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Approval Sheet

Incidence Rates and Predictors of Co-detection of *Clostridioides difficile* and Carbapenem-Resistant Enterobacteriaceae and impact on mortality in Metropolitan Atlanta 2011-2015.

By

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Master of Science

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Abstract Cover Page

Incidence Rates and Predictors of Co-detection of *Clostridioides difficile* and Carbapenem-Resistant Enterobacteriaceae and Impact on Mortality in Metropolitan Atlanta, 2011-2015.

By

Michael Holmes Woodworth

B.S., Emory University, 2006

M.D., Geisel School of Medicine, Dartmouth College, 2012

Advisor: Jesse Jacob, M.D., M.Sc.

An abstract of

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James T. Laney School of Graduate Studies of Emory University

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Abstract

Incidence Rates and Predictors of Co-detection of *Clostridioides difficile* and Carbapenem-Resistant Enterobacteriaceae and impact on mortality in Metropolitan Atlanta 2011-2015.
By Michael Holmes Woodworth

Background
Carbapenem-resistant *Enterobacteriaceae* (CRE) and *Clostridioides difficile* colonize the gut and share risk factors for transmission. However, data are limited on predictors for co-detection of these two urgent public health threats in individual patients and their impact on outcome.

Methods
The Georgia Emerging Infections Program performs active population and laboratory surveillance for *C. difficile* associated disease (CDAD) and CRE in the 8-county metropolitan Atlanta area. CDAD and CRE surveillance datasets from 8/2011 to 12/2015 were merged. Individuals with incident cases found in both datasets were defined as having co-detection. Patient-level covariates significant in bivariable analysis were eligible for inclusion in a multinomial logistic regression comparing CRE mono-detection and CRE/CDAD co-detection to CDAD mono-detection. Kaplan-Meier methods were used to estimate 90-day mortality from time of detection and compared with log-rank tests. Population-level death data were obtained by matching EIP datasets with state vital records death data.

Results
There were 757 incident CRE cases in 566 patients, 32,757 incident CDAD cases in 23,097 patients, and 211 incident CRE/CDAD co-detection cases in 128 patients. In co-detection cases, the median time between detections was 90.0 days (IQR 22-267 days). Both residence in long-term acute care hospitals or long-term care facilities (OR 1.94, 95% CI 1.06-3.57), and Charlson comorbidity index (CCI; OR 1.48, 95% CI 1.37-1.61) were associated with co-detection. Controlling for CCI, black vs not-black race was associated with co-detection (4.37, CI 2.06-9.26). 90-day mortality for patients with CRE/CDI co-detection (32.0%) and CRE mono-detection (29.3%) were worse than for CDI mono-detection (10.8%), $p < 0.0001$.

Conclusions
Black race, residence in long-term care, and higher CCI are associated with CRE/CDAD co-detection, which has worse 90-day mortality than CDAD and similar mortality to CRE mono-detection. Identification of patients with CRE and *C. difficile* co-detection could inform infection prevention strategies, and direct therapeutic interventions such as fecal transplantation.

Cover Page

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Introduction

According to the World Health Organization (WHO), antimicrobial resistance (AR) is 'one of the greatest threats to global health, food security, and development.' (1) In response to mounting concerns about AR, in 2013 the Centers for Disease Control and Prevention (CDC) released an AR threat report for the US, prioritizing three urgent threats, including *Clostridioides difficile* and carbapenem-resistant Enterobacteriaceae (CRE).(2) Despite substantial efforts to describe the frequency, risk factors, cost and impact on mortality of *C. difficile* and CRE individually, co-detection in individual patients is not well understood.

Clostridioides difficile is a Gram-positive, anaerobic bacterium that is the leading cause of antibiotic-associated diarrhea and is intrinsically resistant to many classes of antibiotics. CRE are a family of Gram-negative bacteria that are resistant to carbapenems, cephalosporins, and often other antibiotics that can typically only be treated with toxic last-line antibiotics. Importantly, both infections are frequently preceded by a period of colonization of the lower intestinal tract, when these pathogens are viable and detectable but asymptomatic.(3,4) *C. difficile* and CRE share many risk factors including exposure to hospitals, long-term care facilities (LTCF) and antibiotics.(5,6) Infection with either CRE or *C. difficile* is associated with poor health outcomes and increased costs.(7–9) However, the pipeline for new antibiotics to meet the threat of CRE, *C. difficile* and other multi-drug resistant organisms (MDRO) is dry.(10) The CDC and its partners have outlined infection control approaches and priorities for containing the spread of these infections but these strategies may not be as effective without continued antibiotic development. Additionally, incomplete adherence to these infection control approaches are common, especially with training fatigue or inadequate training.(11,12) Further, any approach short of complete

vigilance will result in spreading endemicity and mounting prevalence. A recent case illustrated the gravity of these threats when a woman in Nevada died from an *Klebsiella pneumoniae* infection that was resistant to all 26 clinically-available antibiotics.(13) Novel strategies in *C. difficile* and MDRO detection, infection control and colonization prevention are urgently needed to meet the challenges that these infections present.

Microbial therapeutics, most broadly applied as fecal microbiota transplantation (FMT), are gaining attention as a new therapeutic approach to eradicate MDRO colonization. Case reports and small open-label trials have reported the efficacy of microbial therapeutics like FMT in reducing MDRO colonization in one series and abundance of AR genes.(14–16) However careful study of the prophylactic use of these therapies depend on appropriate classification of high risk groups for prioritization and appropriate effect estimates in reduction of MDRO carriage. In addition, while turnaround time for sequencing-based diagnostics for microbial diversity is constantly shortening, clinical risk scores and surrogates for dysbiosis have the potential to reduce cost and accelerate clinical decision making but have not been well established.

We sought to use available epidemiologic data to describe a population anticipated to be at high risk of intestinal dysbiosis, patients with co-detection of CRE and *C. difficile*. There were three aims of this study. First, to estimate the incidence of CRE and *C. difficile* mono-detection and co-detection at the patient level in the eight county metropolitan Atlanta area from 1/2012-12/2015. Second, to estimate measures of association for place of residence prior to detection and Charlson comorbidity index score as exposures on the outcome of CRE and *C. difficile* co-detection compared to mono-detection of these pathogens. Third, to compare 90-day mortality for CRE and *C. difficile* co-detection to mono-detection of these pathogens. This epidemiologic approach of examining microbiota-

mediated MDRO colonization could inform development of clinical surrogates for gut dysbiosis and novel microbial therapeutic complements to current infection control practice.

Background

Clostridioides difficile

C. difficile is an anaerobic, Gram-positive, toxin-forming bacillus that is the most common healthcare-associated infection, with an estimated cost to acute care centers of $4.8 billion in 2008 U.S. dollars and $2.8 billion in 2013 U.S. dollars for recurrent *C. difficile* infection (RCDI) alone.(9,17) The number of incident *C. difficile* cases in 2011 using active population- and laboratory-based surveillance Emerging Infection Program (EIP) data across 10 geographic areas in the US was estimated at 453,000 cases, with 29,300 deaths.(5) The crude annual incidence rate per 100,000 population across these EIP sites ranged from 30 to 120 cases for community-acquired infection and 50 to 160 cases for healthcare-associated infection.(5) Higher incidence rates were noted among females, white persons and persons older than 65 years of age.(5)

Antibiotic exposure is an important risk factor for *C. difficile* associated diarrhea (CDAD) and is a key step in the pathogenesis of *C. difficile* infection (CDI). Use of broad-spectrum antibiotics to treat infections can also kill healthy anaerobic bacteria that mediate resistance to *C. difficile* colonization, leading to subsequent *C. difficile* germination into toxin-producing states. *C. difficile* is especially challenging to healthcare systems because it forms spores that are tolerant of ethanol-based hand hygiene products and can persist in rooms despite aggressive cleaning efforts.(18) Indeed, restriction of fluoroquinolone prescribing in England is thought to have accounted for an 88% decrease in *C. difficile* incidence since 2006.(19) Unfortunately, such a concerted effort in the U.S. has not yet been possible and *C. difficile* incidence rates appear to continue to rise.(17)

Carbapenem Resistant Enterobacteriaceae

Enterobacteriaceae is a family of Gram-negative bacteria that are associated with normal colonization of the human intestinal tract but are also common causes of infectious disease when they invade normally sterile body sites. Carbapenems, are the most broad-spectrum antibiotic class and regarded as a last-line therapy, however carbapenem resistance is emerging. There are multiple mechanisms by which an isolate may become resistant to carbapenems, but particularly concerning are carbapenemases, which are enzymes that can degrade carbapenems and cephalosporins (another frequently-used and well tolerated antibiotic class) and many can be transmitted across bacterial species by transfer of plasmids.

