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Carbapenem-resistant Enterobacteriaceae (CRE) Case Definition Change: A Comparative Study of the Georgia Emerging Infections Program, 2011-2015 and 2016

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Carbapenem-resistant Enterobacteriaceae Case Definition Change: A Comparative Study of the Georgia Emerging Infections Program, 2011-2015 and 2016
(Under Direction of Dr. Ike Okosun)

ABSTRACT

Introduction: Carbapenem-resistant Enterobacteriaceae (CRE) infections, with limited treatment options, pose a significant public health challenge. In 2011, the CDC's phenotypic CRE case definition was nonsusceptibility to ≥ 1 carbapenem and resistance to 3rd generation cephalosporins but changed January 2016 to resistance to any carbapenem (including ertapenem). This study seeks to determine if this change influenced significant differences in patient characteristics.

Methods: CRE cases in Metro Atlanta, Georgia were collected from 2011-2016. Cumulative incidence per 100,000, odds ratios, and χ^2 estimates were calculated to identify trends. A univariable analysis was conducted to examine risk factors. Adjusting for covariates, the final multivariable model included invasive infection as the outcome and the new definition as the predictor.

Results: A total of 1,144 CRE cases were confirmed from 2011-2016 in Metro Altanta. CRE incidence rates for all culture sources decreased pre-and post-definition change from 9.4 to 1.6. Central venous catheters and ICU stay 7 days prior, had the strongest association with invasive CRE infections; pre-(OR 5.9, 95% CI 1.4-4.3) and post-(OR 11.2, 95% CI 4.9-25.6) definition change. In the final model, the new definition (OR 0.6, 95% CI 0.4-0.9) predicted invasive infection.

Discussion: CRE cases, following the new CRE case definition, had a 40% lower odds of invasive infections than that of the former. The cause of this shift is unclear as more data on antibiotic resistance profiles is needed to assess the definition's overall performance. However, the impact of the new definition on invasive CRE infections is measurable and warrants further analysis.

KEYWORDS: Carbapenem-resistance Enterobacteriaceae, antibiotic resistance, CRE risk factors, case definition.

Carbapenem-resistant Enterobacteriaceae (CRE) Case Definition Change: A Comparative Study of the Georgia Emerging Infections Program, 2011-2015 and 2016

by

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B.A., EMORY UNIVERSITY

A Thesis Submitted to the Graduate Faculty of Georgia State University in Partial Fulfillment of Requirements for the Degree MASTER OF PUBLIC HEALTH

ATLANTA, GEORGIA
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APPROVAL PAGE

CARBAPENEM-RESISTANT ENTEROBACTERIACEAE (CRE) CASE DEFINITION CHANGE: A COMPARATIVE STUDY OF THE GEORGIA EMERGING INFECTIONS PROGRAM, 2011-2015 AND 2016

By
JEREMIAH WILLIAMS

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Disclaimer: The primary dataset used in this project analysis 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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EDUCATION

MPH, Georgia State University, Atlanta, GA May 2018
Concentration: Epidemiology, GPA 3.9
Thesis: *Carbapenem-resistant Enterobacteriaceae Case Definition Change: A Comparative Study of the Georgia Emerging Infections Surveillance Periods 2011-2015 and 2016*

B.A., Emory University, Atlanta, GA May 2012
Major: Political Science | Minor: Anthropology

HEALTH FIELD EXPERIENCE

Research Interviewer, *Surveillance* February 2017-Present
Georgia Emerging Infections Program, Atlanta, GA
Department of Public Health & Centers for Disease Control and Prevention project
Principal Investigator: Monica Farley, MD.
Focus: Active population-based laboratory surveillance for invasive bacterial disease, incidence of food-borne diseases, and laboratory confirmed influenza-related hospitalizations, and healthcare associated infections.

- Conduct telephone interviews for case-control and cohort studies and vaccine verification
- Collect patient data from physicians' offices and medical facilities
- Process isolates in the laboratory; tracking, database entry, packaging and shipping
- Assist with chart reviews for invasive bacterial diseases, foodborne illness, hospital-associated infections, and laboratory confirmed influenza-related hospitalizations

Graduate Research Assistant, *Project Lead* August 2016 - Present
Georgia State University, School of Public Health, Atlanta, GA
Principal Investigator: Betty S. Lai, Ph.D.
Primary Focus: Growth mindset strategies for teaching Biostatistics Introductory course.

- Project lead for study on growth mindset strategies for teaching Masters-level introductory Biostatistics
- Developing psychoeducation activities and "open" tasks to be integrated in Biostatistics courses and coordinating workshops
- Researching and co-authoring publications on post-traumatic stress symptoms, assessment concerns, and academic performance in children following a natural disaster
- Collaborating with researchers from different fields in the development of manuscripts and abstracts
- Assisting with peer reviews, IRB submission, data entry, and study codebook development

Secondary focus: Posttraumatic stress symptoms, assessment concerns, and academic performance in children following a natural disaster. Duties include:

- Performing preliminary data analyses using SAS and assisting with data entry
- Drafting study codebook, reviewing and proofing manuscripts, proofing and editing grant Applications

Summer Public Health Research Intern June-Aug 2016
Department of Community Affairs-Affordable Housing, Atlanta, GA.

- Evaluated and scored Qualified Allocation Plans for private investors applying for tax credits to create low income housing developments
- Conducted critical policy research on health outcomes associated with low income housing tax credit properties in GA

TEACHING & TRAINING EXPERIENCE

Early Childhood Trainer/Consultant May 2015 – Present

Georgia Training Approval, Bright from the Start, Atlanta, GA

- Customized interactive training to meet the needs of session participants and their respective childcare facilities, awarding training participants Early Childhood Education and Child Development Associate credentials
- Conducting state approved training for Early Childcare Professionals and Childcare facility administrators on topics such as 'Appropriate Health and Safety Practices in Early Childhood Facilities" and "Special Needs and Inclusion: Fostering Social Skills in the Preschool Classroom"

Learning Coach-Advisor Sept 2015-Jan 2016

Strengths-based Family Workers Course, Atlanta, GA

- Assisted family workers such as family advocates and caseworkers in gaining and applying family development knowledge, goal planning skills and other key competencies in their work and communities to earn course credentials
- Assessed advisees' progress through a series of written reports
- Guided advisees in developing a portfolio of all coursework for submission upon course completion

Preschool Lead Teacher-Classroom Manager The Clifton School Decatur, GA Oct 2013-Jan 2016

- Observed children closely, document learning, and use these observations as a basis for planning, facilitated children's expression of knowledge through representational media
- Managed 4 teachers in implementing a developmentally appropriate curriculum for 25 preschoolers ages 3-5
- Provided parents with detailed daily reports that outlining their child's progress, maintaining daily records of children's individual activities, behaviors, identifying early warning signs of emotional and developmental problems in children
- Trained 5 Childhood Development Associate interns in preschool class settings

Special Needs Pre-Kindergarten Lead Teacher Sept 2011-Oct 2013

The Emory Walden Autism Center, Atlanta, GA

- Conducted 1:1 therapeutic sessions with children with autism to develop social and conversational skills
- Oversaw a classroom of 4-5 line teachers and 20 children, 6 of which are children with autism
- Created socialization activities and opportunities with typical peers to teach and build social skills
- Supervised and rotated children to various centers and activities every 15 minutes while keeping a ratio of 1 teacher per 5 children and at least 2 typical children for every child with autism
- Collected data daily to monitor the progress of all skills being taught, implemented treatment plans that increase daily life, visual performance, tacting, manding, motor imitation, intra-verbal, and other verbal skills

LEADERSHIP AND CERTIFICATION

Teacher Council- *Appointed member* The Clifton School, Atlanta, GA Dec 2013-Jan 2016
Drafted proposals to boost school morale and to effectively address teacher and administrative concerns.

Strengths-Based Family Workers Credential (Seven-month professional training) Dec 2014
Strengths-Based Family Workers Course (SFW), Atlanta, GA.
The SFW course is an enhanced training and credentialing program that ensures family development workers have the basic knowledge, skills and values for working with families and are equipped to facilitate a family's ability to obtain and maintain family economic success. Aside from completing a professional portfolio and a final exam, candidates must master the following core competencies to receive course credentials:

- Demonstrate professionalism and commitment to ethical practice
- Recognize strength in diversity and difference; demonstrate sensitivity in practice
- Understand and utilize the power of clear, non-judgmental communication
- Demonstrate self-care and lifelong learning
- Apply strengths-based principles to practice with families
- Apply strengths-based principles to agency and community systems

PEER REVIEWED PUBLICATIONS

Williams, J.D., Shah, H.J., & Lai, B.S. (2017). Traumatic experiences related to 9/11: Homogeneity of severe posttraumatic stress disorder symptom profiles in children and adolescents. *Academy on Violence and Abuse Research Review, 12,* 1-3.

Williams, J.D., Livings, M., Cathey, R. & Lai, B, (2018). Employing a growth mind-set intervention in a graduate-level statistics course: Merging research with teaching. *SAGE Research Methods Cases.*10.4135/9781526449122

Livings, M.S., **Williams, J.D,** & Lai, B.S. (2017). Wenchuan Earthquake aftermath: Trajectories of posttraumatic stress symptoms among adolescent survivors. *Academy on Violence and Abuse Research Review, 11,* 1 – 3.

Lai, B.S., M.J., D'Amico, Livings, M.S., Hayat, **Williams, J.D.,** (2017). (Pending Submission) "A Growth Mindset Pilot Intervention for a Graduate-Level Statistics Course." Journal of Statistics Education.

ABSTRACTS AND POSTER PRESENTATIONS

Williams, J.D., 2016 (Summer) "Health and Housing: The Effectiveness of DCA Affordable Housing Policies on Mitigating Key Social Determinants of Health." Presented at Georgia Department of Community Affairs.

