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Improving Methodology to Identify True Community Carbapenem-resistant *Enterobacteriaceae* (CRE) and Assessing Prior Healthcare Exposures to Quantify Risk for CRE Diagnosis Upon Hospital Admission

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Northeastern University
2018

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An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Public Health in
Epidemiology
2020

ABSTRACT

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By Siyeh Gretzinger

Antibiotic resistant bacteria are a major threat to public health due to the high morbidity and mortality. Carbapenem-resistant *Enterobacteriaceae* (CRE) has been identified as an urgent threat given its difficulty to treat. CRE typically presents asymptomatically, making it challenging to determine patients' colonization status upon hospital admission and whether these infections are arising from the community or from prior healthcare exposures. The purpose of this study was to use information available in the Georgia hospital discharge database to evaluate the misclassification of community-associated CRE and develop a model to predict patient risk of having CRE carriage or infection upon hospital admission. A case-control study was performed using hospital encounter information for 281 cases and 233,786 matched controls obtained from two state-based databases. A set of prior healthcare exposures were evaluated as predictors. Multivariate conditional logistic regression was employed for model development. Odds ratios and respective *p*-values were calculated to determine direction and strength for each predictor. Model performance was evaluated using ROC and AUC values. Six percent of community CRE was identified as having a missed prior hospitalization thereby warranting re-classification. The final model identified the following variables to be associated with an elevated risk of CRE upon admission: current admission to long-term acute care hospital (OR=17.7, 95% CI:1.40 – 223.29), use of federal health insurance (OR=2.22, 95% CI:1.40 – 3.54), hospital admission with an infection diagnosis in prior year (OR=2.02, 95% CI:1.42 – 2.87), number of short-term acute care hospitalizations (STACH) in prior year (OR=1.18, 95% CI:1.09 – 1.27), age (OR=1.03, 95% CI:1.02 – 1.04), and mean prior STACH length of stay (OR=1.02, 95% CI:1.02 – 1.03). The model had good discriminatory performance with an AUC = 0.76. Data from this study demonstrated that state-wide hospital discharge databases are an important tool that can be used to validate prior healthcare exposures and develop prediction rules to detect patients at higher risk for CRE. Such prediction rules have significant implications for hospitals across the country as they enhance active surveillance methods and support preemptively screening for high-risk patients.

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ACKNOWLEDGEMENTS

First and foremost, I would like to thank Dr. Scott Fridkin and Chris Bower for all of their guidance and support throughout the thesis process. I would also like to thank the faculty and staff in the Department of Epidemiology for equipping me with the necessary skills and resources to conduct this thesis.

I would like to thank my amazing co-workers at the GA Emerging Infections Program, especially the MuGSI team, for their encouragement, reassurance, and assistance. In addition, a special thank you to all of my incredible friends who made my time at Rollins such a memorable one. I cannot wait to see all the amazing things you all will accomplish!

Finally, I would not be where I am today without the love and support of my family: Steve, Diana, and Fabiola Gretzinger. And to my Grandmother Marilyn whom I dedicate this thesis to.

DISCLAIMER

The primary dataset used in this project was collected by the Georgia Emerging Infections Program (GAEIP). The GAEIP was not involved in the analyses presented in this thesis.

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CHAPTER I: BACKGROUND

Antibiotics are a type of antimicrobial designed to inhibit growth and replication of bacteria (1). The initial discovery of the first antibiotic, penicillin, in 1928, by Alexander Fleming followed by the introduction of other newly discovered antibiotics completely reshaped contemporary medicine practice (1, 2). Life-threatening bacterial infections once deemed incurable could now be effectively treated. Over time and with repeated use, however, bacteria evolved to become resilient to the effects of the antibiotics that were made to destroy them; this occurrence is known as antibiotic resistance. The emergence and spread of antibiotic resistance threaten to outpace the development of new drugs and consequently place efforts to slow the spread of these organisms as a top public health priority.

Pathways to Antibiotic Resistance

Bacteria develop resistance to antibiotics through one or more biological mechanisms: genetic mutation, intrinsic resistance, or transfer of genetic material (1, 2). Bacteria that develop resistance through genetic mutation do so during the reproductive stage. Typically, sporadic mutations will occur at various intervals and will provide the bacteria with an altered genetic code that allows them to survive when exposed to a particular antibiotic or class of antibiotics (2). Bacteria that develop resistance through genetic mutation use three main properties to help them resist the effects of the antibiotics: minimize the intracellular concentrations of the antibiotics, modify the antibiotic target or pathway, and inactivate the antibiotic entirely (2). Another mechanism by which bacteria are resilient is through intrinsic resistance. During intrinsic resistance bacteria are innately able to survive antibiotic exposure due to their inherent structure and functional properties. For example, bacteria may lack a susceptible target for the antibiotic to act on, thereby rendering the antibiotic useless (1). Lastly, bacteria become resistant by obtaining

a resistance mechanism from other resistant bacteria. This process, known as horizontal gene transfer, involves genetic material transferring between bacterial cells through one of three methods: direct or indirect contact, viruses injecting resistance genes into bacteria, or through the acquisition of free-floating DNA with resistance genes from the environment (1, 2). Resistant bacteria frequently live in small numbers within larger bacteria populations among humans. Nonetheless, when exposed to antibiotics, small populations of resistant bacteria may proliferate and become the predominant strain, eventually causing drug-resistant infection (1, 2).

Carbapenem-resistant Enterobacteriaceae Infections

Carbapenem-resistant *Enterobacteriaceae* (CRE) are a type of Gram-negative bacteria that confer broad resistance to most ß-lactam antibiotics including the "last-line antibiotics" carbapenems (3). The mounting burden of Gram-negative antimicrobial resistance stems primarily from the spread of ß-lactamases, which are enzymes that render ß-lactam antibiotics ineffective by binding and hydrolyzing their ring (3). Carbapenem resistance is conferred through a specific type of ß-lactamase known as a Carbapenemase which grants broad resistance to penicillin, cephalosporins, monobactams, and carbapenem antibiotics. Carbapenemases are a particularly serious public health threat due to their ability to spread to other bacteria through horizontal gene transfer. Carbapenem resistance is also conferred through the combination of porin deficiency, which allows decreased entry of the ß-lactam antibiotic into the cell membrane, expression of efflux pumps, which transport antibiotics out of the cell membrane, and extended spectrum ß-lactamases (ESBLs), which grant resistance to all ß-lactams except carbapenems (3, 4).