The first carbapenemase-producing Enterobacteriaceae isolate in the U.S. was reported in North Carolina in 2001. Since that time, it has been reported in nearly every state.(20) The most recent estimate for CRE incidence across seven diverse EIP surveillance sites was 2.93 cases per 100,000 persons.(6) Healthcare exposures including acute care hospitalization, surgery, residence in a LTCF, and indwelling devices are frequently seen among patients with CRE.(6) Residence in long-term care facilities is of particular interest as a risk factor for CRE as these facilities concentrate patients with a higher level of medical comorbidity, frequent socialization activities of residents, and face issues of staff turnover and fewer resources per admission. The cost to society for a single incident case of CRE is estimated to range from $37,778-83,512, primarily driven by attributable mortality and productivity losses.(7) In a model of societal economic burden of CRE, Bartsch et al projected that if incidence were to rise to 6.0 to 15.0 cases per 100,000 persons that this would have an estimated cost of $1.1 to 2.8 billion respectively.(7)

There are several challenges to accurately estimate the frequency of CRE. For example, case definitions have been in flux, antibiotic susceptibility testing results can vary

by laboratory testing platform, and there are regional differences in endemicity that limit generalizability. In a regional estimate of CRE incidence rates in southeastern US community hospitals, a greater than fivefold increase in incidence was observed from 0.5 isolates per 100,000 patient-days in 2008 to 4.1 isolates per 100,000 patient-days in 2012.(21) The authors concluded that rising rates observed were likely related to both increasing endemicity as well as increases in testing.(21) On the other hand, an analysis of frequency trends of CRE in New York, carbapenem-resistance among clinical *Klebsiella pneumoniae* isolates suggested significant reductions from 25.8% in 2006 to 10.5% in 2014 in hospital acquired infections, but in an anatomic site analysis, this reduction in incidence was present only in urinary isolates.(22) These disparate findings underscore the need for continued surveillance and attempts to understand frequency and risk-factors of CRE detection to optimize prevention efforts.

Recommendations for control or containment of healthcare-associated infections like C. difficile *and CRE*

The CDC has recommended a coordinated, regional network approach across health systems to reduce the spread of *C. difficile* and CRE (among other healthcare associated infections). The CDC has estimated that such coordination could reduce incidence by 55% across 15 years and reduce costs by billions of dollars.(23) Such an approach requires an organized strategy that includes antibiotic stewardship (though this may become increasingly difficult as prevalence of MDRO increase), active surveillance, contact isolation, enhanced hygiene and decolonization attempts and education. Hayden et al studied this type of bundled intervention of rectal screens, contact isolation, daily chlorhexidine bathing and staff education and adherence monitoring and reduced the rectal colonization prevalence of carbapenemase-producing Enterobacteriaceae from 45% to a stable plateau of 34% in long-

term acute-care hospitals (LTACH).(24) Modeling efforts to predict trajectory of CRE incidence in California have suggested that even with aggressive control measures as recommended by the CDC that the spread of CRE could only be reduced by 50%.(25) These changes in prevalence indicate that these approaches as a standard of care will not fully address the threat of rising MDRO prevalence.

Additional MDRO infection preventative interventions like vaccination have been studied but have not yet had widespread success or uptake. For example, attempts at development of a traditional vaccine have failed for *Staphylococcus aureus* and though administration of a non-toxigenic strain of *C. difficile* was shown to reduce risk of CDI, it has not been scaled up for production or marketing.(26) To date, beyond calls for multipronged prevention and containment strategies, there are no population-level treatment strategies in the US once an MDRO become endemic. This limitation in currently available approaches is demonstrated by its spread to most states.(25)

Fecal microbiota transplantation

The microbiota is defined as the sum of microbial community members present in a specific environment. The microbiome is variably defined as the sum genetic content of such a microbiota or the sum total of a given microbiota and its environment. Gut microbiota diversity can provide functional and spatial barriers to MDRO colonization.(27,28) States of low microbiota diversity is termed dysbiosis, which has been shown to be a risk factor for Gram-negative bacteremia.(29,30) Dysbiosis can be effectively treated with an intervention called fecal microbiota transplantation (FMT). FMT is the transfer of processed fecal material from a screened, healthy human donor to a patient, usually via colonoscopy but upper routes via nasogastric tube or encapsulated stool are also

effective. FMT has emerged as an important therapy for recurrent *C. difficile* infection (RCDI). FMT for RCDI has been shown in randomized clinical trials to be approximately 90% effective.(31–33) Case reports and case series have shown that FMT can also effectively reduce the overall number of AR genes carried by organisms like CRE and eradicate gut colonization by MDRO.(34,35) Microbiota diversity is primarily described with next-generation sequencing techniques. However, these approaches are more costly and less widely available than culture-based techniques, and have not been validated for clinical use. These challenges have generated interest in developing techniques to identify dysbiosis using currently available clinical diagnostics or risk scores as a surrogate.

Current knowledge gaps

There is much work to be done in using epidemiologic data to predict intestinal dysbiosis and to appropriately categorize patients with MDRO infection or colonization for further study of microbial therapeutics as treatment to eradicate MDRO carriage. Active surveillance for MDRO infection and colonization with *C. difficile* and CRE informs feedback of best practices for their containment. There are insufficient data on the co-detection of *C. difficile* and CRE within individual patients to understand if these patients have unique risk factors and outcomes like mortality. Evaluation of these risk factors, if modifiable, would support the prioritization of co-detection patients as a group for translational treatments like FMT to prevent infections. The CDC has made the case for development of microbiome diversity indices as important tools for studying impacts of novel antibiotics, the widespread use of antibiotics in agriculture, in finding markers of microbiota health and early warning signs of dysbiosis.(36,37) Others have called for epidemiologists to create well-designed and appropriately powered studies to limit MDRO

spread in healthcare systems.(38) To date, no single approach has effectively eradicated *C. difficile* or CRE from healthcare systems despite their associated costs and poor outcomes and new approaches are clearly needed to augment their response. We sought to identify predictors of CRE and *C. difficile* codetection using epidemiologic data that may be prevention intervention targets.

Methods

Study Design and Aims

This was a retrospective cohort analysis of two existing datasets from the Georgia Emerging Infections Program (EIP), one with surveillance data for C. difficile and the other for CRE (Multi-site Gram-negative Surveillance Initiative, MuGSI) from August 1 2011 to December 31 2015, which were linked for analysis. The first aim was to estimate the incidence of CRE and *C. difficile* co-detection, mono-detection of CRE, and mono-detection of *C. difficile*. The second aim was to estimate associations of place of residence, modified Charlson comorbidity index (CCI) score, demographic, and clinical characteristics of patients with CRE and *C. difficile* co-detection and CRE mono-detection compared to *C. difficile* mono-detection. The third aim was to estimate 90-day survival for patients with CRE and *C. difficile* co-detection compared to mono-detection of CRE or *C. difficile*.

Study Setting and Surveillance Population

C. difficile and CRE surveillance are components of the Georgia EIP, which is one of 10 CDC-funded sites to conduct active population- and laboratory-based surveillance in the US. The EIP has surveilled for *C. difficile* across all 10 sites since 2011, and for CRE, through MuGSI, at 3 sites since 2011 including Georgia, and at 7 sites since 2013. The population under surveillance by the Georgia EIP for both *C. difficile* and CRE includes the eight-county metropolitan Atlanta area, with a U.S. census-estimated population size that ranged from 3,753,452 in 2011 to 3,991,607 in 2015.

Case Definition and Ascertainment

All clinical laboratories providing testing for *C. difficile* and CRE in the metropolitan Atlanta catchment area participate in EIP surveillance, which allows for comprehensive surveillance of all laboratory-detected incident cases in the catchment area and population-level incidence rate estimates. Clinical data were not available for residents of the catchment area who did not have CRE or *C. difficile* detection for control group comparison purposes.

A CRE incident case was defined as a carbapenem-nonsusceptible and extended-spectrum cephalosporin-resistant (ceftriaxone, ceftazidime, ceftizoxime, and cefotaxime) *Escherichia coli*, *Enterobacter aerogenes*, *Enterobacter cloacae* complex, *Klebsiella pneumoniae*, or *Klebsiella oxytoca* isolate recovered from a body site that is normally sterile (eg, bloodstream) or urine from individuals residing in the surveillance area from 8/1/2011 – 12/31/2015.(6) Isolates were identified by local laboratories through a query of automated testing instruments based on the protocols of the laboratories and using the 2010 Clinical and Laboratory Standards Institute breakpoints. An incident CRE case was defined as the first CRE isolate from a patient during a 30-day period that met the surveillance definition. All incident CRE cases underwent medical record review with a standardized abstraction form that included demographic, clinical comorbidity, culture collection location, specimen source, associated infectious syndromes, health care exposures and patient outcomes. Patients with CRE but not linked to a case in the C. difficile dataset were classified as CRE monodetection cases.