Williams, J.D., Lee, M.P., Livings, M.S., Lewis, R.M., Shah, H., & Lai, B.S. 2017 "A Growth Mindset Intervention to Increase Motivation, Self-Efficacy, and Achievement in a Graduate Level Statistics Course." Poster accepted for Annual Georgia Public Health Association Conference.

Williams, J.D, Livings, M.S., Shah, H.J., Lewis, R.M & Lai, B.S., 2017 "Enhancing Graduate Student Motivation and Persistence through a Growth Mindset Intervention." Center for Excellence in Teaching and Learning Conference.

Livings, M.S., Greenbaum, J., Lewis, R.M., **Williams, J.D.,** Self-Brown, S., & Lai, B.S. 2017. "A Screening Tool for Identification of Victims of Commercial Sexual Exploitation of Children." Annual Georgia Public Health Association Conference.

Shah, H.J., Lewis, R., Osborne, M., Malmin, N., Wyczalkowski, C., **Williams, J.D.,** Lee, M., Esnard, A.-M., & Lai, B.S. (2017). "Characterizing discrepancies in school recovery after disasters." Georgia Public Health Association Annual Meeting and Conference.

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1. INTRODUCTION

Carbapenem-resistant Enterobacteriaceae, (CRE) have become a major public health issue across the globe (Tamma, Huang, Opene, & Simner, 2016). These gram-negative organisms are multidrug-resistant pathogens that cause severe infections and have been associated with high mortality rates (Guh et al., 2015). According to a 2013 Morbidity and Mortality Weekly Report (MMWR), CRE-related infections mortality rates can be as high as 40% to 50% (Patel et al. 2008; Schwaber et al., 2011; Chitnis et al., 2012; Vital Signs: Carbapenem-resistant Enterobacteriaceae, 2013). CREs commonly occur in healthcare settings, such as hospitals and long-term care facilities (LTCFs)(Guh et al., 2015). A cause of challenging healthcare-associated infections such as bacteremia, and often hidden throughout the hospital environment, clinicians have fewer treatment options since the emergence of CREs (Guh et al., 2015). In the United States, the percentage of healthcare-associated infections caused by carbapenemase-resistant Enterobacteriaceae rose from 1.2% to 4.2%, 2001-2011 (Jacob et al., 2013; Chea et al., 2015). During which, the *Klebsiella* species accounted for the greatest increase, approximately 10% (Jacob et al., 2013; Chea et al., 2015).

Enterobactericeae are a large diverse family of gram-negative bacteria. Many of which are not pathogenic, however the Georgia Emerging Infections Program (Georgia EIP) tracks carbapenem resistance to *Escherichia coli, Klebsiella* spp., and *Enterobacter* spp through it's Multi-site Gram-negative Surveillance Initiative (MuGSI) (CDC, 2015). MuGSI operates under the direction of the Centers for Disease Control and Prevention's (CDC) Healthcare-Associated Infections Community Interface (HAIC) (CDC, 2015).

Clinical cultures for patients suspected of CRE may present colonization (i.e. presence of CRE bacteria on a body surface but no clinical evidence of an infection) as Georgia EIP's surveillance is limited to urine and sterile sites (i.e. blood, bone, internal body sites, etc.) (CDC,

2015). Likewise, there is constant pressure to refine the case definition used to identify CRE and carbapenemase-producers among CREs, as the carbapenemase enzyme has been recognized as a driving factor in the spread of CRE (Chea et al., 2015).

In November 2011, the CDC developed it's first surveillance definition for CRE: Enterobacteriaceae that are non-susceptible to one of the following carbapenems: doripenem, meropenem, or imipenem AND resistant to all of the following third- generation cephalosporin; ceftriaxone, cefotaxime, and ceftazidime (Chea et al., 2015). January 2016, the CDC modified its surveillance definition for CRE to align with other state reportable definitions and a recently released Council for State and Territorial Epidemiologist (CSTE) position statement (Chea et al., 2015). The new phenotypic case definition added ertapenem, changed the breakpoint for carbapenems to resistant, and dropped the cephalosporin requirement. Resistance to ertapenem was not required in the previous case definition as it was considered too sensitive and had a different breakpoint from the other carbapenems (Chea et al., 2015). However, growing ertapenem resistance among CREs made its inclusion in the new definition necessary (Chea et al., 2015). This new definition was projected to be more sensitive for detecting carbapenemase producers than the previous definition but also had lower specificity (Chea et al., 2015)

Though the case definition change was intended to more accurately identify more positive CRE cases, the effects of the case definition change on the CRE patient population are not well described. As such, a thorough evaluation of how this recent case definition change could provide guidance on how to continue improving CRE surveillance as well as provide valuable epidemiological data specific to the metropolitan Atlanta area.

The aim of this analysis is to compare and describe the differences in CRE cases from 2011-2015 study period (study period 1) and 2016 CRE study period (study period 2) in the

metropolitan Atlanta area. Specifically, the following hypothesis will be tested: If the current CDC CRE surveillance definition was designed to be more simple and sensitive, surveillance efforts in Atlanta should have an impact on patient profiles.

This study will contribute to the Georgia EIP's effort to conduct accurate CRE surveillance and will help provide a better understanding of the CRE patient population. Thus, study findings will also serve as a guide in designing prevention and control measures to combat the spread of CREs. Several questions will direct this study: 1) Was there a significant difference in CRE incidence rates between the two study periods? 2) Did the incidence rates differ between hospitals and long-term care facilities? 3) Were there differences between cases with positive urinary cultures and invasive infections regarding demographics, healthcare exposures, and device-associated infections

2. LITERATURE REVIEW

2.1 Carbapenem Use and Increasing Resistance

Carbapenems were first developed in the 1980s and derived from thyanamycin (Perez, Rodrigues, & Dias, 2015). Imipenem and meropenem were the first of this drug class and are considered broad-spectrum antibiotics, placing them at the forefront in the fight against hard-to-treat nosocomial infections. During this period, carbapenems were effective against the vast majority of Enterobacteriaceae (Papp-Wallace, Endimiani, Taracila, & Bonomo, 2011).
By the 1990s, Enterobacteriaceae began showing resistance to cephalosporins, through developing an enzyme that disables these agents called extended-spectrum β-lactamase (Perez, Rodrigues, & Dias, 2015). Therefore, clinicians were forced to use carbapenems, which remained susceptible (Rahal, 1998). Both are β-lactam antibiotics (beta-lactam antibiotics) which is a class of broad-spectrum antibiotics, comprised of anti-microbial agents that have a β-lactam

ring in their molecular framework (Holten & Onusko, 2000). This class of antibiotics is further divided into several subgroups; cephalosporins (cephems), penicillin offshoots (penams), carbapenems, and monobactams (Holten & Onusko, 2000). Ertapenem, another carbapenem with an extended half-life and once-daily dosing, was introduced in 2001 (Perez, Rodrigues, & Dias, 2015). Consequently, this carbapenem was a favorable option for treating community cases (Livermore, Sefton, & Scott, 2003). Launched in 2005, doripenem is the latest addition to the carbapenem class of antibiotics (Bazan, Martin, & Kaye, 2009).

Similar to imipenem and meropenem, doripenem has broad-spectrum activity and is effective against *Pseudomonas aeruginosa*, prompting more use of carbapenems (Bazan, Martin, & Kaye, 2009). A study, involving 35 university hospitals in the United States, found that carbapenem use rose by 59% from 2002 to 2006 (Pakyz, MacDougall, Oinonen, & Polk, 2008).

By the early 2000's, carbapenem resistance in Enterobactiericeae was documented in North America and began spreading in the United States after a series of hospital-related outbreaks in the Northeast (Perez, Rodrigues, & Dias, 2015). This resistance was due, in part, to the development of another enzyme called carbapenemases. Carbapenemases are β-lactamases with the ability to hydrolyze cephalosporins, monobactams, penicillins, and carbapenems (Queenan & Bush, 2007).

2.2 Emergence of CRE and Mechanisms for Resistance

Like other pathogens, CRE can be transmitted person-to-person. Yet, there are many multiple mechanisms that contribute to carbapenem resistance (Capone et al., 2013). One of which is via plasmids (Capone et al., 2013). Plasmids are particularly predominant among Enterobacteriaceae and can reproduce irrespectively of chromosomal DNA (Carattoli, 2011; Schwaber, Carmeli, & Harbarth, 2011; Plasmid | microbiology, 2018). The resistance gene can

be implanted into plasmids of gram-negative bacteria and can transfer resistance not only from patient to patient but also from ne species of bacteria to another species, resulting in more species becoming drug resistant (Capone et al., 2013).

Carbapenemases are part of several molecular classes; A, B, and D β-lactamases (see Table 1) (Queenan & Bush, 2007).

Table 1: Carbapenemases

Classes	Enzymes	Most Common Bacteria
Class A	*KPC(1-10), SME, IMI, NMC, GES	Enterobacteriaceae (seen rarely in *P. aeruginosa)*
Class B **(metallo-β-lactamases)**	IMP, VIM, GIM, SPM, NDM-1	*P. aeruginosa*, Enterobacteriaceae, *Acinetobacter* spp.
Class D	OXA	*Acinetobacter* spp., *P. aeruginosa* and rare Enterobacteriaceae

***Plasmid, [A] KPC-*K. pneumoniae carbapenemase*, SME- *S. Marcesens* enzyme, NMC-Not Metallo Carbapenemase, IMI-IM hydrolyzing β-lactamase, GES-Guiana extended spectrum; [B] VIM-Verona Integron Encoded MBL; NDM-1-New Delhi β-lactamase; [D] Oxacilin hydrolyzing. Enzyme Specific Activity Spectrum: KPC(1-10)- All β-lactams; SME, IMI, NMC -Carbapenem, Aztreonam but not 3rd & 4th generation Cephalosporins; GES-Imipenem and 3rd / 4th generation; IMP, VIM, GIM,SPM- All β-lactams, susceptible to aztreonam and NDM-1 variable AZT resistance; IMI, NMC, GES- Weak activity against carbapenems.**
(The Pediatric Infectious Disease Journal, 2010).