CRE cause a number of serious infections: intra-abdominal, pneumonia, bloodstream, and most commonly urinary tract (3). Over the last decade, the prevalence of CRE infections has increased, particularly in healthcare settings where they often cause device-associated infections (5). Device-associated infections are those related to equipment used in medical procedures, such

as catheters or ventilators (3, 5). In 2017, the Centers for Disease Control and Prevention estimated that 13,100 CRE infections occurred among hospitalized patients (6). These infections were caused by the two most common types of CRE—*Klebsiella* and *Escherichia* species (6). Patients with carbapenem-resistant infections attributable to *Enterobacteriaceae* pathogens have approximately three times higher mortality than carbapenem susceptible infections (7). CRE infections are extremely concerning due to their high mortality rates, which is estimated to be 6.6% per year in the U.S. (8).

Prominent risk factors for CRE relate to prior healthcare exposures: antimicrobial therapy —specifically carbapenems and fluoroquinolones— admission to an intensive care unit (ICU), presence of indwelling devices, and recurrent hospital admissions in the prior year (9). Other factors such as age and underlying comorbidities have also been shown to heighten the risk of CRE (9). CRE infections are spread primarily by direct contact with an infected person's bodily fluids but transmission also occurs indirectly by touching contaminated fomites (8, 9).

Surveillance for Carbapenem-resistant Enterobacteriaceae Infections

Prior to the 21st century, CRE was relatively uncommon. However, CRE prevalence has nearly doubled in the past 10 years. Drug-susceptible *Enterobacteriaceae* are a common cause of CRE infections, and CDC has warned of CRE's potential to spread in the community. In its most recent threat report, the CDC declared CRE an urgent threat and emphasized the need to boost surveillance efforts to better target interventions (6, 10).

Adequate surveillance of CRE requires accurately classifying the infection into one of three groups: community-associated (CA), healthcare-associated community-onset (HACO), or hospital-onset (HO). These classifications consider two main factors: the existence of prior healthcare exposures and the time at which the culture was collected for testing. CA-CRE infections are those in which the patient has no prior healthcare exposures and the culture is collected within the first three days of hospital admission (10). In contrast, HACO-CRE

infections are those in which the culture was also collected within the first three days of admission, but the patient had prior healthcare exposures (10). Such exposures typically include recent hospitalization, surgery, dialysis, or residence in a long-term care facility less than a year before the onset of illness (10, 11). Lastly, HO-CRE infections are those in which the culture was collected after the 3rd day of admission to the hospital, regardless of prior healthcare exposures (10, 12).

CRE colonization is a major factor contributing to the challenge of accurate disease classification (10-11, 13). Colonization with CRE is typically defined by gastrointestinal tract carriage identified through rectal or fecal sampling. The majority of resistant clone dissemination occurs via colonization in the commensal microflora, which is often undetected unless the colonization leads to infection (11). Despite colonization being a prerequisite for infection, the percentage of colonized patients that progress to active infection is unknown. Recent studies have found that roughly 17% of patients found to be colonized with CRE upon hospital admission progressed to develop clinical infection (11, 13). In 2016, active surveillance employing perirectal swabbing in a US hospital revealed that about 15% of asymptomatic patients admitted to the ICU were colonized with CRE upon admission (14). These asymptomatic patients illustrate how resistant strains spread silently through colonization, posing a serious threat to timely organism identification and containment. Nonetheless, hospitals are unable to culture every hospitalized patient to determine colonization status, making it difficult to determine if CRE cases are arising from the community or from prior healthcare exposures.

Screening for Carbapenem-resistant Enterobacteriaceae Infections in Hospitals

Detecting patients at high-risk of CRE upon admission allows hospital staff to promptly implement infection control guidelines to reduce the risk of transmission. Currently, however, healthcare facilities lack the methods to identify such patients in their facilities. Without these methods in place, high-risk patients that are colonized with CRE are being admitted undetected

and potentially transmitting the infection to other patients causing healthcare associated infections (15-18).

Prior healthcare exposures have been shown to be associated with CRE carriage on admission to an acute care hospital (9, 15-17). Nonetheless, the utility of such variables in the context of a clinical prediction rule to identify high-risk patients for infection control efforts has been minimally evaluated. Studies that have evaluated such a rule, have done so in the setting of other infections including methicillin-resistant *S. aureus* and vancomycin-resistant *Enterobacteriaceae* (15). Findings from these studies suggest that a high proportion of patients who were previously unrecognized carriers were actually colonized (15). The strongest predictor for colonization was a history of more than two previous acute-care hospitalizations in the year before the index culture (18). Such findings illustrate how accurate risk factor profiles of patients harboring antibiotic-resistant strains are useful during the hospitalization assessment stage for selecting cases that require contact precautions.

In addition to improving prompt isolation, the implementation of targeted active surveillance results in cost savings compared with hospital-wide, nontargeted surveillance. Utilizing a prediction rule allows conventional measures for collecting resistant bacterial strains (e.g., rectal swabs) and empirical application of infection control measures to be limited to the subset of individuals deemed “high-risk”, thereby reducing workloads and costs (17-18). To develop a prediction rule, hospitals require access to information pertaining to prior health exposures that involve external facilities. Such information typically resides outside of a given hospital’s internal medical system and is therefore unavailable to healthcare providers. A potential solution to this challenge is to utilize state-wide hospital discharge databases, which contain historical patient-level health information and are becoming increasingly available, to inform predictive models (19).

Researchers at Rush Medical College in Illinois utilized a state-wide discharge database to develop a predictive model for CRE (20). The predictive model successfully incorporated a

patient's prior health exposures to determine their risk of CRE in a hospitalized setting. If other hospitals across the country are able to generate similar models, they will be better equipped to identify high-risk patients during the admission process and consequently target infection control efforts in a more resourceful and efficient way (20). Such forms of active surveillance enhance CRE prevention efforts and help combat the spread of antibiotic resistance.