A *C. difficile* case was defined as a positive *C. difficile* result on a *C. difficile* toxin or molecular assay of a stool specimen obtained from a surveillance-area resident at least 1 year of age who had not had a positive assay in the previous 8 weeks (i.e., incident infection). All incident cases under age 18 underwent full chart review. Due to the higher volume of

incident *C. difficile* cases over age 18, these cases underwent sampling for full chart review. One third of all incident *C. difficile* cases were randomly sampled stratified by age and gender. If a sampled incident case was found to be healthcare facility onset (HCFO) by location of diagnostic assay the case was further randomly sampled with 1/10 of such cases undergoing full chart review and the remaining 9/10 undergoing a partial chart review. If an incident case was sampled and found to not be HCFO, the case underwent full chart review. Incident *C. difficile* cases underwent medical record review using a standardized abstraction form. Both inpatient and outpatient medical records were reviewed for patient demographics, underlying clinical comorbidities, medication exposures, location of culture collection, first laboratory-confirmed recurrence defined as a positive specimen within 2-8 weeks after the last positive test, relevant health care exposures, and patient outcomes.(5) After identification of co-detection patients, 35 were found to have been non-sampled, incident cases in the *C. difficile* dataset and were retrospectively reviewed by EIP staff. Patients in the C. difficile dataset, but not in the CRE dataset were classified as *C. difficile* monodetection cases.

Co-detection Case Linking

Co-detection cases were linked using Link Plus version 2.0, which is a probabilistic record linkage and de-duplication program developed at CDC's Division of Cancer Prevention and Control (Atlanta, Georgia). Co-detection cases were linked using last name, first name, sex, and date of birth to find patients with incident cases in both the CRE and *C. difficile* EIP surveillance datasets. As many patients were found to have multiple incident cases in both datasets (recurrent or duplicate cases), they were linked using three approaches.

For the purposes of incidence rate estimation in Aim 1, cases were linked by the first incident case that occurred in each dataset. For the purposes of patient-level demographic and clinical characteristic comparisons between patients with co-detection of CRE and *C. difficile* or mono-detection of either CRE or *C. difficile*, patients were linked by the incident cases with the shortest time interval as this was thought to most closely approximate the underlying study question of finding epidemiological surrogates for intestinal dysbiosis. For the purposes of 90-day mortality estimation in Aim 3, cases were linked by the last incident case that occurred in each dataset as these would be most likely to appropriately reflect mortality.

Sensitivity analyses were performed to examine differences in classification of co-detection cases by time periods of <180 days, $\underline{\geq}$ 180 & > 365 days, and $\underline{\geq}$365 days and to compare characteristics of co-detection patients using either the time of first or second detection in a co-detection case pair. While there were modal trends in clinical and demographic characteristics by count of days between detections, they did not reach statistical significance.

Mortality and Survival Estimation and Comparison

EIP-abstracted all-cause mortality was determined based on documentation in the medical record at the time of outpatient evaluation for outpatients, at discharge if hospitalized, or at the end of a 30-day period for individuals undergoing outpatient dialysis or residing in a long-term care facility or a long-term acute care hospital. However, as this method was thought to underestimate the overall mortality for these patients (for example, some patients who were discharged to hospice with anticipated near-term mortality were

classified as having survived), patient identifiers were linked with state vital statistics datasets to improve the sensitivity of the estimate of all-cause mortality from time of detection.

Prior analysis from the Georgia EIP has shown that invasive (sterile-site culture) CRE infections have higher associated mortality than patients with CRE detected in urine cultures (unpublished data, Sexton et al). Survival for patients with invasive vs urine cultures among patients with co-detection was also estimated with Kaplan-Meier methods and compared with log-rank tests.

Modified Charlson Comorbidity Index Calculation

The EIP collects data on components of the CCI score, which is a commonly used and validated research tool that quantifies medical morbidity for a patient. The *C. difficile* dataset does not specify level of chronic liver disease severity and both datasets use best estimates of end-organ damage to estimate diabetes severity, resulting in some degree of misclassification, and therefore were labeled as modified CCI scores. For purposes of this analysis, 1 CCI point was assigned for myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, liver disease, diabetes and each decade of age >40. Two CCI points were assigned for hemiplegia, moderate or severe renal disease, diabetes with end organ damage, any non-metastatic solid tumor, leukemia or lymphoma. Three CCI points were assigned for moderate or severe liver disease when so classified (only in the CRE dataset). Six CCI points were assigned for metastatic solid tumor or AIDS. In co-detection cases, the greater of the modified CCI scores (either from the corresponding incident CRE or *C. difficile* case) were used. The sums of CCI scores by detection group were compared.

Data Management and Statistical Analyses

Patient-level demographic and clinical characteristics of CRE and *C. difficile* mono-detection and CRE and *C. difficile* co-detection cases were summarized. Bivariate demographic and clinical characteristics were compared with t-tests, χ^2 and Fisher exact tests as appropriate.

Incidence rates for CRE and *C. difficile* cases were calculated by dividing the incident case count by corresponding catchment area census population estimates as the population at risk and standardized to 100,000 patient-period denominators. As detection events occurred on different days in all but two patients, a separate estimate of incidence rates was made for CRE and *C. difficile* mono-detection using population estimates as the population at risk, and using the total count of incident cases for CRE and *C. difficile* as the population at risk for co-detection cases. Initial annual incidence rate calculations found a dramatic fall in the incidence rates of co-detection cases, suggesting a possible component of surveillance bias as more recent cases had less follow up time to have a detection event identified in the second dataset. As such, incidence rates were calculated in six-month periods from 1/2012 – 6/2012 through 1/2015 – 6/2015 to allow a standardized six-month period of follow up for potential incident co-detection cases to be identified in the last six months of the study period.

As mono-detection of CRE or *C. difficile* and co-detection of both CRE and *C. difficile* are mutually exclusive and non-ordinal, characteristics that were statistically significant in bivariate tests were candidates for inclusion in a multinomial logistic regression model. Place of residence was categorized as home (private residence), LTACH/LTCF/SNF (long-term acute care hospital / long term care facility / skilled nursing facility), or inpatient (admitted to acute care hospital). Separate logistic regression models were avoided in attempt to make

fuller use of the data, increase power, and restrict potential for outcome probability modeling > 1.0. Two multinomial logistic regression models were constructed with *C. difficile* mono-detection as the reference detection outcome compared to CRE mono-detection and co-detection outcomes. Multinomial odds ratios were used to estimate association of place of residence and modified CCI score as primary exposures of interest on the multinomial detection group outcome. Significant covariates from bivariate analyses and from prior epidemiologic studies of *C. difficile* and CRE (age, race, and gender) were included in these models. Interaction effects were tested using chunk tests and comparing AIC values for each model.

After linking incident cases to state vital statistic mortality data, overall 90-day mortality estimates were compared with χ^2 tests and 90-day survival estimates were created using a Kaplan-Meier product-limit approach and compared with log-rank tests.

Information was occasionally missing for some variables given the limitations of medical record review, as such denominators vary for some variables. There were also minor differences in some variable definitions between the surveillance datasets. For example, place of residence was defined by place of residence three days prior to detection in the CRE dataset but as place of residence four days prior to detection in the *C. difficile* dataset. Wherever there were discrepancies in values, positive findings were retained. For example, if a co-detection patient was noted to have diabetes in one dataset but not the other, then they were classified as having diabetes for the purposes of this analysis. Efforts were made by clinical researchers to obtain missing data from clinical records and laboratories when missing.

Amounts and patterns of missing data were examined using frequency statistics as described above. With the exception of presence of decubitus/pressure ulcer, which was

not recorded for cases in the *C. difficile* dataset and history of hematopoietic stem cell transplant, which was not recorded for cases in the CRE dataset and is not a component of the CCI score, there was no obvious violation of missing at random assumptions for these patterns of missing data. Subjects that were missing data on the outcome of interest and were excluded from the corresponding component of analysis.

All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, North Carolina). A 2-sided p-value of <0.05 was considered statistically significant.

Institutional Review Board Approval

The *C. difficile* and MuGSI EIP surveillance program protocols have been reviewed by the Emory and Atlanta Veteran's Affairs Medical Center Institutional Review Boards (IRB) and considered exempt from review.

Results

Identified Cases and Patients for Analysis

From 8/1/2011 to 12/31/2015, there were 757 incident CRE cases in 566 patients, 32,757 incident *C. difficile* cases in 23,097 patients, and 211 incident CRE and *C. difficile* co-detection cases in 128 patients. See **Figure 1** for illustration of patient inclusion flow diagram.

Demographic and Clinical Characteristics

Patient demographic characteristics are presented in **Table 1**. Patients with CRE and *C. difficile* co-detection were a median 66 years old (IQR 46-76), which was similar to patients with CRE or *C. difficile* mono-detection, with median 64 (IQR 54-74) and 62 (IQR 46-76) years old respectively. In all three groups, patients were more commonly female than male, including 58% female in co-detection patients, 58% female in CRE mono-detection patients and 59% in *C. difficile* mono-detection patients. Higher proportions of patients with CRE and *C. difficile* co-detection and CRE mono-detection were black (44% and 54% respectively) compared to patients with *C. difficile* mono-detection (28%, $p < 0.0001$). Asian race and Hispanic ethnicity were similar between all three groups.

