin g , procaine	PENICILLIN
6 - alpha - methylpenicillin n	PENICILLIN
6 - methylpenicillin n	PENICILLIN
acetylcysteine / cefuroxime	PENICILLIN
aefpcnh2	PENICILLIN
ambroxol / amoxicillin	PENICILLIN
ambroxol / ampicillin	PENICILLIN
amoxicillin	PENICILLIN
amoxicillin (as trihydrate)	PENICILLIN
amoxicillin - clavulanate	PENICILLIN
amoxicillin / bromhexine	PENICILLIN
amoxicillin / brovanexine	PENICILLIN
amoxicillin / carbocysteine	PENICILLIN
amoxicillin / clarithromycin / lansoprazole	PENICILLIN
amoxicillin / clarithromycin / omeprazole	PENICILLIN
amoxicillin / clavulanate	PENICILLIN
amoxicillin / clavulanate potassium	PENICILLIN
amoxicillin / clonixin	PENICILLIN
amoxicillin / diclofenac	PENICILLIN
amoxicillin / floxacillin	PENICILLIN
amoxicillin / nystatin	PENICILLIN
amoxicillin / piroxicam	PENICILLIN
amoxicillin / probenecid	PENICILLIN
amoxicillin / sulbactam	PENICILLIN
amoxicillin / sulfinpyrazone	PENICILLIN
amoxicillin monosodium salt	PENICILLIN
amoxicillin sodium	PENICILLIN
amoxicillin trihydrate	PENICILLIN
amoxicillin trihydrate @ @ powder (gm)	PENICILLIN
amoxicillin trihydrate misc . powder (gm)	PENICILLIN
amoxicillin trihydrate powder (gm)	PENICILLIN

amoxicillinan	PENICILLIN
amoxicilloyl extract	PENICILLIN
amoxicilloyl extract (product)	PENICILLIN
amoxil	PENICILLIN
amoxil fiztab	PENICILLIN
amoxil pediatric drops	PENICILLIN
amoxil sf	PENICILLIN
ampicillin	PENICILLIN
ampicillin (anhydrous)	PENICILLIN
ampicillin - dicloxacillin mixture	PENICILLIN
ampicillin - probenecid	PENICILLIN
ampicillin - sulbactam	PENICILLIN
ampicillin - sulbactam novaplus	PENICILLIN
ampicillin / bromhexine	PENICILLIN
ampicillin / brovanexine	PENICILLIN
ampicillin / carbocysteine	PENICILLIN
ampicillin / cloxacillin	PENICILLIN
ampicillin / diclofenac	PENICILLIN
ampicillin / dicloxacillin	PENICILLIN
ampicillin / floxacillin	PENICILLIN
ampicillin / probenecid	PENICILLIN
ampicillin / sulbactam	PENICILLIN
ampicillin anhydrous	PENICILLIN
ampicillin benzathine	PENICILLIN
ampicillin potassium	PENICILLIN
ampicillin sodium	PENICILLIN
ampicillin sodium novaplus	PENICILLIN
ampicillin trihydrate	PENICILLIN
ampicillin trihydrate @ @ powder (gm)	PENICILLIN
ampicillin trihydrate misc . powder (gm)	PENICILLIN
augmentin	PENICILLIN
augmentin 125 - mg chewable	PENICILLIN
augmentin 200 - mg chewable	PENICILLIN
augmentin 250 - mg	PENICILLIN
augmentin 250 - mg chewable	PENICILLIN
augmentin 400 - mg chewable	PENICILLIN
augmentin 500 - mg	PENICILLIN
augmentin 875 - mg	PENICILLIN
augmentin duo	PENICILLIN
augmentin es - 600	PENICILLIN
augmentin junior	PENICILLIN
augmentin xr	PENICILLIN
benethamine penicillin	PENICILLIN
bromhexine / cefaclor	PENICILLIN

bromhexine / penicillin v	PENICILLIN
carbenicillin	PENICILLIN
carbenicillin disodium	PENICILLIN
carbenicillin indanyl sodium	PENICILLIN
carbenicillin phenyl sodium	PENICILLIN
clavulanate / ticarcillin	PENICILLIN
clavulanic acid / ticarcillin	PENICILLIN
clemizolpenicillin	PENICILLIN
clemizolpenicillin / penicillin g	PENICILLIN
cloxacillin	PENICILLIN
cloxacillin anhydrous	PENICILLIN
cloxacillin benzathine	PENICILLIN
cloxacillin sodium	PENICILLIN
cloxapen	PENICILLIN
cloxazepin	PENICILLIN
cloxazepine	PENICILLIN
cloxazolam	PENICILLIN
cpe - penicillin	PENICILLIN
dextrose / nafcillin	PENICILLIN
dextrose / oxacillin	PENICILLIN
dextrose / penicillin	PENICILLIN
dextrose / piperacillin	PENICILLIN
dextrose / ticarcillin	PENICILLIN
dicloxacillin	PENICILLIN
dicloxacillin sodium	PENICILLIN
dicloxicillin	PENICILLIN
dycill	PENICILLIN
floxacillin	PENICILLIN
floxacillin magnesium	PENICILLIN
floxacillin sodium	PENICILLIN
floxapen	PENICILLIN
floxapen forte	PENICILLIN
merbromin / penicillin g	PENICILLIN
metampicillin	PENICILLIN
metampicillin sodium	PENICILLIN
methampicillin	PENICILLIN
methampicillin sodium	PENICILLIN
methicillin	PENICILLIN
methicillin anhydrous	PENICILLIN
methicillin sodium	PENICILLIN
methicillin sodium @ @ powder (gm)	PENICILLIN
methicillin sodium powder (gm)	PENICILLIN
mezlin	PENICILLIN
mezlocillin	PENICILLIN