CHAPTER II

Improving Methodology to Identify True Community Carbapenem-resistant *Enterobacteriaceae* (CRE) and Assessing Prior Healthcare Exposures to Quantify Risk for CRE Diagnosis Upon Hospital Admission

Siyeh Gretzinger, Scott Fridkin, and Chris Bower

ABSTRACT

Antibiotic resistant bacteria are a major threat to public health due to the high morbidity and mortality. Carbapenem-resistant *Enterobacteriaceae* (CRE) has been identified as an urgent threat given its difficulty to treat. CRE typically presents asymptomatically, making it challenging to determine patients' colonization status upon hospital admission and whether these infections are arising from the community or from prior healthcare exposures. The purpose of this study was to use information available in the Georgia hospital discharge database to evaluate the misclassification of community-associated CRE and develop a model to predict patient risk of having CRE carriage or infection upon hospital admission. A case-control study was performed using hospital encounter information for 281 cases and 233,786 matched controls obtained from two state-based databases. A set of prior healthcare exposures were evaluated as predictors. Multivariate conditional logistic regression was employed for model development. Odds ratios and respective *p*-values were calculated to determine direction and strength for each predictor. Model performance was evaluated using ROC and AUC values. Six percent of community CRE was identified as having a missed prior hospitalization thereby warranting re-classification. The final model identified the following variables to be associated with an elevated risk of CRE upon admission: current admission to long-term acute care hospital (OR=17.7, 95% CI:1.40 – 223.29), use of federal health insurance (OR=2.22, 95% CI:1.40 – 3.54), hospital admission with an

infection diagnosis in prior year (OR=2.02, 95% CI:1.42 – 2.87), number of short-term acute care hospitalizations (STACH) in prior year (OR=1.18, 95% CI:1.09 – 1.27), age (OR=1.03, 95% CI:1.02 – 1.04), and mean prior STACH length of stay (OR=1.02, 95% CI:1.02 – 1.03). The model had good discriminatory performance with an AUC = 0.76. Data from this study demonstrated that state-wide hospital discharge databases are an important tool that can be used to validate prior healthcare exposures and develop prediction rules to detect patients at higher risk for CRE. Such prediction rules have significant implications for hospitals across the country as they enhance active surveillance methods and support preemptively screening for high-risk patients.

INTRODUCTION

Antibiotic resistance is a critical public health threat. Each year, more than 2.8 million U.S. residents develop life-threatening infections that are resistant to at least one type of antibiotic used to treat the infection (6). Additionally, more than 35,000 of these people die of resistant infections (6). Treatments for bacterial infections are increasingly limited with the emergence of antibiotic resistance, and in some patients effective treatment options do not exist (6, 21). Antibiotic resistance places a serious burden on the U.S. healthcare system due to costly treatments and production of new broad-spectrum antibiotics.

Carbapenem-resistant *Enterobacteriaceae* (CRE) are multidrug-resistant organisms that pose a significant threat to patients due to their difficulty to treat and associated high mortality rates (6, 21). These organisms have become resistant to all or nearly all antibiotics, including last-resort drugs known as carbapenems (6, 21). The Centers for Disease Control and Prevention (CDC) estimates that roughly 13,000 patients with CRE infections were hospitalized and up to half of patients who developed CRE bloodstream infections died (6). In addition, CRE's ability to spread person-to-person and to other bacteria raises concern that potentially untreatable infections could appear in otherwise healthy people (6).

CRE may present asymptomatically, and therefore it is difficult to determine patients' colonization status upon hospital admission. Many risk factors for CRE colonization are related to prior healthcare exposures including prolonged hospitalization, presence of indwelling devices, severity of underlying disease, low functional status, and exposures to antimicrobials (15, 21). More importantly, patients with a previous hospitalized admission within one year of infection represent a high-risk group for colonization (15-18). If a patient tests positive for CRE in a hospitalized setting, it is difficult to distinguish if the infection is truly arising from the community or from a prior hospitalization that is unknown or undocumented (22). Currently, no simple, cost-effective methods exist to identify these high-risk patients outside intensive care settings (15, 17). Without such methods to determine high-risk patients, colonized patients are being admitted to hospitals undetected and potentially transmitting CRE to other patients (15).

A predictive model is a cost-effective way to identify high-risk patients and target for preemptive isolation (15). As state-based hospital discharge databases become increasingly available, they can be used to obtain historical patient-level healthcare exposures and diagnosis codes from external facilities, which would otherwise be unavailable to hospital providers (19). We hypothesized that the Georgia hospital discharge database could be used to evaluate the misclassification of community-associated CRE and develop a model that discriminates patients with a higher risk of CRE upon hospital admission.

METHODS

Study Design

This study used a retrospective approach to test the hypothesis that the Georgia hospital discharge database could be utilized to evaluate the misclassification of community-associated CRE and develop a model that discriminates patients with a higher risk of CRE. Misclassification was determined by assessing true patient prior hospitalization status. The methodology was based on a model built by Lin et. al. at Rush Medical College in 2019.

Primary Data Source

A matched case-control study was performed using data from two Georgia state-based databases: the health department hospital discharge database and the Georgia Emerging Infections Program (EIP) Multi-site Gram-negative Surveillance Initiative (MuGSI) CRE database. The hospital discharge database contains comprehensive patient-level data for all non-newborn hospitalizations in acute care settings (general hospital and long-term acute care) and inpatient rehabilitation facilities. For this study, a subset of the statewide data was accessed which included all hospitalizations within the 20 county Atlanta Metro Statistical Area (MSA). Hospital encounter data includes a unique patient identifier, facility labels, and encounter-specific characteristics (admission dates, discharge dates, diagnosis codes, length of stay, and patient health insurance). Classification of hospitals were defined as either long-term acute care hospital (LTACH) or short-term acute care hospital (STACH) using both the GA hospital discharge database and the MuGSI CRE database. Data were used from the Centers for Medicare and Medicaid requirements, where the average inpatient length of stay for LTACHs were greater than 25 days, whereas STACH were less than 25 days.

The MuGSI CRE database contains incident CRE cases within the eight counties of metropolitan Atlanta, also known as Health District Three (HD3), identified through active-population and laboratory-based surveillance. An incident case was defined as a patient's first

CRE-positive culture per species including *E. coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, *Klebsiella aerogenes*, or *Enterobacter cloacae* that was resistant to one or more carbapenems (Ertapenem, Imipenem, Meropenem, or Doripenem) according to the Clinical & Laboratory Standards Institute (CLSI) breakpoints and/or new culture collected more than 30 days after the patient's initial case-defining positive culture.