Place of residence, clinical characteristics, and modified CCI scores are shown in **Table 2.** Patients with CRE mono-detection or CRE and *C. difficile* co-detection were more frequently residing in an LTACH, LTCF, or skilled nursing facility in the 3-4 days prior to detection (SNF) (40% and 44% respectively) compared to patients with *C. difficile* mono-detection (13%). Patients with *C. difficile* mono-detection more frequently resided at home or inpatient (24% and 61% respectively) compared to patients with CRE mono-detection or

CRE and *C. difficile* co-detection (17% and 35%; and 34% and 17% respectively; p <0.0001 for χ^2 test of contingency table of all residence and detection groups).

Patients with CRE mono-detection and *C. difficile* and CRE co-detection consistently had several-fold higher proportions of medical comorbidities compared to *C. difficile* mono-detection. Burden of comorbidities were also frequently higher among patients with *C. difficile* and CRE co-detection compared to CRE mono-detection. For example, 35% of co-detection patients had chronic kidney disease compared to 27% and 3% of CRE and *C. difficile* mono-detection cases respectively (p <0.0001). The higher burden of medical comorbidities among patients with CRE mono-detection and *C. difficile* and CRE co-detection compared to *C. difficile* mono-detection was also reflected by higher median (IQR) modified CCI scores (7 (4-9), 6 (3-8), and 4 (2-5) respectively). As age, race, residence, and medical comorbidities were statistically significantly different between detection groups, these covariates were included in the subsequent model development. As most studies of *C. difficile* and CRE frequency have reported higher proportion of female cases, sex was included as a covariate in model development as well.

Time Between Detection Events and Sequence of Detection

The median number of days between detection events among cases with co-detection of CRE and *C. difficile* during the study period was 90 (range 0 – 1,352). The distribution of count of days between detection events by sequence of detection is shown in **Figures 2 and 3**.

Incidence of CRE and C. difficile Mono-Detection and CRE & C. difficile Co-Detection

Estimates for six-month incidence rates and illustration of trend are shown in **Tables 3 and 4, and Figures 4 and 5**. From 1/2012-6/2012 to 1/2015-6/2015, the six-month incidence rate for *C. difficile* detection increased from 94.6 cases/100,000 person-periods to 100.2 cases/100,000 person-periods. The six-month incidence rate for CRE mono-detection remained largely stable through the study period with a slight decrease from 1.8 cases/100,000 person-period in 1/2012-6/2012 to 1.5 cases/100,000 person-period in 1/2015-6/2015. Using catchment area population estimates as a population at risk for co-detection, the six-month incidence rate was relatively stable from 0.6 cases/100,000 person-periods in 1/2012-6/2012 to 0.5 cases/100,000 person-periods in 1/2015-6/2015. Using count of *C. difficile* and CRE incident cases as the population at risk for co-detection (see **Table 4** and **Figure 5**), six-month incidence rates declined from 651.6 cases/100,000 person-periods to 492.6 cases/100,000 person-periods though there were increases and decreases observed across periods.

Multinomial Logistic Regression Modeling of Residence as Exposure and Detection Group as Outcome

CRE mono-detection and co-detection were compared to *C. difficile* mono-detection as the outcome reference group. Residing in an inpatient facility (OR 1.94, 95% confidence limit 1.06-3.57) or LTACH/LTCF/SNF (OR 3.20, 95% confidence limit 1.67-6.11) were associated with co-detection. Residing in an LTACH/LTCF/SNF (OR 3.901, 95% confidence limit 3.07-4.95) was associated with CRE mono-detection. Age was positively associated with co-detection (OR 1.01, 95% confidence limit 1.00-1.03) and CRE mono-detection (OR 1.01, 95% confidence limit 1.00 – 1.01). Black race was associated with co-detection (OR 3.10, 95% confidence limit 1.28-7.51) and CRE mono-detection (2.50, 95%

confidence limit 1.83-3.42). Odds ratio and confidence limit estimates are shown in **Table 5**.

Multinomial Logistic Regression Modeling of Modified CCI Score as Exposure and Detection Group as Outcome

CRE mono-detection and co-detection were compared to *C. difficile* mono-detection as the outcome reference group. Higher modified CCI score was positively associated with co-detection (OR 1.48, 95% confidence limit 1.37-1.61) and CRE mono-detection (OR 1.59, 95% confidence limit 1.53-1.65). White race was associated with CRE mono-detection (OR 2.27, 95% confidence limit 1.59-3.24). Black race was associated with co-detection (OR 4.37, 95% confidence limit 2.06-9.26) and CRE mono-detection (OR 5.00, 95% confidence limit 3.53-7.08). Odds ratio and confidence limit estimates are shown in **Table 6**.

Detection Group Mortality and Kaplan-Meier Survival Estimates

The 90-day overall mortality for patients with CRE and *C. difficile* co-detection (32.0%) and CRE mono-detection (29.3%) were worse than for *C. difficile* mono-detection (10.8%), $p < 0.0001$. Using Kaplan-Meier methods to estimate 90-day survival (**Figure 6**), CRE and *C. difficile* co-detection CRE mono-detection had significantly worse survival than *C. difficile* mono-detection by log-rank test ($p < 0.0001$).

Similar to findings previously reported by the Georgia EIP on data for all CRE detections in the catchment area, among patients with CRE mono-detection, CRE detection in urine culture had better survival compared to CRE detection in sterile-site culture (**Figure 7**). This distinction in survival between urine and sterile-site cultures was not seen among patients with co-detection (**Figure 8**).

Discussion

This study estimated incidence rates, association of clinical characteristics, and mortality of patients with co-detection of *C. difficile* and CRE compared to mono-detection of *C. difficile* or CRE using population- and laboratory-based surveillance data for metropolitan Atlanta from 2011-2015. Six-month incidence rates for co-detection appeared to decline across the study period from 651.6 cases/100,000 person-periods to 492.6 cases/100,000 person-periods. Co-detection compared to mono-detection of *C. difficile* in a multinomial model was associated with black race, residing in a LTACH, LTCF, or SNF, and higher CCI score. Patients with co-detection had similar 90-day overall mortality compared to CRE mono-detection and worse mortality than *C. difficile* mono-detection.

Co-detection six-month incidence rates may be declining in metropolitan Atlanta

There are multiple factors that could contribute to an apparent decrease in six-month incidence rates for co-detection across the study period. The absolute number of co-detection cases per six-month period was relatively low, ranging from 13-24, which was consistently 2-3 fold less frequent than CRE mono-detection and over 200 fold less frequent than *C. difficile* mono-detection, leading to greater changes in standardized rates with small changes in detection counts. Though CRE incidence rates were relatively stable throughout the study period, the *C. difficile* incidence rates increased across the study period, which increased the denominator of incident cases for co-detection incidence-rate calculations, which subsequently decreased the overall rate estimate and is a likely rationale for the observed decrease. Surveillance bias (decreasing follow-up time for a patient to have a second detection event later in the study compared to earlier in the study period) is another

possibility, however we attempted to limit this by assessing six-month period incidence rates, a period of time that is twice the median of 90 days between detection events that was observed in this study. Another plausible reason for a true decrease in co-detection incidence rates is appropriate application of infection prevention interventions that could reduce acquisition of another healthcare associated infection after initial detection. Though this possibility is challenging to test without data on facility-level contact precaution adherence, it was also suggested as an explanation for an observed decline in CRE incidence through multi-site surveillance by the CDC.(39)

There are no other published population-level estimates of co-detection of *C. difficile* and CRE to compare the incidence rates from this study. The estimates for *C. difficile* mono-detection are similar to those that have been reported, and while the estimates for CRE mono-detection are lower than other series, this likely reflects the higher proportion of incident CRE cases with any co-detection (211/757, 27.9%), who by definition were not classified as mono-detection, compared to the proportion of incident *C. difficile* cases with any co-detection (211/32,757, 0.6%). The higher rates of codetection among incident CRE cases compared to *C. difficile* incident cases may reflect the rising frequency of community-acquired *C. difficile*, a group that would be spared the risk factors of heavy antibiotic use and invasive lines that are associated with CRE colonization and infection.

The findings from this study are similar to findings from single-center reports of active surveillance for MDRO among LTCF and acute care hospitals, although single-center MDRO prevalence varies widely and does not necessarily reflect regional prevalence. For example, Prasad et al performed active surveillance for 301 residents in LTCF and found that 19.3% were asymptomatically colonized with *C. difficile*, 18.9% were colonized with CRE, and 5.7% were colonized with both.(40) Banach et al conducted a nested case-control

study of rates of CRE positivity in stool samples from an acute care hospital submitted for *C. difficile* testing. Banach et al found that of 1,045 tested specimens, 90 (8.6%) were positive for *C. difficile* and CRE carriage was similar between *C. difficile* positive and negative groups (2.2% and 2.6% respectively) – findings that would suggest that CRE risk is independent of *C. difficile* risk.(41) In a third point-prevalence survey of LTCFs in Italy in 2015 with 489 patients, asymptomatic *C. difficile* colonization was found in 5.1% (21/409) of patients, and of carbapenemase-producing Enterobacteriaceae of 1% (5/487) and overall colonization by any MDRO of more than 60%.(42) However, any co-detections of CRE were not described in this survey. Further study of the epidemiology of CRE and *C. difficile* co-detections would be feasible by a larger cooperative analysis using data from the 7 EIP sites conducting CRE and *C. difficile* surveillance.