mezlocillin + sulbactam	PENICILLIN
mezlocillin sodium	PENICILLIN
n - (6,7 - difluoroquinolonyl) ampicillin	PENICILLIN
nafcillin	PENICILLIN
nafcillin anhydrous	PENICILLIN
nafcillin sodium	PENICILLIN
nafcillin sodium monohydrate	PENICILLIN
nafcillin sodium novaplus	PENICILLIN
oxacillin	PENICILLIN
oxacillin , monosodium salt , monohydrate	PENICILLIN
oxacillin anhydrous	PENICILLIN
oxacillin sodium	PENICILLIN
oxacillin sodium novaplus	PENICILLIN
pcn	PENICILLIN
pcn - vk	PENICILLIN
pcnu	PENICILLIN
penicillin	PENICILLIN
penicillin - binding protein 2 x , streptococcus	PENICILLIN
penicillin / probenecid	PENICILLIN
penicillin g	PENICILLIN
penicillin g , benzathine	PENICILLIN
penicillin g , benzathine / penicillin g , procaine	PENICILLIN
penicillin g , procaine	PENICILLIN
penicillin g / penicillin g	PENICILLIN
penicillin g benzathine	PENICILLIN
penicillin g clemizole	PENICILLIN
penicillin g potassium	PENICILLIN
penicillin g procaine	PENICILLIN
penicillin g procaine - al stea	PENICILLIN
penicillin g sodium	PENICILLIN
penicillin g sodium / penicillin g , benzathine	PENICILLIN
penicillin g sodium / penicillin g , procaine	PENICILLIN
penicillin v	PENICILLIN
penicillin v benzathine	PENICILLIN
penicillin v calcium	PENICILLIN
penicillin v hydrabamine	PENICILLIN
penicillin v potassium	PENICILLIN
penicillinase	PENICILLIN
penicillins	PENICILLIN
penicillium frequentans extract	PENICILLIN
penicillium frequentans extract (product)	PENICILLIN
penicillium notatum extract	PENICILLIN
penicillium notatum extract (product)	PENICILLIN
piperacillin	PENICILLIN

piperacillin + sulbactam	PENICILLIN
piperacillin - tazobactam inj	PENICILLIN
piperacillin / tazobactam	PENICILLIN
piperacillin sodium	PENICILLIN
pivampicillin	PENICILLIN
pivampicillin hydrochloride	PENICILLIN
pivampicillin pamoate	PENICILLIN
pyridine - 2 - azo - 4 - dimethylaniline cephalosporin	PENICILLIN
raniclor	PENICILLIN
rpcnu	PENICILLIN
sodium cephalothin	PENICILLIN
spectraban	PENICILLIN
spectraban 15	PENICILLIN
spectraban 5.6	PENICILLIN
staphcillin	PENICILLIN
talampicillin	PENICILLIN
talampicillin hcl	PENICILLIN
talampicillin napsylate	PENICILLIN
temocillin	PENICILLIN
temocillin 2 - methylphenyl ester	PENICILLIN
temocillin sodium	PENICILLIN
thd - pcn	PENICILLIN
ticar	PENICILLIN
ticarcillin	PENICILLIN
ticarcillin + clavulanate	PENICILLIN
ticarcillin disodium	PENICILLIN
timentin	PENICILLIN
unasyn	PENICILLIN
unipen	PENICILLIN
veetids	PENICILLIN
viccillin s (combination) , ampicillin sodium salt	PENICILLIN
viccillin s (combination) , cloxacillin sodium salt	PENICILLIN
zosyn	PENICILLIN
zosyn add - vantage	PENICILLIN
switched to	pvsuse
no issues with	pvsuse
had received	pvsuse
had not had issued with	pvsuse
was given	pvsuse
has been on	pvsuse
been on	pvsuse
was taking	pvsuse
has taken	pvsuse
did taken	pvsuse