1. Validation of CRE Classification

Incident CRE cases from 2016–2017 were matched to MSA hospital discharge data from 2015–2017. The discharge database used a longitudinal ID as a unique encounter identifier. Longitudinal ID's were created for CRE cases using their first and last name, gender, and date of birth. Once matched to the discharge data, the number of days between the specimen collection date for community-associated CRE and their last hospital exposure (most recent discharge) were calculated. All matched records with inpatient encounters that preceded the specimen collection date by 0–365 days were flagged as possible misclassified community-associated CRE cases. Flagged cases were compared on prior hospitalization status, which was determined by the medical record reviewers at EIP. Cases where medical record reviewer determination of prior hospitalization was different from hospital discharge data, were classified as discordant.

Discordant cases were categorized into one of two groups. The EIP defined group comprised cases that had a prior hospitalization listed by the medical record reviewers but did not have a prior hospitalization per the GA discharge database. The state defined group were cases that did not have a prior hospitalization listed by the medical record reviewers but did have a prior hospitalization per the GA discharge database. To assess the discrepancy in the prior hospitalization determination, EIP discharge information data were verified by manually checking case report forms and reviewing patient's medical records. In addition, a match-likelihood test was performed using LinkPlus software to ensure that cases from the EIP defined

group were truly not hospitalized in the year prior rather than unmatched due to a misspelling in the longitudinal ID.

2. CRE Predictive Model

Cases & Controls

Index cases were defined as an adult (≥18 years of age) patient that had at least one hospital encounter from January 1st, 2016 to December 31st, 2017 and had a positive CRE culture collected within the first three days of hospitalization (i.e. hospital-onset CRE cases were not eligible). For analyses, only the first CRE-positive culture per patient, regardless of pathogen species, was considered to be a case. In addition, patients were only included if they were hospitalized at a GA hospital (STACH or LTACH) in the three days prior to or within 365 days after the specimen collection date. Patients who had a CRE-positive culture but were never hospitalized or hospitalized more than 365 days after their specimen collection date, were excluded. A 365-day window was chosen because CRE patients remain colonized for extended periods of time (11, 15-17).

Controls were defined as adults (≥18 years of age) without a positive CRE-culture, admitted to the same hospital during the same month and year that an index case was reported. Duplicate controls were removed to ensure that each control was only matched to a single case. Due to the large number of eligible controls, the number of controls that could be matched to a single case were not limited. Consequently, more controls came from larger hospitals with greater number of admissions per month.

Model Development & Performance

A CRE predictive model recently developed by researchers at Rush Medical College was validated and used as a template to construct models for our study population. A set of variables were evaluated based on their availability in the GA hospital discharge database to assess a

patient's prior healthcare exposures and predict their risk of CRE. Variable significance from the model developed was compared to the significance seen by the model developed in Illinois (20).

A list of prior healthcare exposures found to be significant by the Illinois model were used as predictors in our model. These exposures occurred anytime in the 365 days prior to the qualifying hospitalization and included: number of STACH and LTACH hospitalizations and mean length of stay. As a proxy for antibiotic exposure, hospitalizations with an infection diagnosis code were evaluated using the ICD-9 codes associated with each admitting diagnosis available in the GA Hospital Discharge Dataset. These ICD-9 codes were translated to ICD-10 codes using General Equivalence Mappings from the Centers for Medicare and Medicaid Services (23).

In addition to the variables found to be significant by the researchers in Illinois, the type of health insurance used to pay for hospitalization costs was also evaluated to determine if it was associated with patients' predicted risk of CRE. To assess the effect of health insurance, this category was divided into three groups: federal, private, and self-pay. Federal insurance included any form of Medicare or Medicaid. Private insurance included health maintenance organizations, preferred provider organization, Blue Cross Blue Shield, commercial insurance, and worker's compensation. Private insurance was used as the reference category for comparison.

Conditional logistic regression models were constructed to obtain parameter estimates for the predictors of interest. Univariate models were used to evaluate and compare individual parameter estimates for each variable to those obtained from the multivariate models. Two fully adjusted models were developed. The first model contained all of the same variables found to be significant by the Illinois model: age, sex, number of prior STACH and LTACH visits, mean prior STACH and LTACH lengths of stay, current hospital type (STACH versus LTACH), and

prior admission with infection diagnosis. The second model included all of the aforementioned predictors as well as patient health insurance: federal, private, and self-pay.

Using the parameter estimates from the final model that included patient health insurance, predicted CRE probabilities for each observation were generated. Then, each patient's maximum CRE probability was calculated and stratified into the following CRE risk groups: 0%–4%, 5–9%, 10%–14%, 15%–19%, 20%–29%, and ≥30%. To assess the performance of the Illinois model in our population, another set of predicted probabilities was generated for each observation based on the parameter estimates from their model. Receiver operating characteristic (ROC) curves were used to evaluate model performance.

All statistical tests were two-sided *t* tests, and *p* values of <0.05 were considered statistically significant. Data were analyzed using SAS 9.4 (Cary, NC, USA).

RESULTS

Validation of CRE Classification

Overall, 655 CRE cases met the case definition during the study period. Out of all the cases identified, 125 (19%) cases had discrepancies regarding hospitalization in the year prior to their positive CRE culture. From the 125 cases with discrepancies, 73 (11%) were classified as having a prior hospitalization per medical record review but had no prior hospitalization in the hospital discharge database (EIP defined group). Conversely, 52 (8%) cases had a prior hospitalization in the hospital discharge database but had no prior hospitalization per medical record review (state defined group).

EIP Defined Group

A total of 73 cases had a prior hospitalization in the EIP CRE database, but no records in the discharge database. Of these 73 cases, 34 (47%) had a discharge date that occurred more than 12 months before the positive CRE culture. Thirty-nine (53%) cases had no prior discharge

information in the GA hospital discharge database despite confirmation through medical record review that they were admitted.

State Defined Group

A total of 52 cases had a prior hospitalization in the discharge database and no records in the EIP CRE database. Of the 52 cases, only 10 (6%) were reclassified from community-associated CRE to hospital-associated community-onset (HACO) CRE (Table 1). Among these 10 reclassified cases, nine (90%) had a prior hospitalization at a different hospital than where they were treated for the index case. For CRE cases classified as HACO and hospital-onset, 27 (7%) and 15 (13%) respectively, were identified as having a missed prior hospitalization by medical record reviewers (Table 1). However, no reclassification was warranted given these cases were classified as HACO based on other prior healthcare exposures. Among the 27 HACO cases, all had prior hospitalizations at a different hospital than where they were treated for the index case. Across both groups, 52 (8%) of all cases had a missed prior hospitalization (Table 1).