The epidemiology for CRE is distinct from extended-spectrum β-lactamase producing Enterobacteriaceae (ESBL), and the burden of ESBL is much higher than CRE, however, they are the same family of bacteria and transfer of plasmid-mediated CRE and ESBL resistance mechanisms could follow similar trajectories if unchecked. *C. difficile* and ESBL co-detections have also not been extensively studied but there are some informative comparisons. For example, Vervoort et al found in a study of 120 patients with antibiotic-associated diarrhea that patients with *C. difficile* had higher proportions of ESBL-producing Enterobacteriaceae colonization (62% vs 31%).(43) These findings suggest that if CRE prevalence were to increase, that it may concentrate in patients with *C. difficile* given the risk factors these pathogens share in common.

Co-detection is Associated with Residence in a LTACH/LTCF/SNF and Higher CCI Score

In this analysis of clinical characteristics of co-detection and CRE mono-detection cases compared to mono-detection of *C. difficile* using multinomial logistic regression, residing in a LTACH/LTCF/SNF, higher modified CCI score, race, and higher age were factors associated with co-detection. These findings are similar to other population- and health center-level reports of risk factors associated with *C. difficile* or CRE acquisition. For example, in their active surveillance strategy to identify asymptomatic CRE carriers in healthcare facilities by adding stool screening for CRE for patients being tested for *C. difficile,* Banach et al found that CRE detection was associated with admission from SNF, percutaneous tube feeding, ICU admission, mechanical ventilation, and surgery. Prasad et al estimated the prevalence of asymptomatic colonization with CRE and *C. difficile* and found that mechanical ventilation and enteral tube feeding were significantly associated with *C. difficile* and CRE colonization.(40) In Arvand et al's description of *C. difficile* and ESBL-producing Enterobacteriaceae colonization in rehabilitation clinics in Germany, patients in neurologic rehabilitation facilities were more likely to have colonization compared to orthopedic surgery rehabilitation facilities and had higher proportions of patients that were older, had received antibiotics, and device use.(44) Significant risk factors for MDRO colonization (including CRE and *C. difficile*) in a LTCF prevalence survey in Italy included bedridden status, incontinence of urine and/or stool, and for *C. difficile* recent admission for treatment of *C. difficile*.(42) These factors are indicators of critical illness and chronic medical morbidity that would be analogous to higher CCI score.(41) As a higher proportion of CRE incident cases were co-detections, these findings may in part be driven by the distribution of characteristics of patients with CRE detection.

Our results identified similar risk factors but our study adds strength of population level surveillance. This approach of surveilling all *C. difficile* and CRE detections includes

community and healthcare facility associated *C. difficile* and CRE detection and co-detection, which enhances the generalizability of findings across centers, though rates vary by region. Rates of CRE detection in Atlanta are lower than those reported in the metropolitan area of New York city for example. Further study is needed to validate these risk factors in other regions if these risk factors are to be used clinically in identification of patients at risk of CRE and *C. difficile* co-detection. Analysis of these data across EIP sites could further enhance external validity.

NH have been recognized as significant reservoirs of *C. difficile* and MDRO like CRE. Others have pointed out that the burden of these diseases is likely to be higher for NH than for acute care facilities because of the higher numbers of beds and the longer length of stays.(45) In a study of *C. difficile* burden among nursing home residents described higher degrees of comorbidity and mortality than non-nursing home onset *C. difficile*.(46) Further, there are challenges in infection control and prevention that are specific to nursing homes including limited resources for active laboratory surveillance, limited evidence-based guidance that is specific to these care settings and not extrapolated from acute care settings, high staff turnover that may influence adherence to recommended infection control practices, and cultural perceptions about negative effects of isolation on NH residents.(45)

Taken together, these results suggest that targeted screening of patients with *C. difficile* and CRE who are admitted from an LTACH/LTCF/SNF, have invasive lines, or have high CCI scores may inform prioritization for current infection control practices and study of novel interventions to reduce MDRO carriage like FMT.

Mortality for Patients with Co-detection is Similar to CRE Mono-detection and Worse than C. difficile *Mono-detection*

Patients with CRE and *C. difficile* codetection had similar 90-day all-cause mortality compared to CRE mono-detection but much worse mortality compared to *C. difficile* monodetection. This may also be a reflection of the characteristics of CRE patients dominating the features of co-detection patients. However, while invasive infection clearly has worse overall mortality among patients with CRE mono-detection, this distinction was not seen in patients with CRE and *C. difficile* codetection in this study. The most likely explanation for this finding is the high level of medical comorbidity concentrated in this relatively smaller group, and associated 10-year mortality predicted by the CCI score. However, intestinal microbiome studies to assess levels of dysbiosis in these patients could inform whether there is a potential role for microbial therapeutics to modify this risk of mortality, through reduction in MDRO carriage/infection or other potential benefits.

Study Strengths

This study has several strengths. It is large, and the first population- and laboratory-based estimate of incidence, associated factors and mortality of co-detection of *C. difficile* and CRE. In the findings of the seven participating MuGSI sites on their composite estimated incidence rates for CRE, Atlanta had one of the highest incidence rates, suggesting that our site is one of the best-powered for such analyses. As mentioned, population- and laboratory-based surveillance captures all incident cases for the specified population in the study time period, which includes acute care hospitals in addition to patients who reside in long-term care facilities and in the community and is not restricted to a given healthcare facility. However, further study across other EIP sites could further enhance external validity.

Study Limitations

There are multiple limitations of this study design. The relative rarity of CRE incident cases may have biased results of the overall conclusions, however this study is among the larger series of reported CRE cases. As clinical data relied on medical record review, not all data points of interest were available for all incident cases. Further, there is a risk of selection bias with sampling of incident *C. difficile* cases, though this should be minimized by the random sampling procedures used and large differences between sampled and unsampled groups were not seen in sensitivity analyses. In this series, a high proportion of CRE isolates were from urine cultures and many *C. difficile* detections were from polymerase chain reaction-based assays, which have been criticized as overly sensitive – both of these points could contribute higher rates of detection of colonization vs infection. However, from the standpoints of understanding reservoirs of MDRO in healthcare systems, all CRE and *C. difficile* detections, be they colonization or true infection, are of concern. Further, understanding predictors for detection and co-detection of these pathogens may suggest modifiable targets for future microbiota-modifying therapeutics that could *prevent* progression from colonization to infection.

Future Directions

Further study of risk factors for recurrent infection with CRE and *C. difficile* is needed to develop clinical and epidemiologic indicators of intestinal dysbiosis. Inclusion of next-generation sequencing approaches in epidemiologic studies with healthy control populations will allow for improved measures of dysbiosis. Inclusion of other MDRO that are known to be chronic colonizers and related to intestinal dysbiosis like vancomycin-resistant *Enterococcus* may further inform clinical risk scores. These may better identify

patients who might benefit from prophylactic gut microbiota restoration with fecal microbiota transplantation or other therapies.

Antibiotic class exposure is an important risk factor for development of both CRE and *C. difficile* and is available in the *C. difficile* but not CRE datasets. Describing risk of MDRO co-detection could aid clinicians and antibiotic stewardship programs in mitigating risk intestinal dysbiosis. The best evidence for FMT as a treatment for RCDI and its associated dysbiosis is among patients with multiple recurrent infections. Further study of patients with recurrent incident infections in both the *C. difficile* and CRE datasets could further inform attempts to develop clinical and epidemiologic surrogates for intestinal dysbiosis. For example, if *C. difficile* and CRE co-detection is confirmed with sequencing approaches to represent intestinal dysbiosis, then this could suggest a potential benefit of earlier FMT rather than waiting for a second or third recurrent episode of *C. difficile* prior to FMT, which could reduce costs and disability associated with RCDI. As this study has primarily focused on all detection events, a more clinically meaningful approach may be to focus on antigen positive *C. difficile* test results and invasive CRE culture results as not all patients are actively screened for *C. difficile* or CRE outside of outbreak or research settings.

These findings suggest that patients with high CCI scores being admitted from LTACH/LTCF/SNF care could be an important priority group for further study of microbial therapeutic interventions to eradicate MDRO colonization.

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Tables and Figures

Figure 1: Flow diagram of cases and patients identified in the Georgia Emerging Infections Program (EIP) C. difficile and Multisite Gram-negative Surveillance Initiative (MuGSI) CRE surveillance datasets for the Eight County Metropolitan Atlanta Area, 2011-2015.