Enzymes in the A and D classes break down carbapenems through a serine-based process, while those in the B class are metallo-β-lactamases and involve zinc in the process (Queenan & Bush, 2007). The A class carbapenemases consist of the bla_{KPC} (KPC1-10) bla_{SME}, bla_{GES}, bla_{IMI}, and bla_{NMC} enzyme groups (Queenan & Bush, 2007). KPC carbapenemases are widely distributed and originate from plasmids in *Klebsiella pneumoniae* (Queenan & Bush, 2007). Carbapenem resistance due to the presence of a class A carbapenemase was initially observed in 1996 from an isolate of *Klebsiella pneumoniae* in North Carolina (Yigit et al., 2001).

In 2006, KPC-producing strains of *Klebsiella pneumoniae* (KPC-Kp) were connected with outbreaks in the United States; mostly in the Northeast and Arizona (Temkin et al., 2014). In one of these KPC-Kp-associated outbreaks, 24 patients in a New York City Hospital were affected resulting in a 33% fatality rate (Woodford et al., 2004). In 2008, KPC-Kp strains were

also identified in Greece, Israel, and Italy (Leavitt et al., 2007; Maltezou et al., 2009; Mezzatesta et al., 2011; Pournaras et al., 2009; Schwaber et al., 2011).

Due to horizontal transfer, KPC was soon found in other types of the Enterobacteriaceae (Martirosov & Lodise, 2016). Though differences exist between regions, one study found that KPCs exist in 4% of *Escherichia coli* and 10% of *Klebsiella pneumoniae* (Marsik and Nambiar, 2011). KPCs are now the most widespread carbapenemase (Munoz-Price et al., 2013).

The emergence of other carbapenemases is also well documented. The B class carbapenemases consist of the, bla_{IMP}, bla_{VIM}, bla_{GIM}, $bla_{SPM,}$ and bla_{NDM-1}. Initially discovered in 1997 in *Pseudomonas aeruginosa* isolates, bla_{VIM} was detected in Enterobacteriaceae from Greece in 2001 (Lauretti et al., 1999; Miriagou et al., 2003). In 2009, bla_{NDM-1} was reported in isolates from Swedish patient with a urinary tract infection (UTI) in an Indian medical center (Yong et al., 2009).

The D class includes the bla_{OXA} enzymes and are typically found in *Acinetobacter baumannii* (Bush et al., 1995; Queenan and Bush, 2007; Walther-Rasmussen and Hoiby, 2006). There are 120 bla_{OXA} variants, of which over one-third hydrolyze carbapenems (Bush et al., 1995; Queenan and Bush, 2007; Walther-Rasmussen and Hoiby, 2006).

2.3 CRE in the Healthcare Setting

According to the CDC's 2013 Antibiotic Resistance threat report, CRE-related infections in the healthcare environments are increasing and considered an urgent threat (2013). The National Healthcare Safety Network (NHSN) collects antimicrobial susceptibility data on patients with catheter-associated urinary tract and blood stream infections. Data collected in 2006-2007 showed that carbapenem resistance was observed in 0.9% of *Escherichia coli* infections and in 10.8% of *Klebsiella pneumoniae* infections in hospital patients with central

line–associated bloodstream infections (CLABSIs) (Hidron et al., 2008). NHSN reported a rise in carbapenem resistance, in 2009-2010, from 10.8% to 12.8% of *Klebsiella pneumoniae* cultures associated with CLABSIs (Sievert et al., 2013).

At least one healthcare associated CRE infection occurred in 3.9% of short-stay acute-care hospitals (ACH) and 17.8% of LTACHs in 2012 (Martirosov & Lodise, 2016; Vital Signs: Carbapenem-Resistant Enterobacteriaceae, 2013). By 2012, CRE had spread to 42 states, and the number of Enterobacteriaceae that were CREs had risen fourfold over a 10-year span (Vital Signs: Carbapenem-resistant Enterobacteriaceae, 2013). During this time frame, carbapenem resistance in *Klebsiella pneumoniae* catheter-associated UTIs (CAUTIs) rose from 10.1% to 12.5% as well (Hidron et al., 2008; Sievert et al., 2013; Martirosov & Lodise, 2016). Similarly, increasing rates of carbapenem resistance can be seen in patients with ventilator-associated pneumonia (VAP) (Hidron et al., 2008; Sievert et al., 2013; Martirosov & Lodise, 2016). Carbapenem resistance among *Klebsiella pneumoniae* and *Escherichia coli* cases with VAP increased from 3.6% and 1.8% to 11.2% and 3.5%, respectively (Hidron et al., 2008; Sievert et al., 2013; Martirosov & Lodise, 2016). CRE infections occur at varying rates and are not limited to the hospital environment as they are found in all types of healthcare facilities; such as convalescent facilities and long-term acute care hospitals (LTACHs) (Martirosov & Lodise, 2016; Hayden et al., 2014; Marquez et al., 2013).

2.4 Risk Factors for CRE

Understanding the epidemiology of the risk factors associated with CRE infections essential in developing effective control strategies such as early intervention in terms of treatment and appropriate antibiotic therapy. According to a landmark comprehensive study that examine the emergence of CRE across the globe, “Carbapenem-resistant Enterobacteriaceae:

Epidemiology and Prevention," by Gupta et al., the most prominent risk factors for CRE infections are extensive time in medical facilities, exposure to medical instruments, such as indwelling devices, and previous exposure to antibiotics (2011). All of which were demonstrated in a matched-case control study conducted by Patel et al. (2008). The researchers uncovered a strong association between carbapenem-resistant *Klebsiella pneumoniae* infections and organ or stemcell transplants, artificial ventilation to support breathing, number of hospitalizations, prolonged length of stay, and previous use of carbapenems or cephalosporins (Patel et al., 2008). Studies that have examined the clinical characteristics of CRE cases have found that the severely-ill, debilitated, elderly, immunosuppressed, and those with extensive comorbidities are at risk for CRE infections (Gupta et al., 2011; Kim et al., 2014; Martirosov & Lodise, 2016; Patel et al., 2008; Perez & Van Duin, 2013; Zurawski, 2014). Specifically, the elderly, burn victims, and severely-ill patients with bacteremia commonly experience the most challenging outcomes (Perez & Van Duin, 2013; Tumbarello et al., 2012; Zarkotou et al., 2011). Furthermore, patients in intensive-care units (ICU) had an increased risk of CRE-related infections compared those in non-critical care wards (Gupta et al., 2011; Kim et al., 2014; Martirosov & Lodise, 2016; Patel et al., 2008; Zurawski, 2014).

Considering the frequency in which microbes change and adapt, many find the association between previous antibiotic therapy with carbapenems a primary cause of rising CRE rates. However, results from several studies show that it is, actually, the cumulative treatment of antibiotics rather than treatment of a single antibiotic class, that fuels CRE rates (Gallagher et al., 2014; Marchaim et al., 2012; Patel et al., 2011). This response to a consistent influx of and collective exposure to antimicrobials occurs by disturbing the colonization of the "good

bacteria," rendering patients more susceptible to resistant pathogens like CRE (Patel et al., 2011).

2.5 The Role of Long-Term Care Facilities in the Spread of CRE

The association between LTCFs and the spread of CREs has been highlighted in a number of studies and evidence suggests LTCFs may play a central role among the list of risk factors responsible for the proliferation of CREs (Perez et al., 2010; Perez & Van Duin, 2013). Additionally, researchers determined from a retrospective observational study, that over 50% of CRE-linked infections were transferred from an LTCF (Perez et al., 2010). Data collected from an investigation on carbapenem-resistant *Acinetobacter baumannii* and *Klebsiella pneumoniae* in a group of medical facilities showed 75% of carbapenem-resistant *Klebsiella pneumoniae* came from LTCFs (Perez & Van Duin, 2013). One study that focused on movement of patients with carbapenem-resistant associated bloodstream infections between hospitals and LTCFs determined that of the 42% that survived their index admission, just 32% were discharged, and overall, readmissions occurred frequently (Perez & Van Duin, 2013; Neuner et al., 2011). Transfers from LTCFs or another medical facility is linked to carbapenem-resistance in patients colonized or infected with Enterbacteriaceae. Though researchers recognize LTCFs to be at the forefront of the emergence and transmission of CREs, it is important to note that location of care can and often overlaps with other risk factors.

2.6 Rationale for Case Definition Change

Carbapenem resistance within the Enterobacteriaceae family is uniquely challenging. There are over 70 Enterobacteriaceae classes with a variety of mechanisms that can create carbapenem resistance (CDC, 2015). Irrespective of the mechanism behind the carbapenem resistance, all CRE are typically multidrug-resistant pathogens that warrant immediate attention in healthcare settings to prevent and control transmission. However, carbapenemase-producing

CREs (CP-CRE) are considered to be the prime cause for the proliferation of CRE in the United States and thus have been the focus for aggressive prevention strategies (CDC, 2015; Chea et al., 2015). Distinguishing CP-CRE from non-CP-CRE is the most reliable approach to thwarting the spread of CRE (CDC, 2015; Chea et al., 2015). Mechanism testing, however does not serve as a guide in making therapeutic decisions and it is not commonly performed in clinical laboratories across the US (CDC, 2015; Chea et al., 2015). In the absence of mechanism testing, phenotypic definitions, regarding a pathogens antibiotic susceptibility pattern, are the principal method for identifying CP-CRE (CDC, 2015). It is important to note that no phenotypic definition is 100% accurate in differentiating CP-CRE from non-CP-CRE (CDC, 2015; Chea et al., 2015).