CRE Model Derivation & Performance

The subset of cases that were eligible for model development was limited to those who were hospitalized within the specified window and had their specimen collected within the first three days of hospitalization. Consequently, only 281 from the 655 identified cases were eligible. These 281 index cases were matched to 233,786 controls from 28 different hospitals. The distributions of age, race, and gender for both cases and controls are shown in Tables 2 and 3, respectively. The common CRE isolated from the 281 cases were *Klebsiella pneumoniae* (39.9%), *E. coli (36.3%)*, *Enterobacter cloacae (19.6%), Klebsiella aerogenes (2.5%)*, and *Klebsiella oxytoca* (1.8%). CRE was isolated from urine (92.5%), blood (5.0%), peritoneal fluid (1.8%), and joint/synovial fluid (0.7%). The types of infection associated with CRE included urinary tract (73.3%), bacteremia/sepsis (5.3%), and peritonitis (1.8%) (Table 2).

Patient characteristics of cases were compared to those of their corresponding controls and are shown in Table 4. Cases tended to represent older patients (average age 65 vs. 52 years) who had more STACH hospitalizations in the prior 365 days (average number 2.4 vs. 1.5 hospitalizations) and a higher mean STACH length of stay (7.9 vs. 4.7 days) and LTACH length of stay (32.8 vs. 21.9 days). In addition, cases compared to controls were two times more likely to have an admitting infection diagnosis (OR=2.02, 95% CI:1.42 - 2.87, p<.0001), and two times more likely to have federal health insurance (OR=2.22, 95% CI:1.40 - 3.54, p=0.0007).

Additional patient characteristics of cases are reported in Tables 5a and 5b. From 281 cases, 62.6% were found to have been hospitalized on the same day as or within 30 days of their specimen collection date. Two hundred and thirty-five (84%) cases had some type of healthcare exposure in the 365 days before their positive culture. From these 235 cases, 70.8% had a prior hospitalization, 57.3% had an indwelling device, 39.1% were a resident at a long-term care facility, 29.5% had surgery, and 28.5% had a hospitalization where they were treated with antibiotics. Additionally, 44.8% of all cases had between one and three prior hospitalizations, which occurred at an STACH facility that was different from the facility where they were treated for CRE.

The variables found to be associated with an elevated risk of CRE are reported in Table 4 and include: current admission to LTACH (OR=17.7, 95% CI:1.40 - 223.29, p=0.03), federal health insurance (OR=2.22, 95% CI:1.40 - 3.54, p=0.0007), prior hospital admission with an infection diagnosis (OR=2.02, 95% CI:1.42 - 2.87, p<.0001), number of prior STACH hospitalizations (OR=1.18, 95% CI:1.09 - 1.27, p<.0001), age (OR=1.03, 95% CI:1.02 - 1.04, p<.0001), and mean STACH length of stay (OR=1.02, 95% CI:1.02 - 1.03, p<.0001). Results from variable significance comparison between the Illinois model and the model developed in this study are presented in Table 6. Variables including age (OR=1.04, 95% CI:1.03 – 1.05, p<.0001 and OR=1.02, 95% CI:1.01- 1.03, p<.0001), number of prior STACH hospitalizations

(OR=1.20, 95% CI:1.11 – 1.30, P p<.0001 and OR=1.03, 95% CI:1.01 – 1.06, p=0.02), mean STACH length of stay (OR=1.02, 95% CI: 1.02 – 1.03, p<.0001 and OR=1.04, 95% CI:1.03 – 1.06, p<.001), and prior infection diagnosis (OR=2.03, 95% CI:1.43 – 2.87, p<.0001 and OR=3.03, 95% CI:2.23 – 4.12, p<.001) were all associated with a greater risk of CRE in both models. However, the number of prior STACH hospitalizations was both more significant and associated with a greater risk of CRE in the Georgia model than in the Illinois model (OR=1.20, 95% CI:1.11 - 1.30, p< .0001 vs. OR=1.03, 95% CI:1.01 – 1.06, p=0.02). Conversely, the number of prior LTACH hospitalizations was not significant in the Georgia model but was found to be significant in the Illinois model (OR=1.66, 95% CI:0.52 - 5.35, p=0.39 vs. OR=2.32, 95% CI:1.94 – 2.78, p<.001).

The AUC for the fully-adjusted model without health insurance was 0.74 and the AUC for the fully-adjusted model including health insurance was 0.76 (Figure 1). Both models performed similar to the model developed in Illinois, which had an AUC value of 0.81. Forcing the Illinois model parameter estimates onto our data to evaluate its performance yielded an AUC value of 0.73.

Of all admissions in the months studied, the predicted frequency of admission in distinct CRE probability categories were as follows: 39.0% of patients in risk 0–4%, 19.4% of patients in risk 5–9%, 13.0% of patients in risk 10–14%, 12.2% of patients in risk 15–19%, 9.5% of patients in risk 20–29%, and 6.9% of patients in risk ≥30% (Table 7).

DISCUSSION

Discharge Database Validation of CRE Data

The state-wide hospital discharge database is an important tool to validate prior hospitalization status for CRE cases captured in Georgia EIP population-based surveillance. In assessing whether an incident CRE case is community-acquired or healthcare-associated community-onset, medical record reviewers are prone to miss a CRE patient's hospitalization history. In this study, 19% of all 655 eligible CRE cases were found to have discrepancies regarding hospitalization in the year prior to their positive CRE culture. For CRE patients that were hospitalized prior to index case, patient's previous hospitalization occurred at a different facility and was not noted in the medical record. For CRE patients that were treated in outpatient settings, the outpatient records may not detail previous hospitalizations.

Through the evaluation, 11% of cases were unexpectedly found to have a prior hospitalization listed by the medical record reviewers but none found in the state-wide hospital discharge database. One reason for this was a misclassified hospitalization, wherein the patient was not actually admitted for hospitalization but instead only visited the emergency department or underwent an outpatient surgery. A secondary reason was that a prior hospitalization at a different hospital was noted in the patient's medical record, but reviewers were unable to verify if it occurred in the year prior due to lack of access to outside hospital medical records. Lastly, a third reason that was identified was that cases were hospitalized out-of-state and therefore not captured by the discharge database.