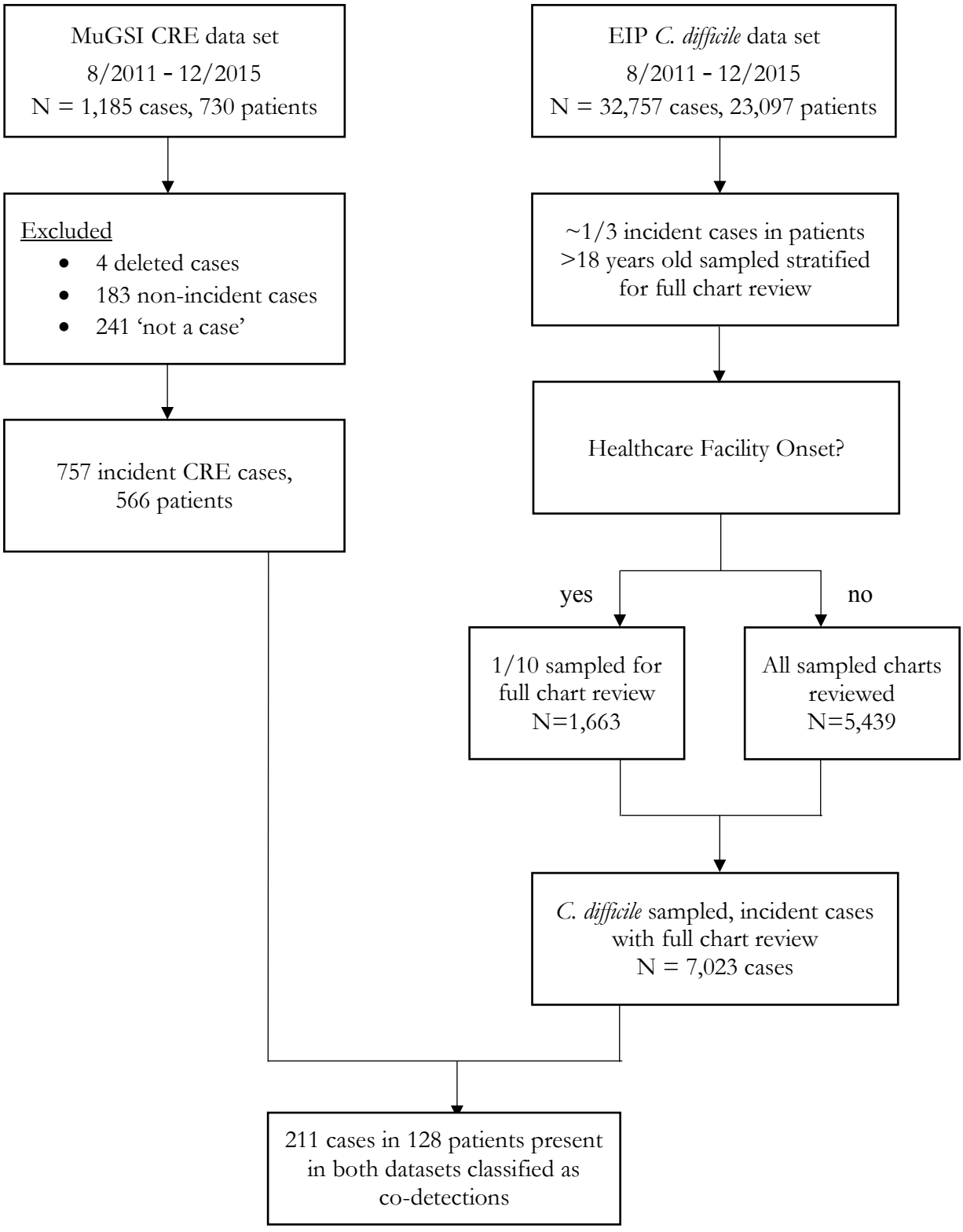

Table 1: Demographic characteristics of patients with mono-detection of C. difficile or CRE and co-detection of C. difficile & CRE in metropolitan Atlanta, 2011-2015 linked by closest time of co-detection.

	Mono-detection		Co-detection	
Characteristic	*C. difficile* (n = 15,476)	CRE (n = 564)	*C. difficile* and CRE (n = 124)	*p*-value
Median age in years (IQR)	62, (46-76)	64, (54-74)	66, (54-77)	
Female sex, n (%)	9, 176 (59.2%)	325 (57.6%)	72 (58.1%)	0.26
Race[a]				
Asian	204 (1.3%)	9 (1.6%)	2 (1.6%)	0.90
Black	4,367 (28.2%)	304 (53.7%)	54 (43.6%)	<0.0001
White	6,125 (39.6)	193 (34.1%)	22 (17.7%)	<0.0001
Unknown	1,367 (8.8%)	58 (10.3%)	5 (4.0%)	0.22
Ethnicity				
Hispanic or Latino	338 (2.8%)	16 (2.9%)	3 (2.4%)	
Not Hispanic or Latino	10,001 (83.2%)	345 (61.4%)	102 (82.3%)	<0.0001
Unknown	1,681 (14.0%)	201 (35.8%)	19 (15.3%)	

CRE – carbapenem-resistant Enterobacteriaceae, IQR – interquartile range

Table 2: Residence, comorbidities and modified Charlson comorbidity index (CCI) scores of patients with mono-detection of C. difficile or CRE and co-detection of C. difficile & CRE in metropolitan Atlanta, 2011-2015 linked by closest time of co-detection.

	Monodetection		Co-detection	
Characteristic	*C. difficile* (n = 6,079)	CRE (n = 525)	*C. difficile* and CRE (n = 121)	*p*-value
Residence before detection				
Inpatient	1,440 (23.7%)	91 (17.3%)	21 (17.4%)	<0.0001
LTACH/LTCF/SNF	821 (13.4%)	211 (40.2%)	53 (43.8%)	
Home	3,717 (61.1%)	186 (35.4%)	31 (33.9%)	
Other	110 (1.8%)	37 (7.1%)	6 (5.0%)	
Comorbidities[a]				
AIDS	51 (0.3%)	8 (1.4%)	2 (1.6%)	<0.0001
Chronic Kidney Disease	532 (3.4%)	150 (26.5%)	43 (34.7%)	<0.0001
Chronic Liver Disease	93 (0.6%)	11 (1.9%)	0	0.002
Chronic Lung Disease	500 (3.2%)	137 (23.2%)	32 (25.9%)	<0.0001
Decubitus/Pressure ulcer	-	172 (30.4%)	46 (37.1%)	0.87
Dementia	204 (1.3%)	129 (22.8%)	29 (23.4%)	<0.0001
Diabetes Mellitus	729 (4.7%)	251 (44.4%)	53 (42.7%)	<0.0001
Heart Failure	316 (2.0%)	135 (23.9%)	39 (31.5%)	<0.0001
Hematologic malignancy	128 (0.8%)	7 (1.2%)	3 (2.4%)	<0.0001
Hemiplegia/Paraplegia	31 (0.3%)	75 (13.3%)	21 (16.9%)	<0.0001
HIV	110 (0.7%)	11 (1.9%)	2 (1.6%)	0.004
HSCT	22 (0.1%)	-	-	-
Myocardial Infarction	81 (0.5%)	37 (6.5%)	9 (7.3%)	<0.0001
PVD	98 (0.6%)	47 (8.3%)	9 (7.3%)	<0.0001
Solid Organ Transplant	48 (0.4%)	15 (2.7%)	5 (4%)	<0.0001
Solid tumor no mets	282 (1.8%)	39 (6.9%)	6 (4.8%)	<0.0001
Solid tumor with mets	129 (0.8%)	12 (2.1%)	3 (2.4%)	<0.0001
Stroke	234 (1.5%)	140 (24.7%)	30 (24.2%)	<0.0001
Modified CCI				
Median (IQR)	4 (2 – 5)	7 (4 – 9)	6 (3 – 8)	
Range	1 – 17	0 – 19	1 – 16	

CRE – carbapenem-resistant Enterobacteriaceae, AIDS – acquired immunodeficiency syndrome, HIV – human immunodeficiency virus, PVD – peripheral vascular disease, HSCT – hematopoietic cell transplant, IQR – interquartile range, - data not available, mets – metastases, [a] – comorbidity data were available for 15,476 *C. difficile* patients, 440 CRE patients, and 94 co-detection patients

Figure 2: Count of days between detection of *C. difficile* or carbapenem-resistant Enterobacteriaceae in metropolitan Atlanta, 2011-2015. N=125.