completed	pvsuse
has taken	pvsuse
previous regimen of	pvsuse
was started on	pvsuse
started on	pvsuse
was used	pvsuse
treated with	pvsuse
given	pvsuse
received	pvsuse
included	pvsuse
tolerates	pvsuse
will tolerates	pvsuse
has tolerated	pvsuse
has been start	pvsuse
been given	pvsuse
cover the patient with	pvsuse
been covered with	pvsuse
covered with	pvsuse
was on	pvsuse
administered	pvsuse
was treated with	pvsuse
treated with	pvsuse
she took	pvsuse
he took	pvsuse
took	pvsuse
treated the patient with	pvsuse
treated her with	pvsuse
treated him with	pvsuse
did receive	pvsuse
doses of	pvsuse
continued	pvsuse
started on	pvsuse
initiated	pvsuse
was treated with	pvsuse
treated with	pvsuse
doses of	pvsuse
was placed on	pvsuse
was put on	pvsuse
had been placed on	pvsuse
placed on	pvsuse
switched from	pvsuse
switched	pvsuse
was continuing	pvsuse
was continuing on	pvsuse

had been continuing	pvsuse
disconinued on	pvsuse

Appendix 6-2: Export of Qualtrics Survey to Evaluate Utility of Simulated CDS Alerts Containing NLP-derived Beta-Lactam Usage Information

Penicillin Allergy Alert Evaluation

Survey Flow

Group: Solution Embedded Data
EmbeddedData ProjectCategory = PX ProjectType = ConceptTesting
Standard: Intro (1 Question) Standard: Respodant Background (3 Questions) Standard: Alert 1 - no NLP (4 Questions) Block: Alert 1 (4 Questions) Standard: Alert 2 - No NLP (4 Questions) Standard: Alert 2 (4 Questions) Block: Alert 3 - No NLP (4 Questions) Block: Alert 3 (4 Questions) Standard: Summary Questions (12 Questions)

Page Break

Start of Block: Intro

Introduction: Thank you for completing the following short survey. Our study team has developed an NLP-enriched process to provide additional information to clinicians when presented with an EHR beta-lactam drug allergy alert. We have developed simulated EHR decision support alerts with the goal of assisting clinicians in evaluating the legitimacy of Beta-lactam allergies. You will first be presented with simulated alerts which do not contain the additional information followed by the same alerts but which do contain the NLP-enriched additional information.

Please review the following alerts and answer the short survey following each simulated alert. At the end of the survey, you will be asked to evaluate specific aspects of the alert. Finally, you will be provided space to provide any free-text feedback on the alert's current design, usefulness, or future direction.

We sincerely appreciate your feedback and assistance!

For additional context on erroneous Beta-lactam allergies and the study purpose please click the button below. Additional Information

Many patients are labelled erroneously with Beta-Lactam allergies which cause harm through altering prescribing practices and limiting treatment options. Many health systems have recent instituted programs to systematically evaluate and remove erroneous allergies. One of the recommendations when encountering a Beta-Lactam allergy is that any antimicrobial agent a patient has previously tolerated is predicted to be able to be safely used in the future. However, it is often unclear what agents a patient has previously tolerated and it may be overly time-consuming to fully evaluate a medication history.

In order to assist clinicians in this medication history evaluation, our study team has developed of an alerts system which utilizes natural-language processing to quickly identify prior Beta-Lactam usage. The following simulated alerts have been generated using this alerts system. All information contained in the alerts has been generated using real patient data, but names and dates have been modified to protect patient identities.

The alerts are not intended to take the place of clinician evaluation of allergy legitimacy, but instead are designed to reduce the effort that is required by the clinician in navigating the EHR to locate relevant information. The goal of the alert is to promote the use of preferred Beta-Lactam products in patients who report Beta-Lactam allergies by enabling clinicians to make informed decisions regarding prior antimicrobial usage.

End of Block: Intro

Start of Block: Respodant Background

Q52 Please answer the following two questions describing your current clinical role and background to the best of your ability.

Clinical Background Please select the description which best matches your current clinical role:

- ○ Nurse (1)
- ○ Pharmacist (2)
- ○ Advanced Practice Provider (3)
- ○ Physician (4)
- ○ Surgeon (5)
- ○ Other (Please specify) (7) _____
- ○ I prefer not to answer (9)

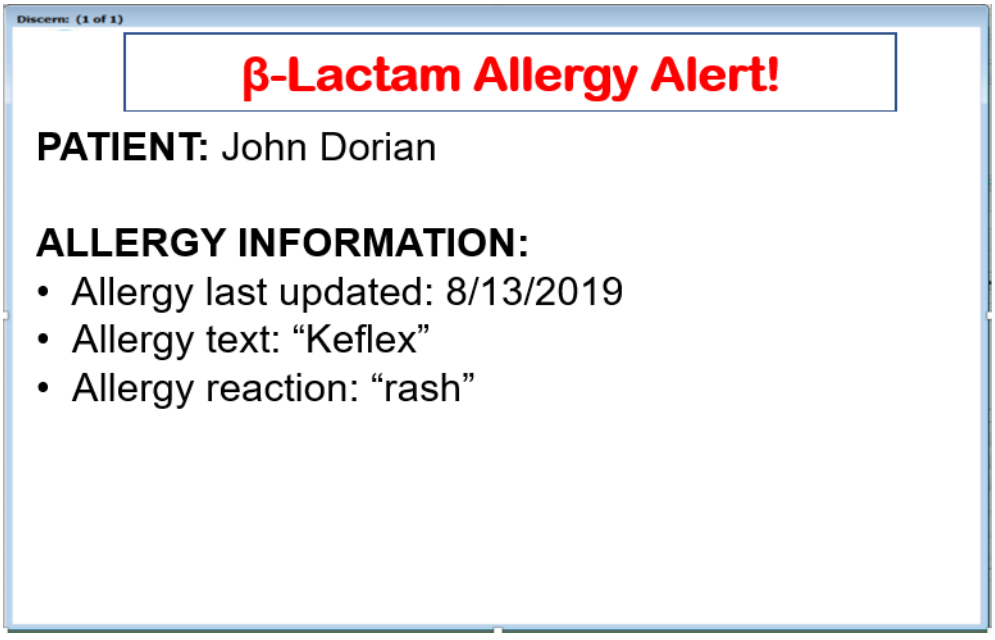
Clinical Specialty Please indicate if you are specialized in any of the following clinical areas:

- ☐ Infectious Disease / Infection Prevention (1)
- ☐ Allergist (2)
- ☐ Emergency Medicine (3)
- ☐ Critical Care (4)
- ☐ Other (Please specify) (5) _____

End of Block: Respodant Background

Start of Block: Alert 1 - no NLP

Q1 Alert 1 – no NLP



The following link will direct you to a chart created by Northwestern University which details the cross-reactivity of commonly used beta-lactam products:

Beta-lactam Cross Reactivity Chart

Use of this chart is not required to answer the following questions but it may be referenced if desired.

Q1-2 Using only the information in this alert, how confident would you feel prescribing/verifying **Cefazolin** for the patient contained in the alert? Please answer below with 1 being not confident at all and 10 being fully confident.

	1	2	3	4	5	6	6	7	8	9	10
Confidence prescribing/verifying Cefazolin ()											

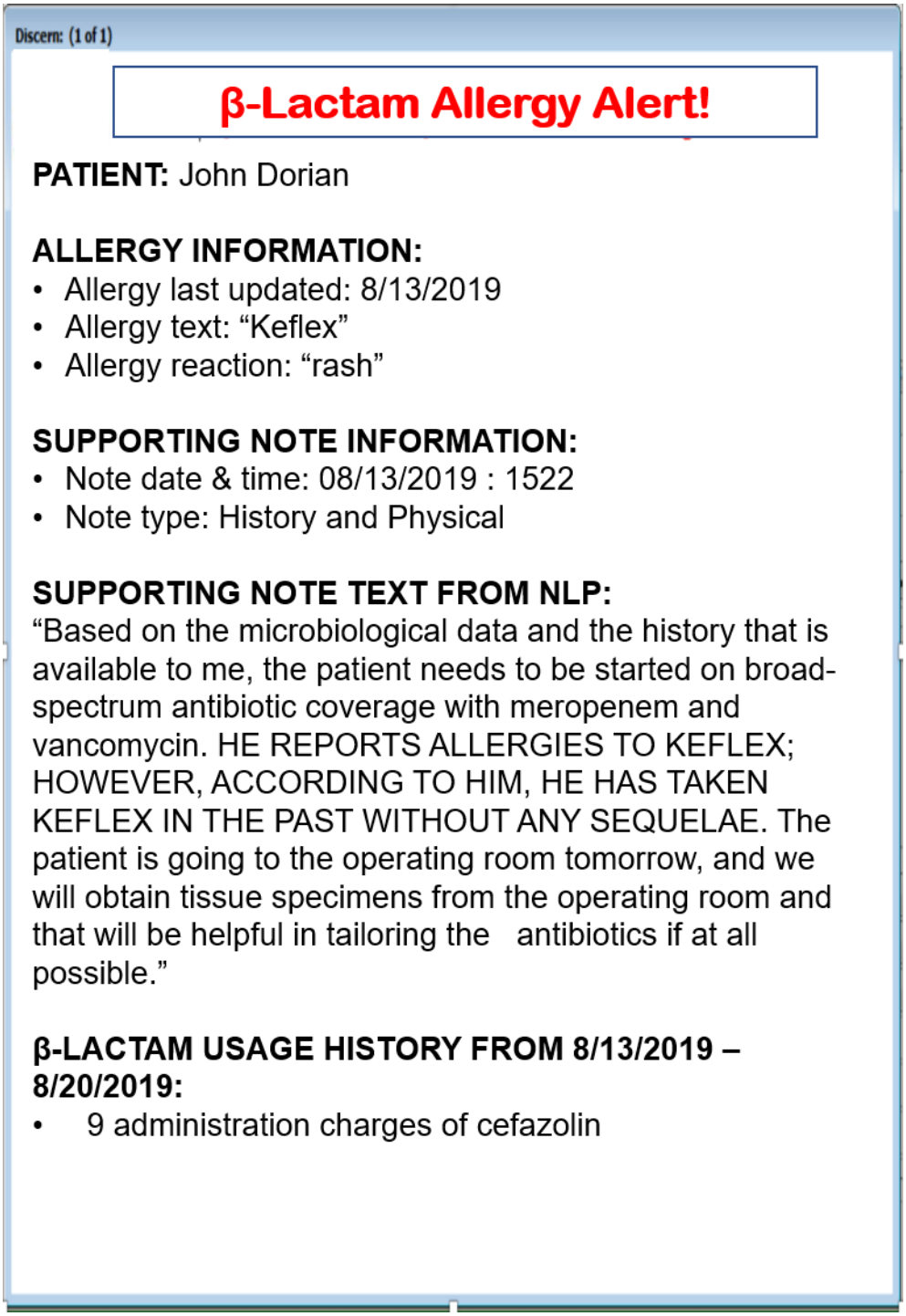
Q1-3 Using only the information in this alert, how confident would you feel prescribing/verifying **Ceftriaxone** for the patient contained in the alert? Please answer below with 1 being not confident at all and 10 being fully confident.