The previous phenotypic CRE surveillance definition (nonsusceptibility to doripenem, meropenem, or imipenem AND resistant to all third-generation cephalosporins; ceftriaxone, cefotaxime, and ceftazidime) was intended to capture more CP-CRE (Chea et al., 2015). However, there were several issues; automated testing instruments were not testing low enough, the CDC CRE case definition did not align with state-reportable definitions, and low sensitivity for capturing CP-CRE (CDC, 2015; Chea et al., 2015). The challenge was due to the sheer number of antibiotics involved and the different standards for specific antibiotics (i.e. nonsusceptibility for carbapenems and resistance for cephalosporins). Moreover, ertapenem, another carbapenem, was initially excluded in the definition because of apprehension regarding its low cutoff for nonsusceptibility ($\geq$1 mcg/ml) (CDC, 2015; Chea et al., 2015).

In time, concerns over whether the original definition missed CP-CRE prompted more investigation on its performance. Eventually, the CDC began identifying CRE that contained the KPC gene (bla_{KPC}) and showed resistance to ertapenem but were susceptible other carbapenems (Humphries & McKinnell, 2016). The results from a validation study conducted by the CDC

indicated that some of KPC-producing *Klebsiella* species might be overlooked by not including ertapenem in the definition (Arnold et al., 2011). Also, some clinical laboratories only tested ertapenem, meaning CRE would not be identified with the previous definition (CDC, 2015). Lastly, CRE producing OXA-48 carbapenemases may not be resistant to third-generation cephalosporins and thus would not be identified using the former definition (CDC, 2015). Therefore, to make testing more simple and reliable, considerable effort was put into creating a more suitable set of criteria for identifying CREs (CDC, 2015; Chea et al., 2015). By January 2016, the CDC changed its CRE definition to resistance to imipenem, meropenem, doripenem, or ertapenem (see Table 2) (CDC, 2015; Chea et al., 2015).

Table 2: CRE Case Definitions

2011-2015		
Category	Species	Carbapenem susceptibility phenotype
Carbapenem-nonsusceptible Enterobacteriaceae	*Escherichia coli* *Klebsiella pneumoniae* *Klebsiella oxytoca* *Enterobacter cloacae* *Enterobacter aerogenes*	Intermediate or resistant to: Imipenem (MIC ≥2), Meropenem (MIC ≥2), or Doripenem (MIC ≥2) AND resistant to: Ceftazidime (MIC ≥16), Ceftriaxone (MIC ≥4), and Cefotaxime (MIC ≥4
2016		
Carbapenem-nonsusceptible Enterobacteriaceae	*Escherichia coli* *Klebsiella pneumoniae* *Klebsiella oxytoca* *Enterobacter cloacae* *Enterobacter aerogenes*	Resistant to: Imipenem (MIC ≥4), Meropenem (MIC ≥4), Doripenem (MIC ≥4), or Ertapenem (MIC ≥2)

Including ertapenem in the new definition increased the likelihood of capturing more non-CP-CRE than that of the former definition (CDC, 2015). Resistance to all third-generation cephalosporins was omitted from the new CDC CRE definition for several reasons: to make the definition easier to implement; to adequately address the rise in OXA-48 producing CRE, as they

may not show resistance to this group of antibiotics and; there was a sufficient amount of evidence that the inclusion of cephalosporins requirement did not significantly increase sensitivity and specificity for CP-CRE (CDC, 2015).

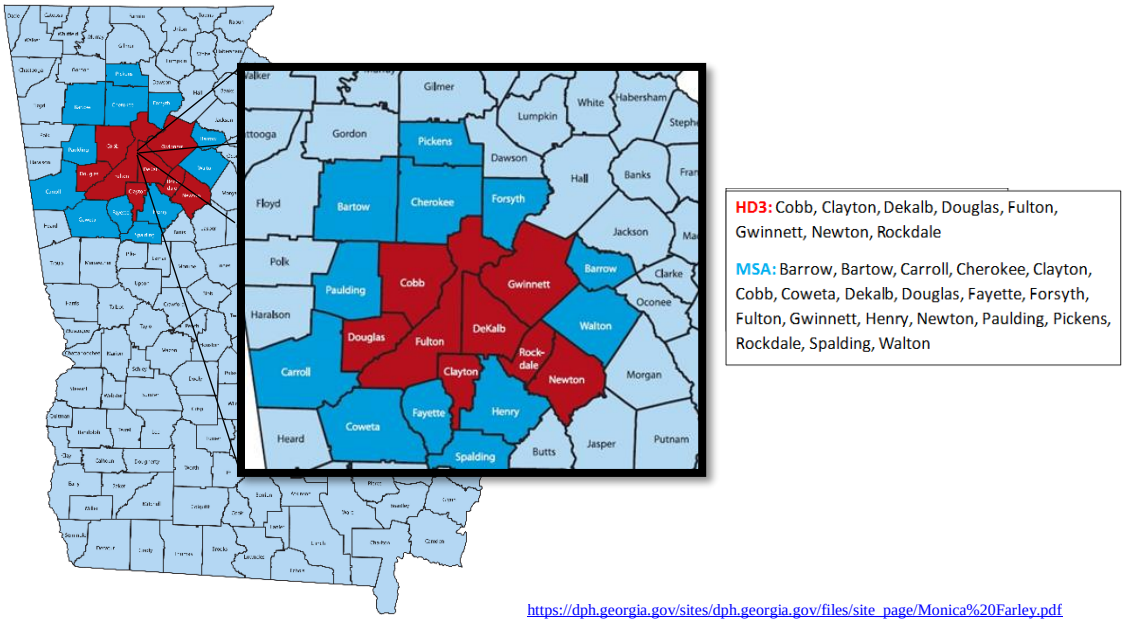
A standardized, reliable phenotypic surveillance definition for CRE is vital for prevention. Accurate diagnoses of CREs, especially those of greatest epidemiological interest such as CP-CRE, aids in prevention efforts. A standardized surveillance definition is also essential for obtaining national burden estimates as it ensures consistent reporting from laboratories across the country (CDC, 2015; Chea et al., 2015).

3. METHODS AND PROCEDURES

3.1 Surveillance Population

The Multi-site Gram Negative Surveillance Initiative (MuGSI), as part of the Center for Disease Control (CDC)'s Emerging Infections Program (EIP), conducts active, population-based laboratory surveillance for carbapenem-resistant gram-negative bacteria.

Figure 1: Georgia Emerging Infections Program Surveillance Area



https://dph.georgia.gov/sites/dph.georgia.gov/files/site_page/Monica%20Farley.pdf

Georgia is one of eight EIP sites nationwide that conducts surveillance for carbapenem-resistant Enterobacteriaceae (CRE). The surveillance catchment area for the Georgia site is the Health District 3 (HD3), which contains eight counties in the metropolitan Atlanta area: Cobb, Clayton, Dekalb, Douglas, Gwinnett, Fulton, Newton, and Rockdale (Figure 1). Therefore, this study includes confirmed CRE cases in HD3.

3.2 Case Definition

In order to be considered a case, the specimen must be, initially, collected from urine or normally sterile body site (blood, bone, pleural fluid, etc.). It must meet the phenotypic case definition, and the patient must be a resident of the surveillance area (HD3). The phenotypic case definition from 2011-2015 (study period 1) required that the isolate be nonsusceptible to at least one of the following carbapenems: doripenem, meropenem, or imipenem AND resistant to the following third-generation cephalosporins; ceftriaxone, cefotaxime, and ceftazidime. In 2016 (study period 2), the phenotypic case definition was changed to resistant to imipenem, meropenem, doripenem, or ertapenem. If a new culture meeting the case definition is collected more than 30 days after the patient's initial positive culture, it will be reported as a new incident case. If a positive culture is collected within 30 days after the initial positive culture than it will be considered persistent disease and recurrent case.

Susceptibility results were closely reviewed to verify resistance. Minimum Inhibitory Concentrations (MIC) were established using the Clinical and Laboratory Standards Institute (CLSI), Seventieth Information Supplement (M100-S26) (Outreach Working Group of the CLSI Subcommittee on Antimicrobial Susceptibility Testing, 2016)

3.3 Data Collection

Cases of CRE are identified through querying of automated testing instruments at clinical laboratories serving residents of the surveillance population (Reno et al., 2014). Epidemiological

data included: are captured through retrospective medical record review for all incident cases by trained EIP staff members. Epidemiological data extracted include: demographic data, underlying conditions, location of culture collection, types of infection associated with the positive culture, outcome, susceptibility testing results, risk factors/healthcare exposures (including invasive devices, residence in long-term care facilities, previous hospitalizations/surgeries, travel).

3.4 Data Analysis

The following variables were included in this analysis: age-group, year of incident and corresponding study period, gender, race, ethnicity, CRE diagnosis, origin of incident (whether a case was nosocomial, transferred from an LTCF, or other), and outcome (whether a patient survived or died). Variables pertaining to healthcare exposures were also examined: residence in a long-term care facility within year before date of initial culture, culture collection at least 3 calendar days after hospital admission, hospitalization in ICU in the 7 days prior or after to their initial culture, hospitalization or surgery in the previous year before date of initial culture, and admission to a LTACH wihin year before initial culture date. Other risk factors for CRE infection or other epidemiologically significant information were chronic dialysis within year before date of initial culture, culture source (urine or invasive, from normally sterile site), presence of indwelling devices (i.e. urinary catheter, central vascular catheter, tracheostomy, etc) in place on the day of culture or at any time in the 2 calendar days prior to initial culture, and comorbidities (diabetes, immunocompromised, HIV, etc.)