Recent public health surveillance data suggests that a majority of CRE occurs outside of hospital settings and may be indicative of colonization (10-11, 13). However, it remains unclear if these infections are truly arising from the community or from prior healthcare exposures that are either unknown or undocumented (9, 14-17). This study found that 8% of all cases had a missed prior hospitalization and 6% of cases warranted reclassification, indicating that validation of prior

hospitalization status proves worthwhile. Given the degree of comprehensive information available in the hospital discharge database, results from this study underscore the importance of utilizing this database as a resource for surveillance epidemiologists to routinely validate patients' prior hospitalization status to help improve prior healthcare exposure data and epidemiological classification accuracy (17-20). In doing so, it is possible to gain a better understanding of true infection origin and consequently target public health efforts to mitigate transmission.

CRE Predictive Model

The model built using information available in the state-wide hospital discharge database was found to have good discriminatory performance in identifying patients with a greater risk of CRE. Specifically, information pertaining to frequency (OR=1.18, 95% CI:1.09 - 1.27, p<.0001) and duration of healthcare exposure (OR=1.02, 95% CI:1.02 - 1.03, p<.0001), prior infection diagnosis (OR=2.02, 95% CI:1.42 - 2.87, p<.0001), and type of health insurance (OR=2.22, 95% CI:1.40 - 3.54, p=0.0007) were found to be strong predictors of CRE infection. Moreover, this study demonstrated that the model developed by researchers in Illinois performed just as well as the model developed in this study. This suggests that the Illinois model could be applicable to other regional healthcare networks by integrating the parameter estimates from their model to obtain predictive CRE probabilities for their unique population in the future.

The model developed in this study employs data pertaining to the year before admission made available through the state-wide hospital discharge database and has the potential to be automated to alert infection control personnel at the time of a patient's admission. In addition, the model developed incorporates information from all prior hospitalizations including those that occurred at different hospitals, making this method of CRE detection more accurate than current methods employed at hospitals. Existing strategies to identify high-risk patients for CRE or other multidrug-resistant organisms are suboptimal (25-29). Generally, hospitals screen patients being admitted directly from other healthcare facilities, including LTACHs. However, this method

misses patients being admitted directly from home who were previously admitted to a healthcare facility (16, 24). Another approach includes relying on patients themselves to report prior healthcare exposures, which has the potential for recall bias and requires that hospital staff invest more time asking questions (15, 25-27). Lastly, current prediction models that exist to identify high-risk patients rely solely on the information available in medical records which are typically limited to the admitting hospital's system (26-27). The predictive model developed in this study withstands these limitations, making it a reliable tool for active hospital surveillance.

In addition to providing a prediction rule for hospitals to detect high-risk patients, this study validated the performance of an external model to determine if it could be applicable in other geographic regions. Evaluation of the Illinois model in this study population resulted in good discriminatory performance (AUC = 0.73), indicating that one standardized model may be transferrable to other patient populations in different geographic regions. Such findings have important implications for healthcare facilities across other states as it provides a framework for them to both streamline and improve prompt detection and isolation of high-risk individuals. Nonetheless, each health jurisdiction may want to modify the model to incorporate characteristics that are specific to their patient population. For example, in this study incorporating the type of health insurance improved model performance (AUC=0.74 vs. AUC=0.76). Similarly, other health jurisdictions may have access to different variables pertaining to patients' hospitalization encounters, which would inform their predictive models.

There were limitations to this study. First, obtaining access to the information available in the state-wide hospital discharge database in a timely manner proved challenging. The effectiveness of the models relies on having data in real-time to actively detect patients at high risk of CRE upon admission. However, due to the sensitive nature of patient health data, getting access to these databases typically takes long periods of time. If health departments can find ways to enable hospitals with consistent access to these databases, predictive models can be implemented in real-time during the admission assessment stage. Second, the hospital discharge

database does not contain information pertaining to exposures in skilled nursing facilities, which have been shown to play an important role in CRE carriage (24, 30-31). Third, the hospital discharge database does not capture out-of-state hospitalizations, which would potentially bias results. Fourth, the hospital discharge database relies on reporting from hospitals, which they sometimes fail to do or do incorrectly, causing gaps and misinformation. Lastly, the model was developed to fit the epidemiology of CRE in the Atlanta metropolitan area using patients who were captured by GA EIP surveillance, which only encompasses eight counties that are part of Atlanta's metropolitan area. Thus, results may not be generalizable and would warrant validation. As with our validation of the Illinois model, other health jurisdictions may find that some variables need not be retained in the model to maintain good performance or that additional variables must be included to improve performance.

Despite these limitations, this study had several strengths. To our knowledge, this study was the first to assess the performance of an external CRE predictive model and evaluate its use in a different geographical setting. In addition, it was the first time that the hospital discharge database was used to validate routine GA EIP MuGSI surveillance. Lastly, this study provides support for previous research findings indicating that prior healthcare exposures play an important role as risk factors for CRE infection (9-11, 15, 17). Particularly, having multiple hospital admissions (OR=1.18, 95% CI:1.09 - 1.27, p<.0001) and receiving antibiotic treatment for a prior infectious diagnosis (OR=2.02, 95% CI:1.42 - 2.87, p<.0001) elevated the risk for infection. Such data can help inform hospital clinicians about the best course of action for preemptive infection control measures (30, 32-36).

In summary, this study demonstrated how state-wide hospital discharge databases are used to validate prior healthcare exposures and develop prediction rules to detect patients at higher risk for CRE. Validation of the Illinois model showed how a model developed in one geographical region could serve as a template for other health jurisdictions to adopt or generate unique models that better fit their target patient population. This study provides further evidence

that prediction rules can enhance active surveillance methods in hospitals and prevent ongoing transmission of high-risk infections not limited to CRE, thereby helping combat the proliferation of antibiotic resistant bacteria.