	1	2	3	4	5	6	6	7	8	9	10
Confidence prescribing/verifying Ceftraixone ()											

End of Block: Alert 1 - no NLP

Start of Block: Alert 1

Q2 Alert 1 - NLP



The following link will direct you to a chart created by Northwestern University which details the cross-reactivity of commonly used beta-lactam products:

Beta-lactam Cross Reactivity Chart

Use of this chart is not required to answer the following questions but it may be referenced if desired.

Q2-1 Using only the information in this alert, how confident would you feel prescribing/verifying **Cefazolin** for the patient contained in the alert? Please answer below with 1 being not confident at all and 10 being fully confident.

	1	2	3	4	5	6	6	7	8	9	10
Confidence prescribing/verifying Cefazolin ()											

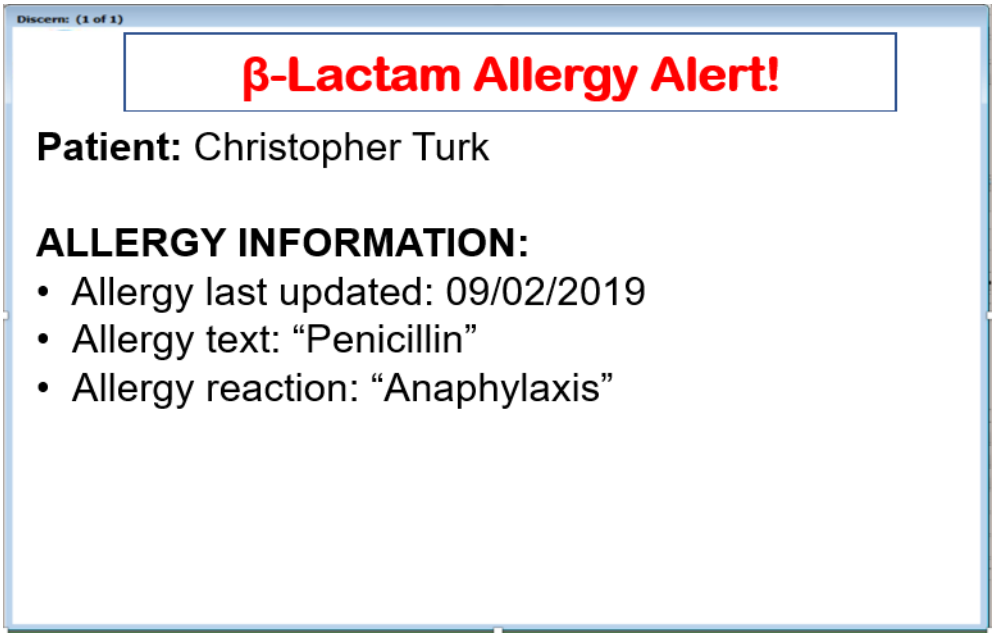
Q2-2 Using only the information in this alert, how confident would you feel prescribing/verifying **Ceftriaxone** for the patient contained in the alert? Please answer below with 1 being not confident at all and 10 being fully confident.

	1	2	3	4	5	6	6	7	8	9	10
Confidence prescribing/verifying Ceftriaxone ()											

End of Block: Alert 1

Start of Block: Alert 2 - No NLP

Q3 Alert 2 – no NLP



he following link will direct you to a chart created by Northwestern University which details the cross-reactivity of commonly used beta-lactam products:

Beta-lactam Cross Reactivity Chart

Use of this chart is not required to answer the following questions but it may be referenced if desired.

Q3-1 Using only the information in this alert, how confident would you feel prescribing/verifying **Cefepime** for the patient contained in the alert? Please answer below with 1 being not confident at all and 10 being fully confident.

1 2 3 4 5 6 6 7 8 9 10

Confidence prescribing/verifying Cefepime ()	

Q3-2 Using only the information in this alert, how confident would you feel prescribing/verifying **Piperacillin/tazobactam** for the patient contained in the alert? Please answer below with 1 being not confident at all and 10 being fully confident.