Data were analyzed using SAS software (v. 9.4). Cumulative incidence rates were calculated using Census Bureau data from 2011-2016 per 100,000 population (Data Access and Dissemination Systems (DADS), 2018). Univariable demographic and risk factor comparisons were done between patients with positive urine or sterile site cultures. Chi^2 or Fisher's exact tests

were calucated for categorical variables. P-values <0.05 were considered significant. Univariable logistic regression was done with each risk factor as the sole predictor of outcomes of invasive infection by study period. Multivariable modeling was conducted using invasive infection as the outcome of interest and the new case definition as the primary exposure. Backward, forward, stepwise, and manual selection techniques utilized to identify the best-fitting model at $p<0.05$. Variables were used in the final multivariable model to control for each covariate. The model included culture source type as the dichotomous outcome variable and predictors (old and new case definition, hospitalization three days or more of initial culture, hospitalization in the year prior to the initial culture, presence of a urinary catheter, central venous catheter, or other indwelling devices.

4. RESULTS

4.1 Descriptive Analysis

A total of 1,144 confirmed cases of CRE infections were reported from 2011-2016 in HD3. In study period 1, the population in the HD3 increased from 3,753,452 (38% of the state population) to 3,991,607 (39% of the state population). The first study period consists of 757 CRE cases, of which 149 (19.7%) were invasive infections. The second study period had 387 CRE cases, with 31 (2.7%) that were invasive infection. In both periods, the number of non-invasive CRE infections greatly exceeded the number of invasive infections (blood and all other sterile sites) (Figures 2-3) (Tables 3-4).

From 2011 to 2016, 8.5% (97/1144) of all CRE infections resulted in death. We measured outcome at 30 days for non-hospitalized patients or at discharge from acute care hospital for hospitalized patients. There were more deaths in the first period than in the second,

as study period one had more years; 72/757 vs. 25/387 respectively (Table 3-4). During study period 1, however the mortality rate for invasive CRE infections increased from 3.8 to 6.7, but-

Table 3: Study Period 1 Patient Characteristics by Culture Source

Participant Characteristics	INVASIVE 149 (19.7)	NON-INVASIVE 608 (80.3)	Overall N=757	p-value
**Age Group				
0-9	3 (13.6)	19 (86.4)	22	<.0001
10-19	0	3 (100.0)	3	
20-29	14 (40.0)	21 (60.0)	35	
30-39	16 (42.1)	22 (57.9)	38	
40-49	14 (24.1)	44 (75.9)	58	
50-59	28 (23.9)	89 (76.1)	117	
60-69	37 (21.3)	137 (78.8)	174	
70-79	16 (12.6)	111 (87.4)	127	
80-89	11 (11.9)	81 (88.0)	92	
90+	2 (6.9)	28 (93.3)	30	
**Gender				
Female	76 (17.9)	349 (82.1)	425	.3176
Male	73 (22.1)	258 (77.9)	331	
**Race				
American Indian	0	1 (100.0)	1	0.0931
Asian	4 (44.4)	5 (55.6)	9	
Black	95 (21.9)	339 (78.1)	434	
White	40 (16.5)	203 (83.5)	243	
**Ethnicity				
Hispanic or Latino	6 (27.3)	16 (72.7)	22	0.6610
Non-Hispanic or Latino	88 (19.5)	363 (80.5)	451	
**Location of Culture				
ER	37 (19.1)	157 (80.9)	194	<.0001
ICU	34 (38.6)	54 (61.4)	88	
LTACH	7 (20.6)	27 (79.4)	34	
LTCF	6 (3.3)	175 (96.7)	181	
OBS	0	3 (100.0)	3	
OPCL	2 (4.4)	43 (95.6)	45	
OPSUR	0	1 (100.0)	1	
OR	4 (66.7)	2 (33.3)	6	
OTHIP	53 (28.8)	131 (71.2)	184	
OTHOP	3 (21.4)	11 (78.6)	14	
RAD	2 (100.0)	0	2	
**Outcome				
Died	26 (36.1)	46 (63.9)	72	<.0001
Survived	123 (18.7)	534 (81.3)	657	

**Missing: Age group(61). Variables: Origin of Culture indicates whether a case was nosocomial, transferred from a longterm care facility (LTCF), or other
Chi-square was used to calculate p-values using 95 % confidence interval (CI) for the association between patient character and culture source pre-case definition (2011-2015)
Origin of Culture variable abbreviations: CU=ICU, OR=Surgery/OR, RAD=Radiology, OTHIP=Other Hospital IP Unit, ER=Emergency Room, OPCL=Outpatient Clinic/Doctor's office OPSUR=Outpatient Surgery, OTHOP=Other Outpatient, DIAL=Dialysis Center, OTHER = Other, OBS=Observational Unit/Clinical Decision Unit, LTCF=LTCF, LTACH=LTACH, AUTO=Autopsy, and UNK=Unknown.

peaked at 9.8 in 2014 (Figure 3). During the same period, the mortality rate for non-invasive infections increased from 1.3 to 2.5 per 100,000 but peaked at 6.4 in 2013. In the second study

period, the mortality rate for invasive infections increased to 4.5. and to 2.5 per 100,000 for non-invasive infection (Figure 3).

Table 4: Study Period 2 Patient Characteristics by Culture Source

Participant Characteristics	Invasive 31 (8.1)	Non-Invasive 356 (91.9)	Overall N=387	p-value
**Age Group				
0-9	0	7 (100.0)	7	<.8959
10-19	1 (25.0)	3 (75.0)	4	
20-29	1 (5.9)	16 (94.1)	17	
30-39	2 (6.9)	27(93.1)	29	
40-49	2 (7.4)	25 (92.6)	27	
50-59	4 (11.4)	31 (88.6)	35	
60-69	7 (8.4)	76 (91.6)	83	
70-79	7 (8.2)	78 (91.8)	85	
80-89	2 (3.9)	49 (96.1)	51	
90+	2 (9.5)	19 (90.5)	21	
**Gender				
Female	10 (4.7)	205 (95.4)	215	0.0222
Male	21 (12.3)	150 (87.7)	171	
**Race				
American Indian	0	0	0	0.0094
Asian	3 (21.4)	11 (78.6)	14	
Black	20 (11.8)	150 (88.2)	170	
White	7 (4.6)	145 (95.4)	152	
**Ethnicity				
Hispanic or Latino	1 (7.7)	12 (92.3)	13	0.1643
Non-Hispanic or Latino	30 (9.0)	305 (91.0)	335	
**Location of Culture				
ER	3 (3.1)	93 (96.9)	96	<.0001
ICU	9 (36.0)	16 (64.0)	25	
LTACH	4 (18.2)	18 (81.8)	22	
LTCF	0	80 (100.0)	80	
OBS	0	1 (100.0)	1	
OPCL	1 (1.4)	72 (98.6)	73	
OPSUR	0	1 (100.0)	1	
OR	4 (80.0)	1 (20.0)	5	
OTHIP	10 (12.9)	67 (87.0)	77	
OTHOP	0	1 (100.0)	1	
OTH	0	3 (100.0)	3	
**Outcome				
Died	9 (36.0)	16 (64.0)	25	<.0001
Survived	22 (6.6)	311 (93.4)	333	

**Missing: Age group(28) & Outcome (1). Variables: Origin of Culture indicates whether a case was nosocomial, transferred from a longterm care facility (LTCF), or other Chi-square was used to calculate p-values using 95 % confidence interval (CI) for the association between patient character and culture source for post case definition change (2016) Origin of Culture variable abbreviations: CU=ICU, OR=Surgery/OR, RAD=Radiology, OTHIP=Other Hospital IP Unit, ER=Emergency Room, OPCL=Outpatient Clinic/Doctor's office OPSUR=Outpatient Surgery, OTHOP=Other Outpatient, DIAL=Dialysis Center, OTHER = Other, OBS=Observational Unit/Clinical Decision Unit, LTCF=LTCF, LTACH=LTACH, AUTO=Autopsy, and UNK=Unknown.

Much of the disease burden of all CRE infections, in both study periods, was between ages 60-69; 22.9% and 21.5% respectively (Tables 3-4). All subjects in the dataset were stratified into ten age groups.

Females accounted for the majority of CRE infections in both periods; 56.1% and 55.6% respectfully (Tables 3-4). Blacks had the greatest number of CRE infections, invasive and non-invasive, before and after the case definition change; 57.3% (170/387) and 43.9% (434/757) (Tables 3-4). In the first study period, most cultures were originally collected from the emergency room-ER, 194 (25.6%), an LTCF 181 (23.9%), other hospital in-patient unit-OTHIP 184 (24.3%), or ICU 88 (11.6%) (Table 3). Similarly, most cultures in the second study period were collected in the ER 96 (24.8%), LTCF 80 (100.00%), OTHIP 77 (19.9%), or outpatient clinic/doctor's office-OPCL 73 (18.9%) (Table 4).

CRE incidence rates for both invasive and non-invasive infections decreased during study period 1 from 9.4 to 2.5 per 100,000 (Figure 2). These rates continued to decrease in study period 2 to 1.6 per 100, 000, following the CRE case definition change.