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TABLES

Table 1. Number of missed prior hospitalizations in first-time CRE cases by epi classification, 2016–2017 EIP Cohort

	Epi classification of first-time CRE cases			
	Community-associated N=155	**Healthcare-associated community-onset** N=384	**Hospital** N=116	**Total** N=655
Total number (%)	10 (6)	27 (7)	15 (13)	52 (8)

Table 2. Demographics and clinical characteristics of community-onset incident [a] CRE cases obtained from 2016-2017 EIP surveillance data

	Patients with Positive CRE Culture (N=281)	
	No. / Mean	**% / SD**
Patient Demographics		
Sex		
Female	168	59.8
Male	113	40.2
Age (y)	65.3	18.4
Age Categories (y)		
0-17	0	0.0
18-49	61	21.7
50-64	52	18.5
65-79	98	34.9
80+	70	24.9
Race		
White	118	42.0
Black/African American	138	49.1
American Indian	0	0.0
Asian	6	2.1
Hawaiian/Pacific Islander	1	0.4
Unknown	16	5.7
Ethnicity		
Hispanic or Latino	9	3.2
Not Hispanic or Latino	262	93.6
Unknown	9	3.2
Infection Characteristics		
Culture Source		
Non-sterile site		
Urine	260	92.5
Any sterile site		
Blood	14	5.0
Peritoneal fluid	5	1.8
Joint/synovial fluid	2	0.7
Organism		
Klebsiella pneumoniae	112	39.9
Escherichia coli	102	36.3
Enterobacter cloacae	55	19.6
Enterobacter aerogenes	7	2.5
Klebsiella oxytoca	5	1.8

Type of Infection Associated with Culture		
UTI	206	73.3
Bacteremia/Sepsis	15	5.3
Peritonitis	5	1.8
Pneumonia	0	0.0
None	40	14.2
Underlying clinical conditions		
None	19	6.8
Chronic obstructive pulmonary disease	62	22.1
Chronic renal insufficiency	69	24.6
Congestive heart failure	65	23.1
Decubitus/pressure ulcer	72	25.6
Diabetes	120	42.7
Neurologic problems	74	26.3
Urinary Tract Problems/Abnormalities	48	17.1
Obesity	53	18.9
Stroke	65	23.1
Dementia	64	22.8
Hemiplegia	36	12.8
Paraplegia	0	0.0
Surgical Wound	0	0.0
Burn	0	0.0
Peripheral vascular disease	12	4.3
Malignancy	34	12.1

a Case definition: Only patients who were hospitalized subsequent to positive CRE culture were included and only the first positive CRE culture per patient was eligible, regardless of organism type

Table 3. Demographics of adult matched [a] controls obtained from 2015–2017 GA hospital discharge database

	Controls (N = 233,786)	
	No. / Mean	**% / SD**
Patient Demographics		
Sex		
Female	146,356	62.6
Male	87,430	37.4
Age (y)	52.0	20.1
Age Categories (y)		
0 – 17	0	0.0
18 – 49	107,613	46.0
50 – 64	52,782	22.6
65 – 79	50,673	21.7
80+	22,718	9.7
Race		
White	111,937	47.9
Black/African American	98,856	42.3
American Indian	760	0.3
Asian	6,623	2.8
Hawaiian/Pacific Islander	147	0.1
Multiracial	15,463	6.6
Admitting Hospital		
Emory Decatur	15,671	6.7
Emory Hillandale	1,009	0.4
Emory Johns Creek	1,535	0.7
Emory Rehabilitation	57	0.02
Emory University	16,866	7.2
Emory Midtown	13,373	5.7
Emory St. Joseph's	5,647	2.4
Eastside Medical Center	1,581	0.7
Grady Memorial	26,504	11.3
Gwinnett Medical Center	12,323	5.3
Gwinnett Medical Center-Duluth	365	0.2
Kindred Hospital-Atlanta	14	0.01
Miller County	47	0.02
Northside	30,888	13.2
Peachford	689	0.3
Piedmont Fayette	2023	0.9

Piedmont Henry	3112	1.33
Piedmont	27283	11.7
Piedmont Newton	1347	0.6
Rockdale Medical Center	2108	0.9
Select Specialty Hospital-Atlanta	31	0.01
Southern Regional Medical Center	2575	1.1
Wellstar Atlanta Medical Center	16623	7.1
Wellstar Cobb	16179	6.9
Wellstar Douglas	2114	0.9
Wellstar Kennestone	31783	13.6
Wellstar North Fulton	918	0.4
Wellstar Paulding	1121	0.5

a Controls were matched on admission to the same hospital during the same month and year as a case

Table 4. Adjusted Predictors for Carriage of CRE Upon Hospital Admission, 2016–2017 EIP Cohort

Covariate	Cases (n = 281)	Controls (n = 233,786)	aOR	95% CI	*p*-value
Age, y	65	52	1.03	1.02 – 1.04	<.0001
Female sex, %	60	63	1.09	0.81 – 1.47	0.58
STACH a hospitalizations in prior year, No.	2.4	1.5	1.18	1.09 – 1.27	<.0001
LTACH b hospitalizations in prior year, No.	0.05	0.003	1.72	0.54 – 5.47	0.36
Mean STACH length of stay, d.	7.9	4.7	1.02	1.02 – 1.03	<.0001
Mean LTACH length of stay, d.	32.8	21.9	1.04	1.00 – 1.07	0.05
Current facility is an LTACH, %	2.1	0.01	17.66	1.40 – 223.29	0.03
Prior infection diagnosis, %	28.5	9.3	2.02	1.42 – 2.87	<.0001
Federal insurance, %	83.3	53.1	2.22	1.40 – 3.54	0.0007
Self-pay insurance, %	2.1	10.5	0.14	0.019 – 1.037	0.05

a STACH: short-term acute care hospital

b LTACH: long-term acute care hospital

Table 5a. Characteristics of CRE-associated hospitalization and prior healthcare exposures of CRE cases

	CRE Incident Cases (N=281)	
Characteristics of Incident CRE Hospitalization a	**No. / Mean**	**% / SD**
Time between specimen collection date (days) and subsequent CRE hospitalization		
Same day	110	39.2
1 – 7 days	33	11.7
8 – 30 days	33	11.7
31– 90 days	45	16.0
91 – 180	26	9.3
181 – 365	34	12.1
More than 365 days	0	0.0
Duration of Incident CRE Hospitalization (days)	9.5	9.6
ICU Care b	33	11.8
Discharge Disposition		
Private residence	92	56.1
Long-term care facility	59	36.0
Long-term acute care hospital	10	6.1
Other	2	1.2
Unknown	1	0.6
Died	7	2.5
Characteristics of Prior Healthcare Exposures		
Prior healthcare risk factors		
Any healthcare exposure	235	83.6
Surgery in prior year	83	29.5
Current chronic dialysis	19	6.8
Current indwelling device c	161	57.3
Long-term care facility resident in prior year	110	39.1
Long-term acute care hospitalization in prior year	24	8.5
Prior hospitalization with intravenous antibiotics	80	28.5
Any hospitalization in prior year	199	70.8
None of the above	46	16.4

a Patient was hospitalized anytime within a year of positive CRE culture

b Patient received care in the ICU on or up to 6 days after the date of specimen collection

c Indwelling device present on date of specimen collection or any time in 2 d before specimen collection