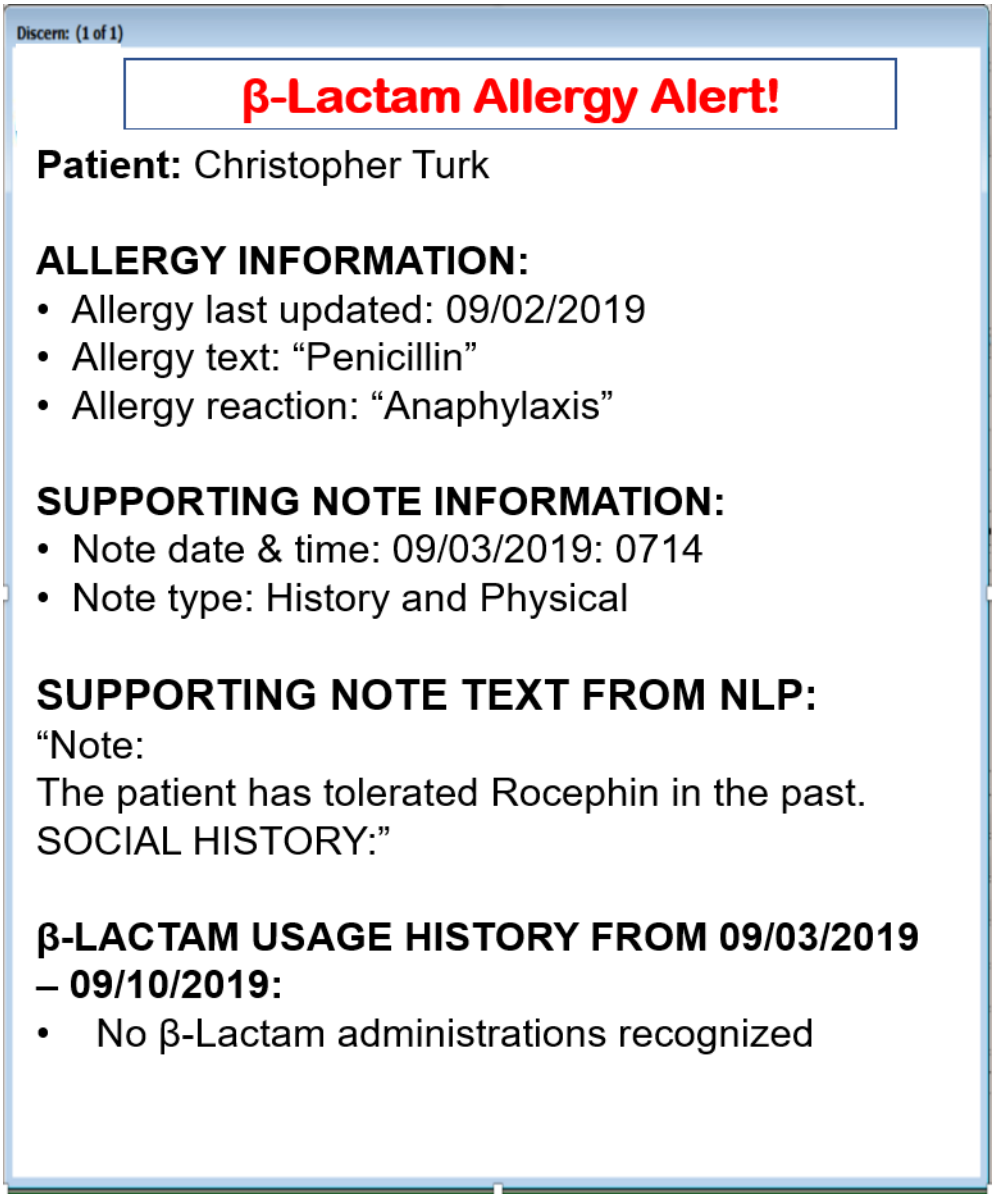
1 2 3 4 5 6 6 7 8 9 10

Confidence prescribing/verifying Piperacillin / tazobactam ()	

End of Block: Alert 2 - No NLP

Start of Block: Alert 2

Q4 Alert 2 – NLP



The following link will direct you to a chart created by Northwestern University which details the cross-reactivity of commonly used beta-lactam products:

Beta-lactam Cross Reactivity Chart

Use of this chart is not required to answer the following questions but it may be referenced if desired.

Q4-1 Using only the information in this alert, how confident would you feel prescribing/verifying **Cefepime** for the patient contained in the alert? Please answer below with 1 being not confident at all and 10 being fully confident.