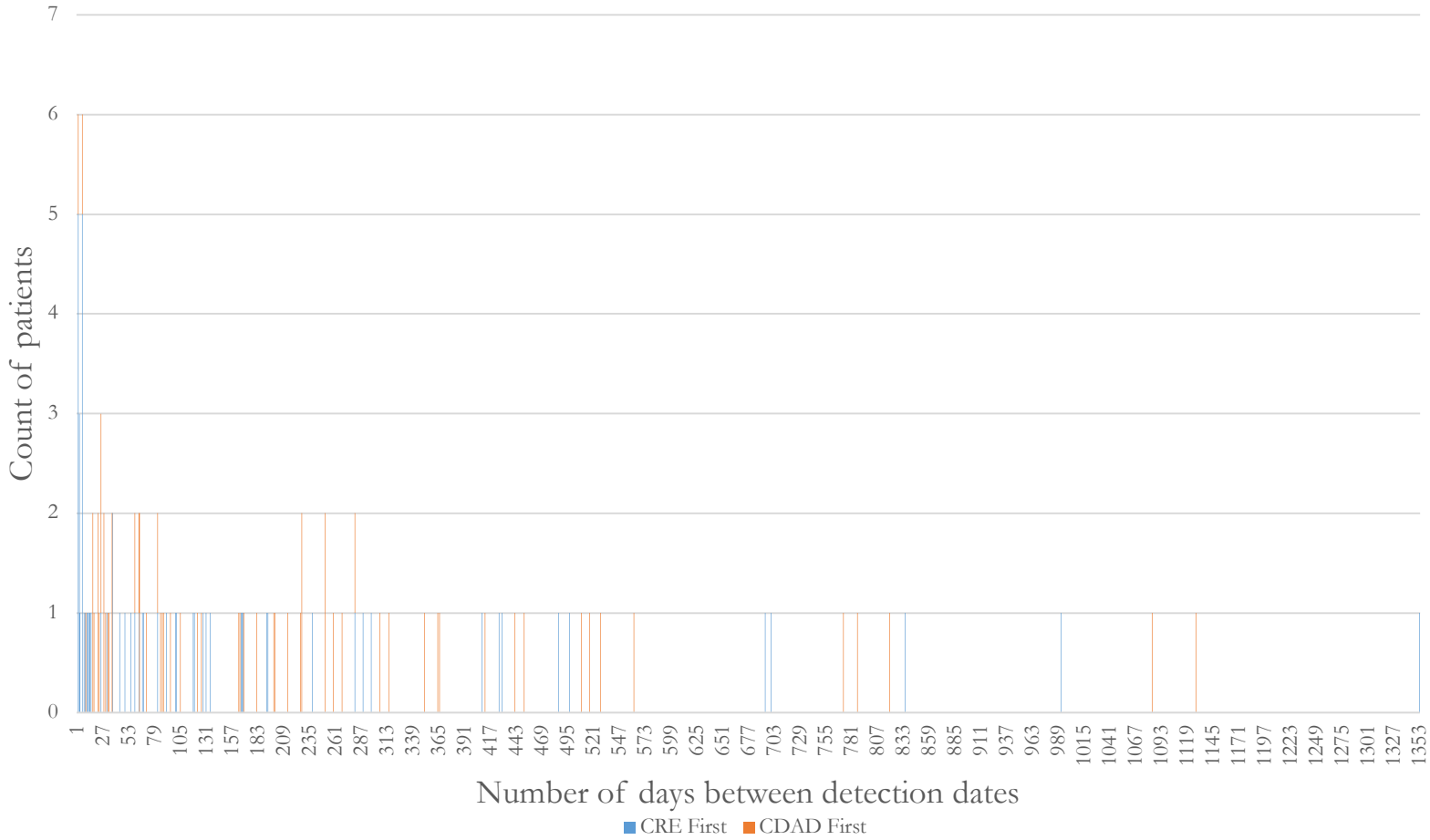

Figure 3: Count of days between detection of *C. difficile* or carbapenem-resistant Enterobacteriaceae within 180 days in metropolitan Atlanta, 2011-2015. N=78.

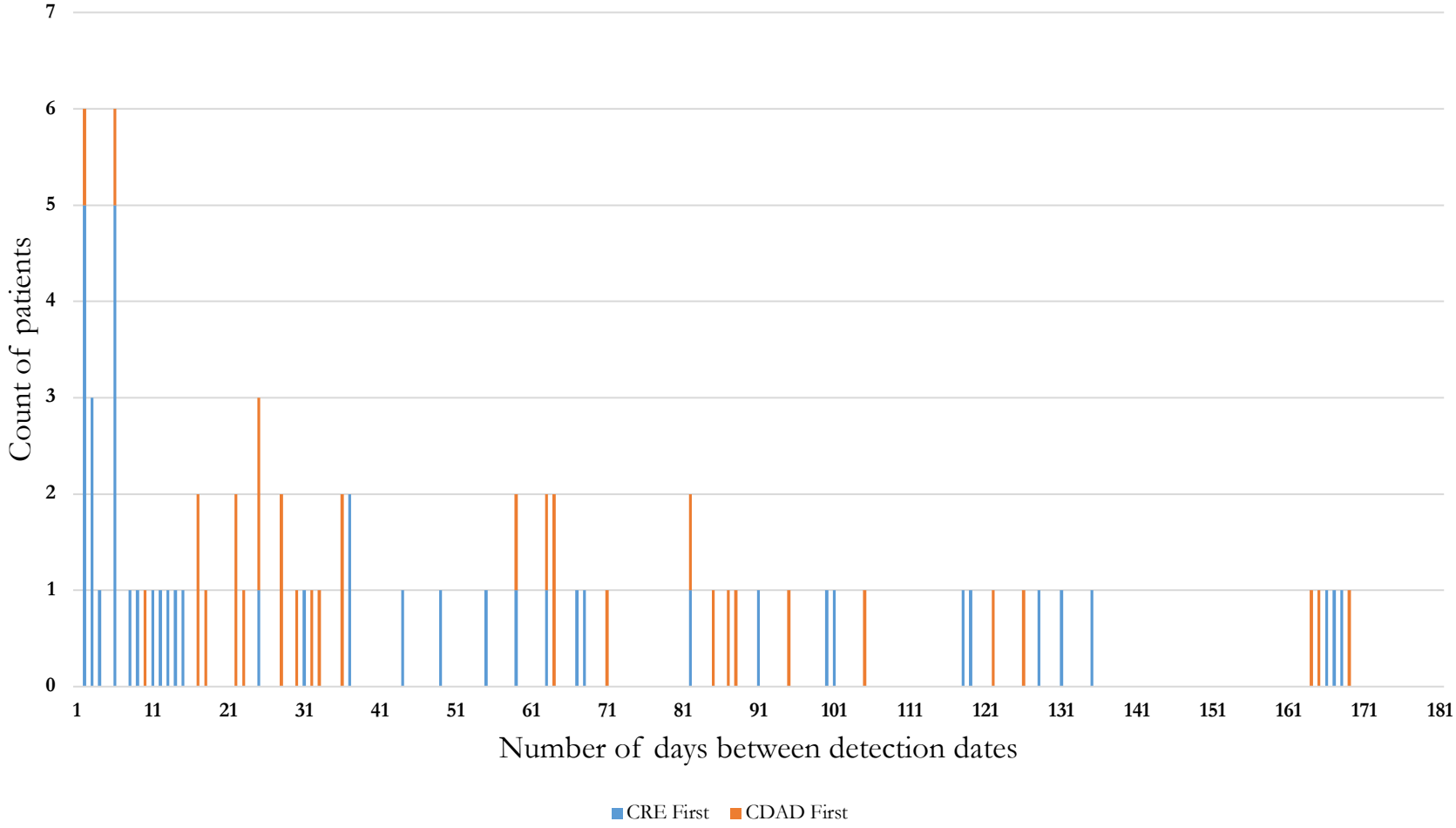

Table 3: Estimated Six-month Incidence rates for *C. difficile* and carbapenem-resistant Enterobacteriaceae (CRE) mono-detection and *C. difficile* & CRE co-detection in metropolitan Atlanta, 1/2012-6/2015.

Time Period	Detection	Detection Frequency	Denominator	Incidence (case/100,000 person-periods)
1/2012-6/2012	CDAD Monodetection	3,614	3,821,534	94.6
	CRE Monodetection	69	3,821,534	1.8
	CDAD and CRE Co-detection	24	3,821,534	0.6
7/2012-12/2012	CDAD Monodetection	3,334	3,821,534	87.2
	CRE Monodetection	79	3,821,534	2.1
	CDAD and CRE Co-detection	20	3,821,534	0.5
1/2013-6/2013	CDAD Monodetection	3,691	3,864,091	95.5
	CRE Monodetection	79	3,864,091	2.0
	CDAD and CRE Co-detection	18	3,864,091	0.5
7/2013-12/2013	CDAD Monodetection	3,653	3,864,091	94.5
	CRE Monodetection	70	3,864,091	1.8
	CDAD and CRE Co-detection	19	3,864,091	0.5
1/2014-6/2014	CDAD Monodetection	3,568	3,925,130	90.9
	CRE Monodetection	73	3,925,130	1.9
	CDAD and CRE Co-detection	13	3,925,130	0.4
7/2014-12/2014	CDAD Monodetection	3,844	3,925,130	97.9
	CRE Monodetection	72	3,925,130	1.8
	CDAD and CRE Co-detection	17	3,925,130	0.4
1/2015-6/2015	CDAD Monodetection	4,001	3,991,607	100.2
	CRE Monodetection	59	3,991,607	1.5
	CDAD and CRE Co-detection	20	3,991,607	0.5

Table 4: Estimated Six-month Incidence rates for *C. difficile* and carbapenem-resistant Enterobacteriaceae (CRE) mono-detection and *C. difficile*/CRE co-detection in metropolitan Atlanta, 1/2012-6/2015.