Figure 2: Crude Annual Cumulative Incidence of CRE Cases in HD3

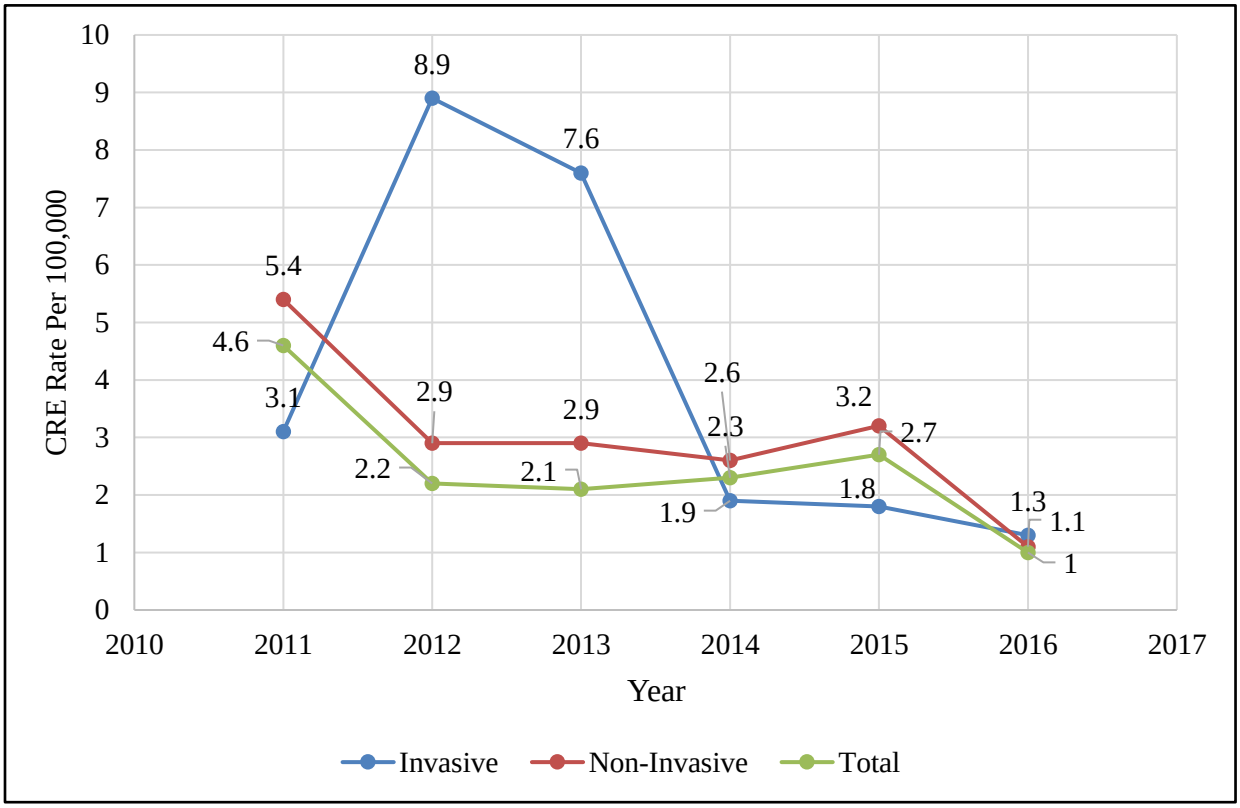


Figure 3: Crude Annual Mortality Rate for CRE Deaths in HD3

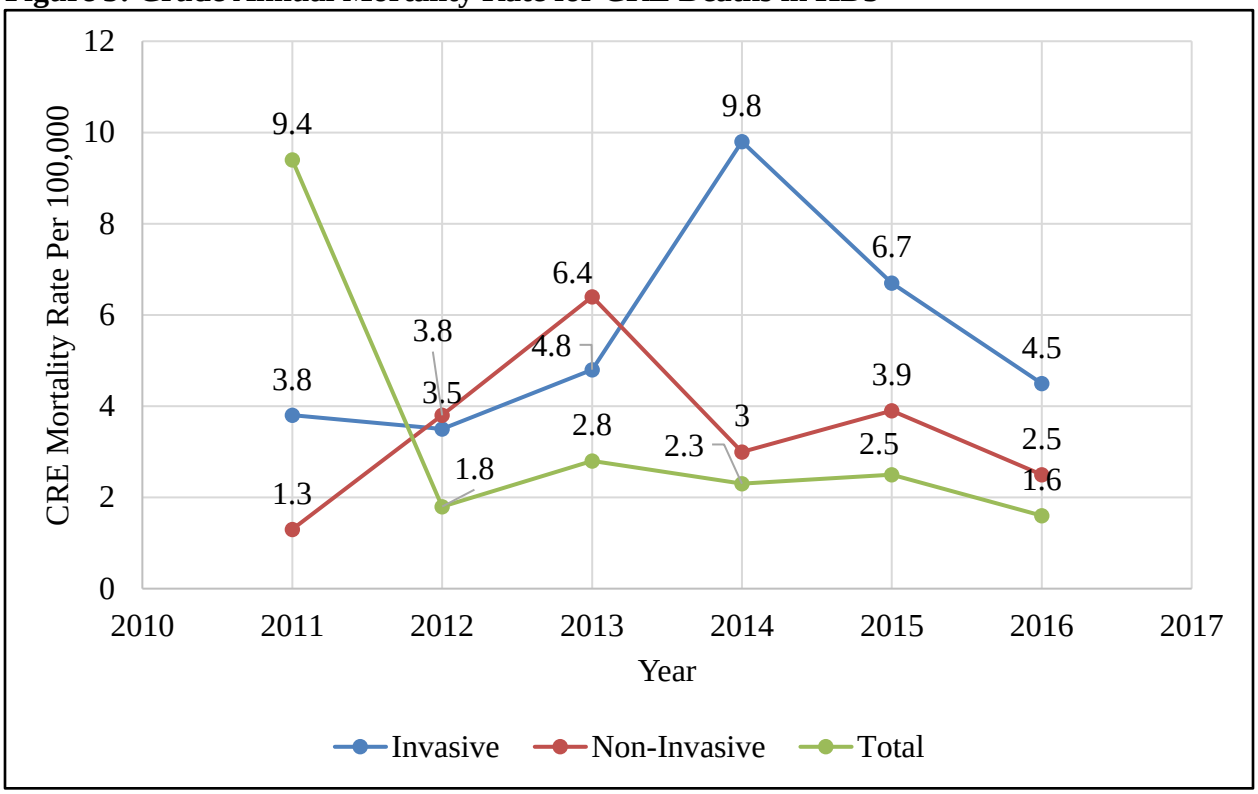
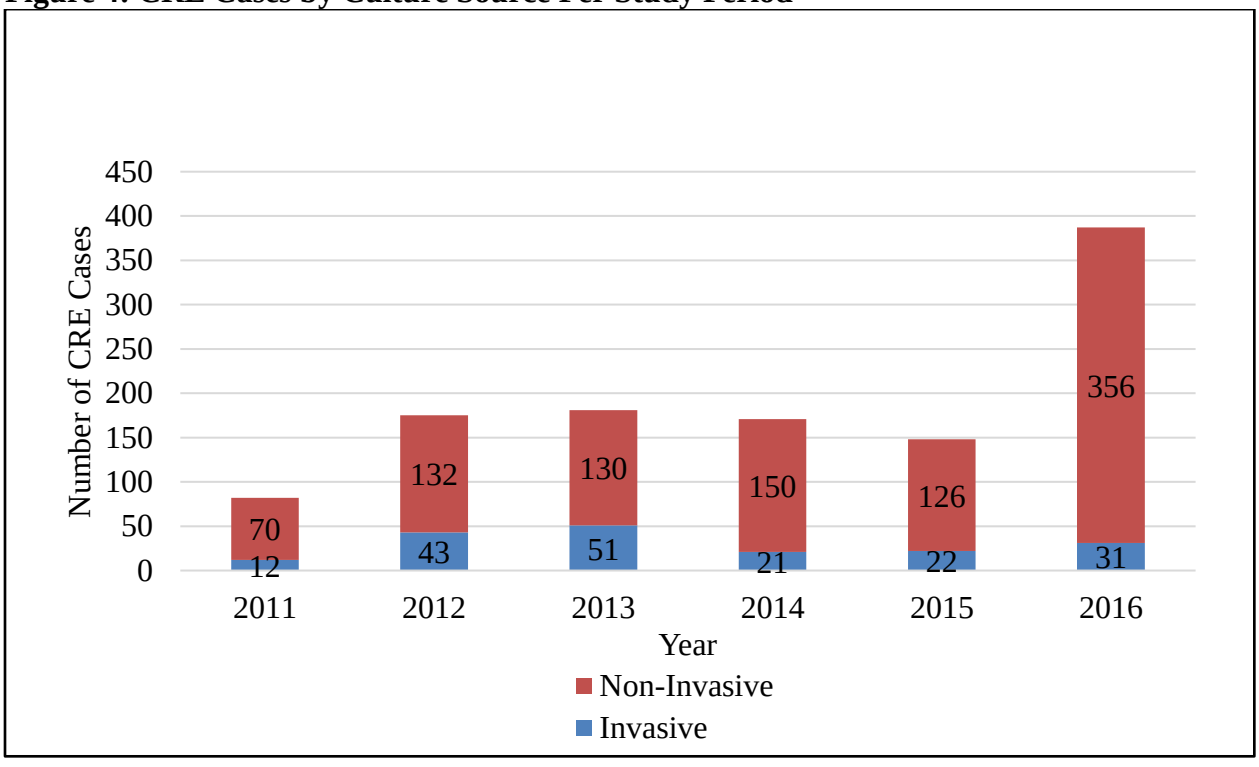