Table 5b. Characteristics of prior hospitalizations in the year before CRE-associated hospitalization of CRE cases

	CRE Incident Cases (N=281)	
Details of all prior hospitalizations	**No.**	**%**
Number of prior hospitalizations		
None	82	29.2
1 – 3	126	44.8
4 – 10	67	23.8
> 10	6	2.1
Facility type of prior hospitalizations		
Short-term acute care hospital	665	-
Long-term acute care hospital	15	-
Details of most recent prior hospitalization		
Prior hospitalization facility same as facility of CRE-associated hospitalization		
Yes	78	27.8
No	125	44.5
No prior hospitalization	82	29.2
Facility location by county		
Carroll	1	0.4
Clayton	21	7.5
Cobb	43	15.3
Coweta	1	0.4
DeKalb	94	33.5
Douglas	6	2.1
Fayette	2	0.7
Fulton	75	26.7
Gwinnett	24	8.5
Henry	4	1.4
Newton	4	1.4
Paulding	3	1.1
Rockdale	3	1.1

Table 6. Comparing Results for Adjusted Predictors Between Georgia and Illinois Models

	GA Model			IL Model		
Covariate	**aOR**	**95% CI**	**P-value**	**aOR**	**95% CI**	**P-value**
Age	1.04	1.03 – 1.05	<.0001	1.02	1.01 – 1.03	<.001
Sex	1.15	0.85 – 1.56	0.35	1.07	0.85 – 1.35	0.58
Number of STACH a hospitalizations in prior year	1.20	1.11 – 1.30	<.0001	1.03	1.01 – 1.06	0.02
Number of LTACH b hospitalizations in prior year	1.66	0.52 – 5.35	0.39	2.32	1.94 – 2.78	<.001
Mean STACH length of stay	1.02	1.02 – 1.03	<.0001	1.04	1.03 – 1.06	<.001
Mean LTACH length of stay	1.04	1.00 – 1.08	0.04	1.02	1.02 – 1.03	<.001
Current facility is an LTACH	21.56	1.72 – 270.09	0.02	5.80	4.15 – 8.12	<.001
Prior infection diagnosis	2.03	1.43 – 2.87	<.0001	3.03	2.23 – 4.12	<.001

a STACH: short-term acute care hospital

b LTACH: long-term acute care hospital

Table 7. Predicted CRE probability among entire study cohort, 2015-2017

	Risk Groups					
	0–4%	**5–9%**	**10–14%**	**15–19%**	**20–29**	**≥30%**
Total number (%)	91,286 (39.0)	45,409 (19.4)	30,429 (13.0)	28,556 (12.2)	22,236 (9.5)	16,151 (6.9)

FIGURES

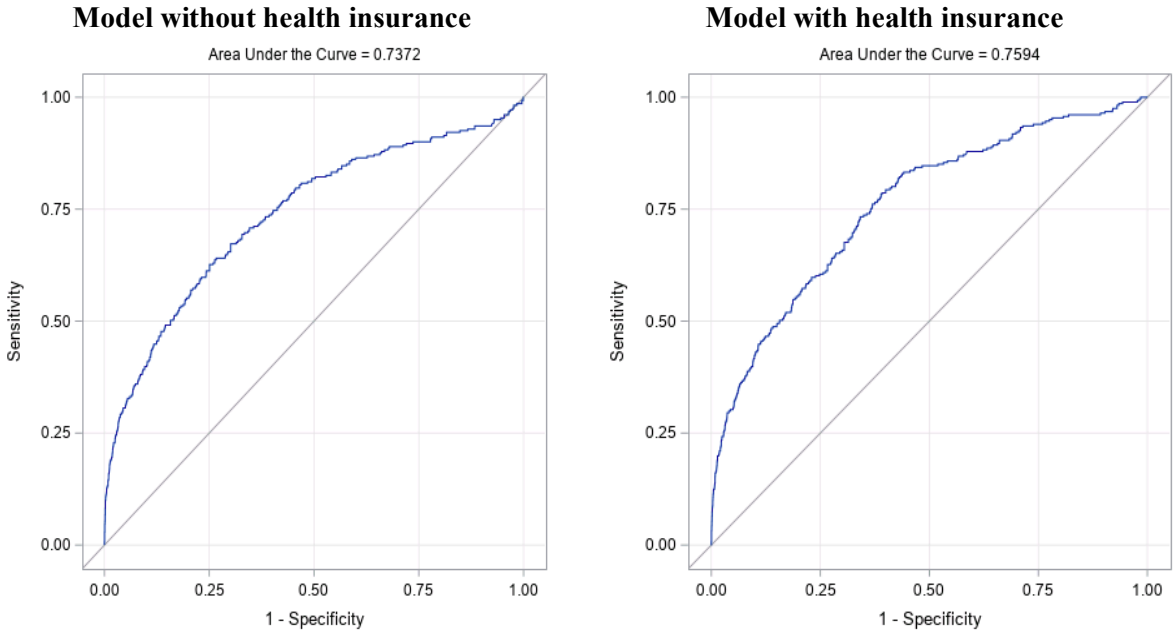

Figure 1. ROC curves for comparing performance of model with and without health insurance predictor

CHAPTER III: PUBLIC HEALTH IMPLICATIONS

The case-control study emphasized the usefulness of state-wide hospital discharge databases as a resource to inform routine public health surveillance and active hospital-based methods to identify high-risk patients. Although challenging, all metropolitan health jurisdictions should aim to obtain access to such data to help improve the accuracy of information pertaining to patients' prior healthcare exposures. For hospitals looking to implement a general prediction model, this study found that applying an external model performed well in discriminating patients at higher risk of CRE. Therefore, future research on CRE detection should focus on evaluating the performance of models generated in different geographic areas to identify the most generalizable model applicable to many regional healthcare networks. Lastly, findings from this study are pertinent to the development and implementation of predictive models for other high-risk diseases not limited to CRE and should thus be prioritized in future healthcare-associated infections research.