	1 2 3 4 5 6 6 7 8 9 10
Confidence prescribing/verifying Cefepime ()	

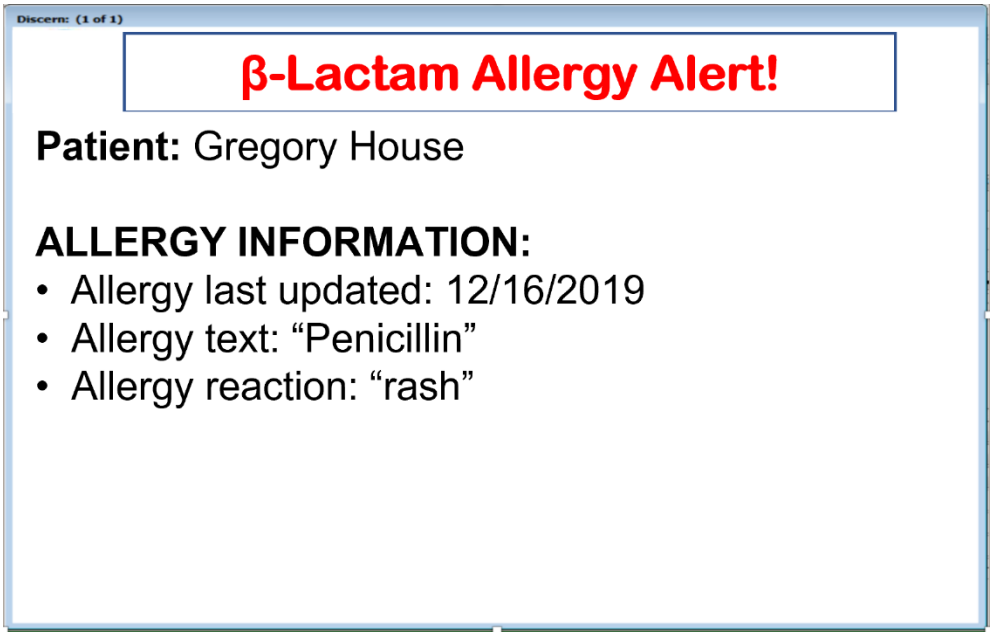
Q4-2 Using only the information in this alert, how confident would you feel prescribing/verifying **Piperacillin/tazobactam** for the patient contained in the alert? Please answer below with 1 being not confident at all and 10 being fully confident.

	1 2 3 4 5 6 6 7 8 9 10
Confidence prescribing/verifying Piperacillin / tazobactam ()	

End of Block: Alert 2

Start of Block: Alert 3 - No NLP

Q5 Alert 3 – no NLP



The following link will direct you to a chart created by Northwestern University which details the cross-reactivity of commonly used beta-lactam products:

Beta-lactam Cross Reactivity Chart

Use of this chart is not required to answer the following questions but it may be referenced if desired.

Q5-1 Using only the information in this alert, how confident would you feel prescribing/verifying **Ceftriaxone** for the patient contained in the alert? Please answer below with 1 being not confident at all and 10 being fully confident.

	1	2	3	4	5	6	6	7	8	9	10
Confidence prescribing/verifying Ceftriaxone ()											

Q5-2 Using only the information in this alert, how confident would you feel prescribing/verifying **Piperacillin/tazobactam** for the patient contained in the alert? Please answer below with 1 being not confident at all and 10 being fully confident.