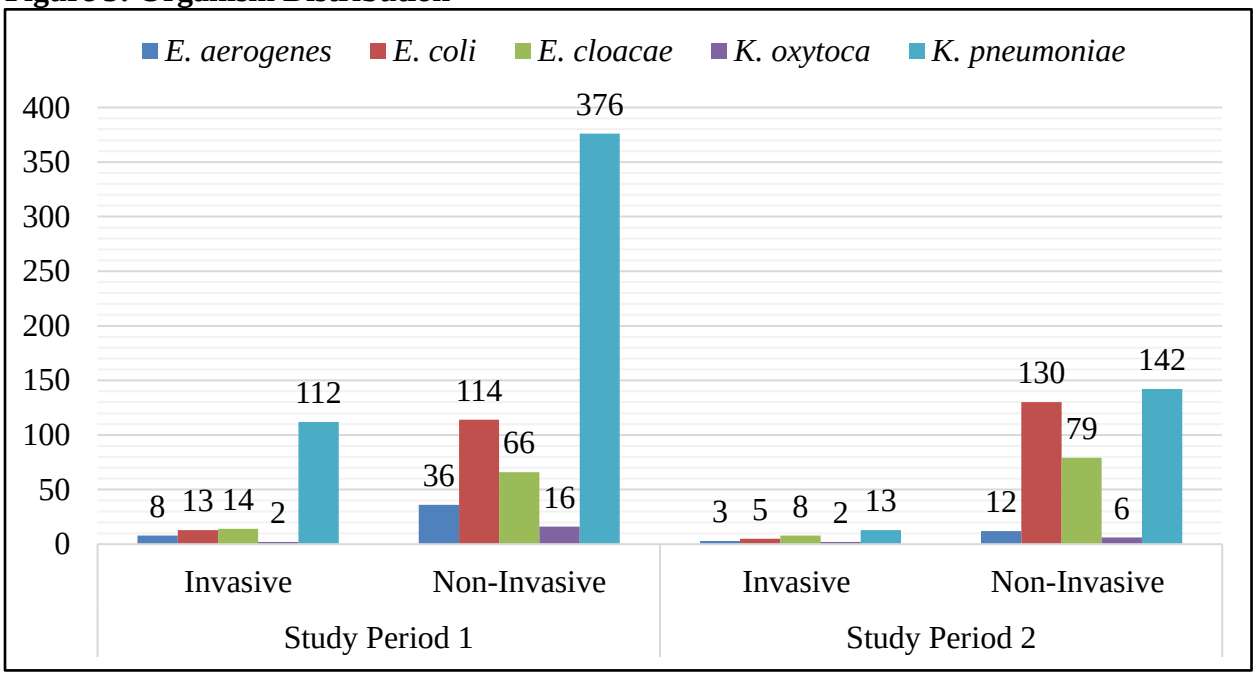
Figure 4: CRE Cases by Culture Source Per Study Period



4.2 CRE Organism Distribution

The distribution of CREs prior to the case definition change shows that *Klebsiella pneumoniae* infections accounted for 64% (488) of all CRE infections; 14.8% (112) of which were invasive (Figure 4). *Escherichia coli* CRE infections 18.8% (114) were the second most common in this sample, with 8.7% (13) (Figure 4). Distributions for the remaining CRE infections were as were: *Enterobacter aerogenes* 5.4% (8), *Enterobacter cloacae* 9.4% (14), and *Klebsiella oxytoca* 2% (0.3). Most these infections were non-invasive as well. In study period 1, *Escherichia coli* CRE infections, 34.9% (135), were the second most present in this sample, with 16.1% (5) (Figure 5).

Figure 5: Organism Distribution



The distribution of CREs in the second study period reveals that *Klebsiella pneumoniae* infections accounted for 36.7% (142) of all CRE infections during 2016; 41.9% (13) of these infections were invasive (Figure 5). Percentages for the remaining CRE infections were:

Enterobacter aerogenes-15% (3.9), *Enterobacter cloacae*-22.5% (87), and *Klebsiella oxytoca* 2.1% (8) (Figure 5). In both study periods, most CRE infections were non-invasive.

4.3 Risk Factors

For study period 1, the relationship between eleven risk factors for CRE infections and invasive infections was assessed (see Table 5). Of these risk factors, having chronic dialysis and being hospitalized for three or more days during culture collection showed the greatest percentages. Of those with chronic dialysis, 39.6% (36/91) were invasive. For those hospitalized for three or more days at the time of culture collection, 34.3% (50/146) were invasive. Percentages of invasive infections in patients with the following risk factors were similar; central venous catheters 33.1% (83/251 cases), indwelling devices 27.5% (83/302), and surgery in the year prior to culture collection 27.1% (51/188). All five risk factors were statistically significant with p-values <.0001.

Table 5: Study Period 1 - Risk Factors for Invasive Infection

Risk Factors	Invasive 149 (19.7)	Non-Invasive 608 (80.3)	Overall N=757	pvalue
ICU prior to positive culture	32 (34.0)	62 (66.0)	94	<.0001
Hospitalized for ≥3 days	50 (34.2)	96 (65.8)	146	<.0001
Hospitalized in the last year	97 (18.7)	423 (81.3)	520	.0049
Surgery within the last year	51 (27.1)	137 (72.9)	188	<.0001
Urinary catheter present	69 (17.6)	323 (82.4)	392	.2492
Central venous catheter	83 (33.1)	168 (66.9)	251	<.0001
Other indwelling device	83 (27.5)	219 (72.5)	302	<.0001
In an LTCF in the year prior	46 (11.6)	350 (88.4)	396	.0004
In an LTACH in the year prior	20 (24.4)	62 (75.6)	82	.0309
Chronic dialysis	36 (39.6)	55 (60.4)	91	<.0001
Immunocompromised	84 (18.5)	370 (81.5)	454	.0289

Chi-square was used to calculate p-values using 95 % confidence interval (CI) for the association between patient risk factors and culture source for pre-CRE case definition change (2011-2015).
Abbreviation: ICU-Intensive Care Unit and LTACH-longterm acute care hospital.
Variable information: data for variables regarding culture collection "after hospitalized for ≥ 3 days" or " in an LTACH in the previous year" was largely incomplete; Immunocompromised is a composite variable comprised of diabetes, chronic renal failure, solid tumor malignancy, connective tissue disease, solid organ transplant metastatic solid tumor, cirrhosis/liver failure, AIDS, hematologic malignancy.

Similar percentages were reported in the second study period. The top five most notable predictors of invasive CRE infections were stay in the ICU, hospitalization for three or more days at the time of culture collection, the presence of a central venous catheter, chronic dialysis,

and stay in LTACH in the year prior to original collection (see Table 6). Of which, stay in the ICU (34) and chronic dialysis (29) presented the highest percentages for invasive infections; 41.2% (14/34) and 31.1% (9/29) respectively. Percentages of the patients with the other riskfactors in this subset, that had invasive infections were hospitalization for three or more days at the time of culture collection 29.5% (18/61), central venous catheters 25.3% (23/91 cases), and stay in LTACH in the year prior to original culture collection 21.9% (9/41). All five risk factors were statistically significant with p-values no greater than .0016.

Table 6: Study Period 2 - Risk Factors for Invasive Infection

Risk Factors	Invasive 31 (8.1)	Non-Invasive 356 (91.9)	Overall N=387	pvalue
ICU prior to positive culture	14 (41.2)	20 (58.8)	34	<.0001
Hospitalized for ≥3 days	18 (24.5)	43 (75.5)	61	<.0001
Hospitalized in the last year	23 (10.9)	188 (89.1)	211	.1076
Surgery within the last year	13 (12.6)	90 (87.4)	103	.1084
Urinary catheter present	22 (12.2)	158 (87.8)	180	.0259
Central venous catheter	23 (25.3)	68 (74.7)	91	<.0001
Other indwelling device	21 (21.0)	79 (79.0)	100	<.0001
In an LTCF in the year prior	10 (8.3)	111 (91.7)	121	.8071
In an LTACH in the year prior	9 (22.0)	32 (78.0)	41	.0016
Chronic dialysis	9 (31.1)	20 (68.9)	29	<.0001
Immunocompromised	21 (10.3)	183 (89.7)	204	.2683

Chi-square was used to calculate p-values using 95 % confidence interval (CI) for the association between patient risk factors and culture source for pre-CRE case definition change (2016).
Abbreviation: ICU-Intensive Care Unit and LTACH-longterm acute care hospital.
Variable information: Immunocompromised is a composite variable comprised of diabetes, chronic renal failure, solid tumor malignancy, connective tissue disease, solid organ transplant metastatic solid tumor, cirrhosis/liver failure, AIDS, hematologic malignancy.

In both study periods, having a central venous catheter, hospitalization for three or more days at the time of culture collection and chronic dialysis are among the top five most prevalent risk factors for the invasive CRE infections. However, not all risk factors being study periods are statistically significant. For example though statistically significant in as a prevalent risk factor for invasive CRE infections post case definition change, the presence of a urinary catheter was not statistically signicant pre-case definition change (p=.2492). On the other hand, after the case definition change, unlike those in study period one, some risk factors were not statistically

significant; hospitalization in the last year (p=.1076), surgery within the last year (p=.1084), being immunocompromised (p=.2683), and stay in an LTCF in the previous year (p=.8071).

4.4 Univariable Analysis

A univariable logistic regression analysis was conducted to gauge the strength of the association between the eleven risk factors for CRE infections and invasive infection with both study periods.

Table 7: Study Period 1 - Risk Factors for Invasive Infection

Risk Factors	*Crude OR	95% CI	Adjusted OR	95% CI
Central venous catheter	6.8	4.7-9.8	*5.9	3.9-8.9
Other indwelling device	4.6	3.2-6.6	*4.0	2.7-6.1
Immunocompromised	1.6	1.1-2.3	*1.6	1.1-2.4
Surgery within the last year	2.3	1.6-3.3	*2.6	1.7-3.9
Hospitalized in the last year	2.1	1.4-3.1	*1.9	1.2-3.1
Hospitalized for ≥3 days	4.7	3.-6.8	*3.9	2.6-5.9
ICU prior to positive culture	4.4	2.9-6.6	*3.1	1.9-4.5
In an LTCF in the year prior	0.6	0.5-0.9	*0.5	0.3-0.7
In an LTACH in the year prior	2.2	1.4-3.4	*1.8	1.1-3.1
Urinary catheter present	1.5	1.1-2.1	1.3	0.8-1.9
Chronic dialysis	4.9	3.3-7.5	*4.1	2.7-7.1

Chi-square was used to calculate p-values using 95 % confidence interval (CI) for the association between patient risk factors and culture source for pre-CRE case definition change (2011-2015). *denotes statistical significance.
Abbreviation: ICU-Intensive Care Unit and LTACH-longterm acute care hospital.
Variable information: data for variables regarding culture collection "after hospitalized for ≥ 3 days" or " in an LTACH in the previous year" was largely incomplete; Immunocompromised is a composite variable comprised of diabetes, chronic renal failure, solid tumor malignancy, connective tissue disease, solid organ transplant metastatic solid tumor, cirrhosis/liver failure, AIDS, hematologic malignancy.

Table 8: Study Period 2 - Risk Factors for Invasive Infection

Risk Factors	*Crude OR	95% CI	Adjusted OR	95%CI
Central venous catheter	6.8	4.7-9.8	*8.8	4.01-18.9
Other indwelling device	4.6	3.2-6.6	*5.6	2.7-11.7
Immunocompromised	1.6	1.1-2.3	1.5	0.7-3.1
Surgery within the last year	2.3	1.6-3.3	1.8	0.9-3.8
Hospitalized in the last year	2.1	1.4-3.1	1.8	0.9-3.9
Hospitalized for ≥3 days	4.7	3.3-6.8	*8.1	3.9-17.1
ICU prior to positive culture	4.4	2.9-6.6	*11.2	4.9-25.6
In an LTCF in the year prior	0.6	0.5-0.9	0.91	0.4-1.9
In an LTACH in the year prior	2.2	1.4-3.4	*3.6	1.6-8.4
Urinary catheter present	1.5	1.1-2.1	*2.3	1.1-4.7
Chronic dialysis	4.9	3.3-7.5	*5.9	2.5-14.5

Chi-square was used to calculate p-values using 95 % confidence interval (CI) for the association between patient risk factors and culture source for pre-CRE case definition change (2016). * denotes statistical significance.
Abbreviation: ICU-Intensive Care Unit and LTACH-longterm acute care hospital.
Variable information: Immunocompromised is a composite variable comprised diabetes, chronic renal failure, solid tumor malignancy, connective tissue disease, solid organ transplant metastatic solid tumor, cirrhosis/liver failure, AIDS, hematologic malignancy.

In the study period 1, the presence of a central venous catheter was strongly associated with invasive CRE infections (OR 5.9, 95% CI 1.4 - 4.3). Thus, cases involving a central venous catheter in this study were 5.9 times more likely to have an invasive infection than those without a central venous catheter. There were strong associations found between invasive CRE infection and other risk factors as well; chronic dialysis (4.4, 95% CI 2.7-7.1) and other indwelling devices (4.0, 95% CI 2.7-6.1).

In the study period 2, staying in an ICU prior to having a positive culture had the strongest association with invasive CRE infections (OR 11.2, 95% CI 4.91-25.6). Patients with ICU stay in prior seven days are 11.2 times more likely to have an invasive CRE culture than patients that did not have an ICU stay in previous seven days.

Along with ICU status prior to having a positive culture, markedly strong associations were found invasive CRE infections and the following risk factors: central venous catheter (OR 8.8 , 95% CI 4.1-18.9), or other indwelling devices (OR 5.6, 95% CI 2.7-11.7), and hospitalization for three of more days (OR 8.1, 95% CI 3.9-17.1)

4.5 Multivariable Analysis

A multivariable logistic regression model was constructed to test the following hypothesis: If the current CDC CRE surveillance definition was designed to be more simple and sensitive, surveillance efforts in Atlanta should have an impact on patient profiles. This analysis was performed using invasive infection as the outcome of interest and study period (pre and post case definition change) as the predictor of interest. Manual, backward, forward, stepwise selection methods were employed to ascertain the best-fitting model (Figure 6).

Figure 6: Final Multivariable Logistic Regression Model of the Association between New Case Definition and Invasive CRE Infections

$$\text{Logit Invasive AND Non Invasive CRE Infections} = \beta 0 + \beta 1(\text{New Case Definition}) + \beta 2(\text{Hospitalized} >= 3 \text{ days}) + \beta 3(\text{Hospitalized in the year prior}) + \beta 4(\text{Central venous catheter present}) + \beta 5(\text{Other indwelling device}) + \beta 6(\text{LTCF}) + \beta 7(\text{Chronic Dialysis})$$

$$\frac{\text{Logit } Invasive\ CRE\ Infections\ (New\ Case\ Definition) = \beta 0 + \beta 1(1) + \beta 2(1) + \beta 3(1) + \beta 4(1) + \beta 5(1) + \beta 6(1) + \beta 7(1)}{\text{Logit } Invasive\ CRE\ Infections\ (Old\ Case\ Definition) = \beta 0 + \beta 1(0) + \beta 2(1) + \beta 3(1) + \beta 4(1) + \beta 5(1) + \beta 6(1) + \beta 7(1)}$$

*These covariates were pulled from literature and exhibit statistically significant bivariate associations.
The final model was derived from stepwise selection.

Table 9: Final Multivariable Model for the Association between New Case Definition and Invasive CRE Infection

Covariates	Crude OR	Adjusted OR
Hospitalized >=3 days		
No	1.00	1.00
Yes	*4.7 (3.3-6.8)	*8.11(3.9-17.1)
Hospitalized in the prior year		
No	1.00	1.00
Yes	*2.1 (1.4-3.1)	1.84 (0.9-3.9)
Central Venous Catheter present		
No	1.00	1.00
Yes	*6.8 (4.7-9.8)	*8.76 (4.1-18.9)
Other indwelling device		
No	1.00	1.00
Yes	*4.6 (3.2-6.6)	*5.68 (2.7-11.7)
Chronic Dialysis		
No	1.00	1.00
Yes	*4.9 (3.3-7.5)	*5.99 (2.5-14.5)
LTCF		
No	1.00	1.00
Yes	*0.6 (0.5-0.9)	0.91 (0.4-1.9)
Case Definition		
Old	1.00	1.00
New	*0.5 (0.3-0.8)	*0.61 (0.4-0.9)

* Indicates statistical significance.Multivariable logistic regression; adjusted model included the following covariates:Study Period Case Definition, Hospitalized >=3 days, Hospitalized in the year prior, central venous catheter present, other indwelling device, chronic dialysis, and stay in longterm care facility. Old case definition was reference group. * Indicates statistical significance. All ORs were statistically significant.

In multivariable analysis new case definition (OR 0.6, 95% CI 0.4-0.9), culture ≥ 3 days (OR 8.1, 95% CI 3.9-17.1), hospitalization in ≤1 year (OR 1.8, 95% CI 0.9-3.9), central venous catheter (OR 8.8, 95% CI 4.08-18.9), other indwelling device (OR 5.7, 95% CI 2.7-11.7), chronic dialysis (OR 5.9, 95% CI 2.5-14.5), and LTCF (OR 0.9, 95% 0.4-1.9) predicted invasive CRE infection (Table 9).

5. DISCUSSION AND CONCLUSION

Regarding culture source, the final results in the analysis show how the new case definition change may have impacted the patient population under surveillance. For instance, 2016 had the highest number non-invasive infections of all previous years in the study. The heaviest burden of disease remains among CRE patients 60-69 years of age in both study periods. Further, although most cultures were originally collected in the ER, LTCF, and OTHIP for both study periods, a more substantial number of cultures were collected in OPCLs in the first study period and a greater number of cultures were collected in ICUs in the second study period (Table 3-4).

The univariable analysis revealed presence of a central venous catheter to have the strongest association with invasive CRE infections (OR 5.9, 95% CI 1.4 - 4.3). In the second study period, staying in an ICU prior to having a positive culture had the strongest association with invasive CRE infections (OR 11.2, 95% CI 4.9-25.6).

Though slightly, the new case definition is predictive of invasive infections. Controling for notable risk factors, cases of CRE infections in the metropolitan Atlanta area following the new CRE case definition change had a 40% lower odds of invasive infections than that of the previous case definition. Ultimately, considering the limitations in this analysis, it is uncertain whether the new case definition directly led to this shift. Perhaps this impact is indicative of a more effective case definition as it was intended for the new case definition to be more specific and sensitive in detecting CRE infections. Nevertheless, this association warrants further investigation as few studies have examined the impact of the new CRE case definition on CRE surveillance efforts. The ability to more accurately capture invasive CRE infections is paramount

in controlling the spread of CRE, as invasive infections are far more severe than non-invasive infections.

3.5 Limitations

There are some limitations restricting the results of this study. The new case definition was also designed to capture more carbapenemase-producing CREs, however it is unclear if this goal was met regarding this sample as the presence of a carbapenemase was unknown for the majority of cases. Thus, the MuGSI surveillance personnel, are unable to evaluate sensitivity and specificity for detecting carbapenemase. The surveillance population is not representative of entire state or country, which produces low generalizability of results. Susceptibility testing capabilities may differ across laboratories and some testing instruments may not test low enough to detect non-susceptibility during 2011-2015. Lastly, not all reference labs serving the catchment area participated therefore CRE burden may be underestimated.

5.2 Recommendations and Future Studies

Moving forward, the Georgia EIP MuGSI surveillance efforts should differentiate CP-CREs from all other CREs in future samples, as this was a key goal for employing the new definition. Including and examining these elements, would help create a clearer picture of how the new case definition is being employed across the HD3 catchment area.

In short, the initial CDC CRE case definition, with its limited carbapenem criteria and poor ability to detect some CP-CREs, proved to be inadequate in identifying CREs (Chea et al., 2015). Case criteria that include non-susceptibility to any one of the four carbapenems is certainly simpler and capable of missing carbapenemase-producing strains, but with potential for capturing more non-carbapenemase producing CRE (Humphries & McKinnell, 2016). Thus, readjustments to the CRE case definition in the future may be necessary. All pathogens that are

resistant to a carbapenem represent isolates with high levels of drug resistance and warrant utilization of prevention and control strategies such as contact precautions to mitigate transmission. Medical facilities in Atlanta and beyond, could opt to designate more direct interventions, such as screening patient contacts and patient cohorting, for cases with cultures that meet these new criteria (Chea et al., 2015). Medical facilities desiring to curtail the work and cost that comes with more aggressive prevention and control strategies could conduct resistance-mechanism testing on cultures meeting the criteria outlined in the new case definition and reserve interventions for the isolates that show the production of carbapenemases (Chea et al., 2015).

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