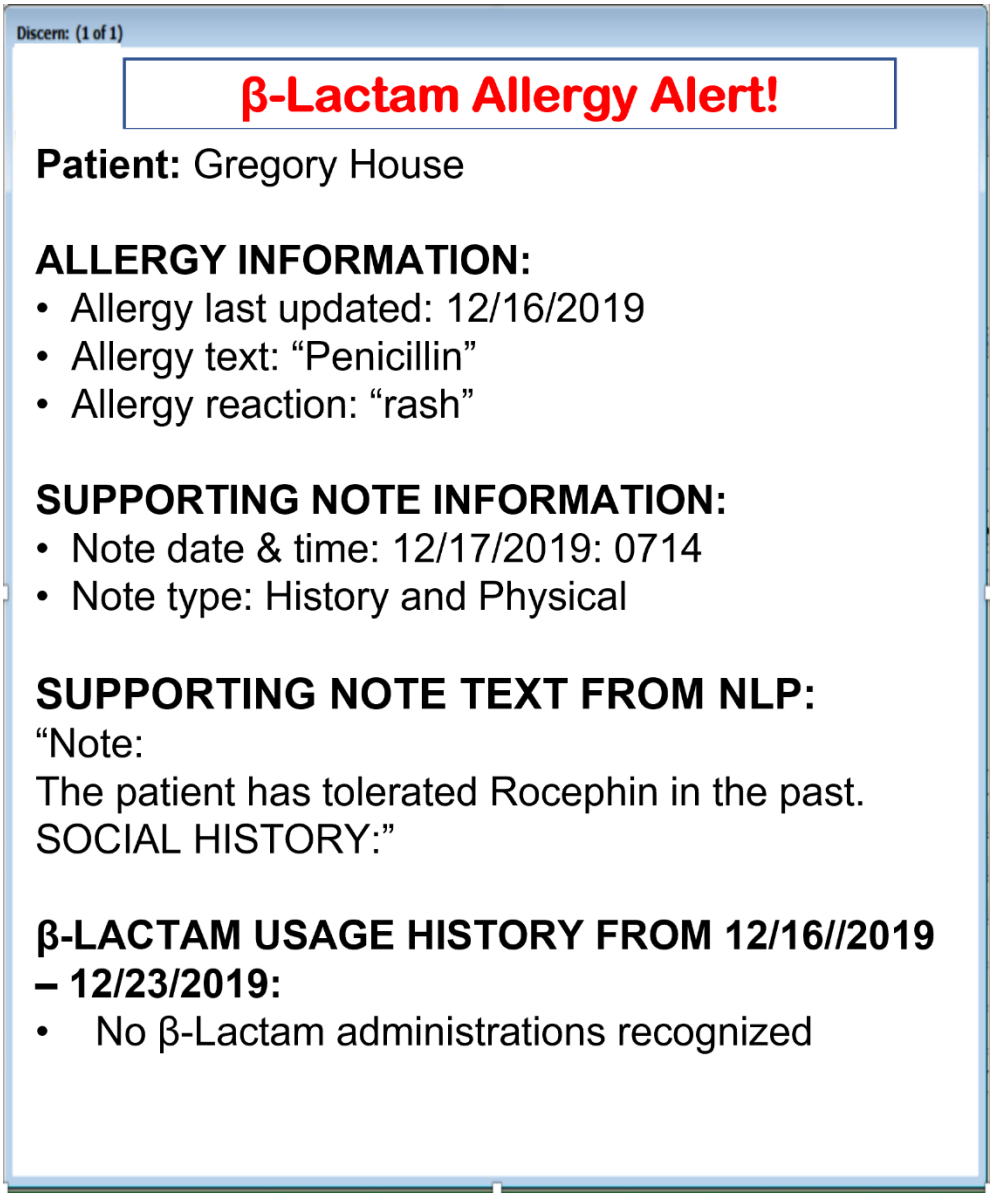
1 2 3 4 5 6 6 7 8 9 10

Confidence prescribing/verifying Piperacillin / tazobactam ()	

End of Block: Alert 3 - No NLP

Start of Block: Alert 3

Q6 Alert 3 – NLP



The following link will direct you to a chart created by Northwestern University which details the cross-reactivity of commonly used beta-lactam products:

Beta-lactam Cross Reactivity Chart

Use of this chart is not required to answer the following questions but it may be referenced if desired.

Q6-1 Using only the information in this alert, how confident would you feel prescribing/verifying **Ceftriaxone** for the patient contained in the alert? Please answer below with 1 being not confident at all and 10 being fully confident.

	1 2 3 4 5 6 6 7 8 9 10
Confidence prescribing/verifying Ceftriaxone ()	

Q6-2 Using only the information in this alert, how confident would you feel prescribing/verifying **Piperacillin/tazobactam** for the patient contained in the alert? Please answer below with 1 being not confident at all and 10 being fully confident.

	1 2 3 4 5 6 6 7 8 9 10
Confidence prescribing/verifying Piperacillin / tazobactam ()	

End of Block: Alert 3

Start of Block: Summary Questions

Q7

Q 7-1 Please rank the **Allergy Information portion** of the alert in terms of **usefulness of determining the legitimacy of the beta-lactam allergy**:
With 5 being Extremely useful and 0 being not useful at all.

	Not at all useful		Moderately useful		Extremely useful	
	0	1	2	3	4	5
Allergy Information ()						

Page Break

Q8

Q 8-1 Please rank the **Supporting Note Information and Text portion** of the alert in terms of **usefulness in determining the legitimacy of the beta-lactam allergy**:
With 5 being Extremely useful and 0 being not useful at all.

	Not at all useful		Moderately useful		Extremely useful	
	0	1	2	3	4	5
Supporting Note Information ()						

Page Break

Q9

Q 9-1 Please rank the **Beta-Lactam Usage History portion** of the alert in terms of **usefulness in determining the legitimacy of the beta-lactam allergy**:
With 5 being Extremely useful and 0 being not useful at all.

	Not at all useful		Moderately useful		Extremely useful	
	0	1	2	3	4	5
Supporting Note Text ()						

Page Break

Q10

Q10-1 Please rank the **alert as a whole** in terms of **usefulness in determining the legitimacy of the beta-lactam allergy**:
With 5 being Extremely useful and 0 being not useful at all.

	Not at all useful		Moderately useful		Extremely useful	
	0	1	2	3	4	5
Supporting Note Text ()						

Page Break

Q 10-2 When considering the **format and content of the simulated alert as a whole**, rank your agreement with the following statements:

	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree
	0	1	2	3	4
The format of the alert is understandable ()					
The content of the alert is understandable ()					
I know where in the electronic health record the alert information was obtained ()					

Page Break

Q 10-3 When considering the **usefulness and application of the simulated alert as a whole**, rank your agreement with the following statements:

	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree
	0	1	2	3	4
This alert would reduce the time required to evaluate Beta-lactam allergies ()					
This alert would be useful for my care setting ()					
This alert would improve the care of my patients ()					

Page Break

Q Q11-1 What additional information would be helpful to be contained in the alert?

_____

Q 11-2 What other comments or feedback would you like to provide concerning the alert?

_____

End of Block: Summary Questions

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