Time Period	Detection	Detection Frequency	Denominator	Incidence (case/100,000 person-periods)
1/2012-6/2012	CDAD Monodetection	3,614	3,821,534	94.6
	CRE Monodetection	69	3,821,534	1.8
	CDAD and CRE Co-detection	24	3,683	651.6
7/2012-12/2012	CDAD Monodetection	3,334	3,821,534	87.2
	CRE Monodetection	79	3,821,534	2.1
	CDAD and CRE Co-detection	20	3,413	586.0
1/2013-6/2013	CDAD Monodetection	3,691	3,864,091	95.5
	CRE Monodetection	79	3,864,091	2.0
	CDAD and CRE Co-detection	18	3,770	477.5
7/2013-12/2013	CDAD Monodetection	3,653	3,864,091	94.5
	CRE Monodetection	70	3,864,091	1.8
	CDAD and CRE Co-detection	19	3,723	510.3
1/2014-6/2014	CDAD Monodetection	3,568	3,925,130	90.9
	CRE Monodetection	73	3,925,130	1.9
	CDAD and CRE Co-detection	13	3.641	357.0
7/2014-12/2014	CDAD Monodetection	3,844	3,925,130	97.9
	CRE Monodetection	72	3,925,130	1.8
	CDAD and CRE Co-detection	17	3,916	434.1
1/2015-6/2015	CDAD Monodetection	4,001	3,991,607	100.2
	CRE Monodetection	59	3,991,607	1.5
	CDAD and CRE Co-detection	20	4,060	492.6

Figure 4: Estimated Six-month Incidence rates for *C. difficile* (CDI) and carbapenem-resistant Enterobacteriaceae (CRE) mono-detection and CDI & CRE co-detection in metropolitan Atlanta, 1/2012-6/2015.

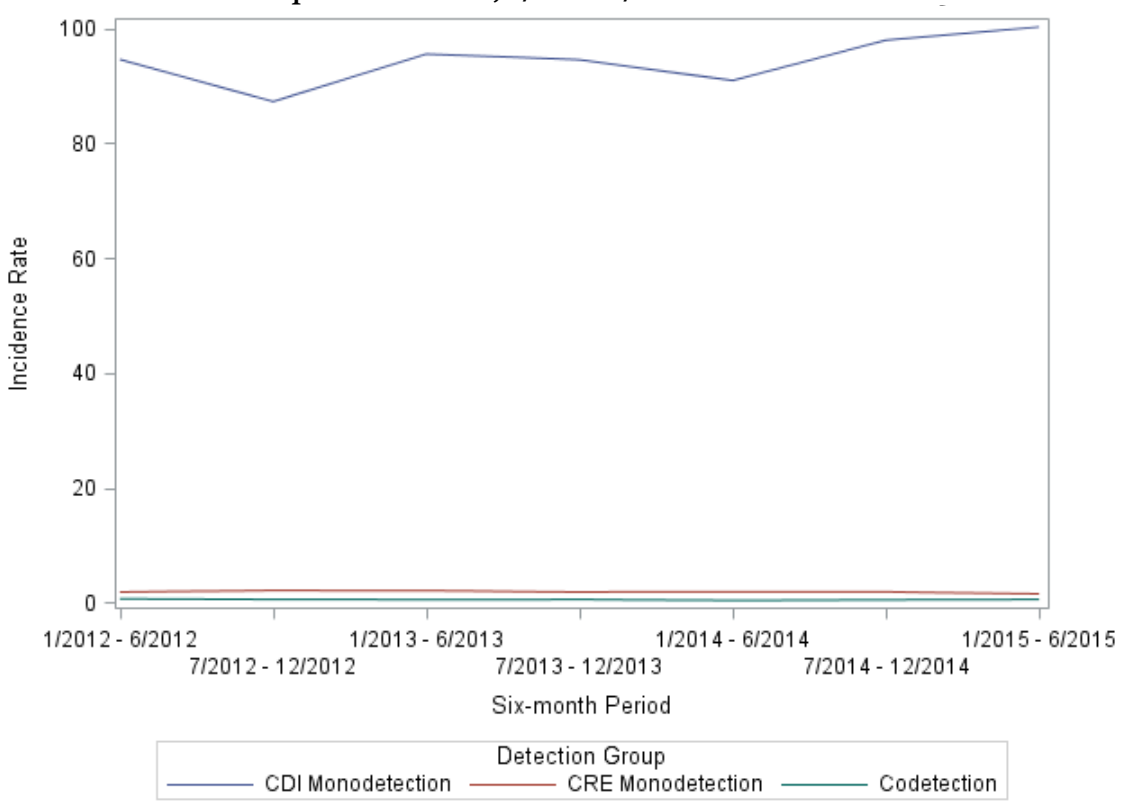

Figure 5: Estimated Six-month Incidence rates for *C. difficile* (CDI) and carbapenem-resistant Enterobacteriaceae (CRE) mono-detection and CDI & CRE co-detection in metropolitan Atlanta, 1/2012-6/2015.

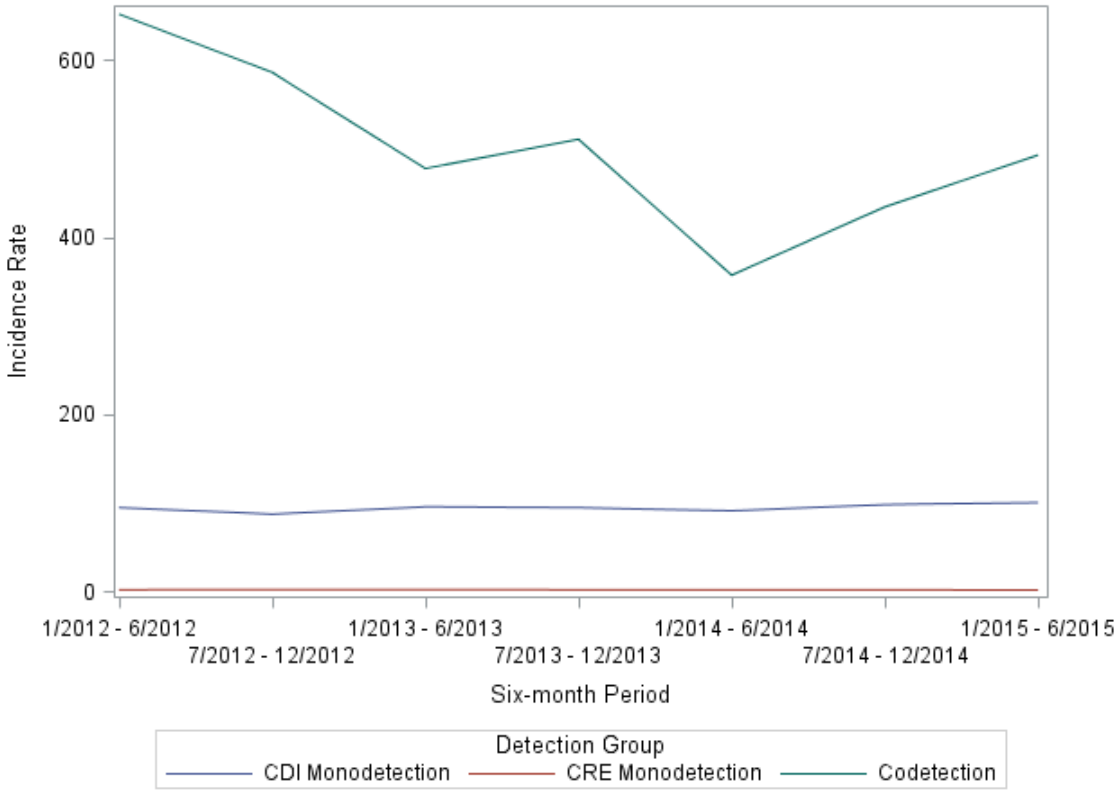

Table 5: Evaluation of the effect of residence on detection group controlling for age, sex, and race.

Effect	Detection Group	OR	95% Wald Confidence Limits	
Inpatient	**Co-detection**	**1.94**	**1.058**	**3.568**
Home	Co-detection	-	-	-
Inpatient	CRE mono-detection	0.981	0.752	1.281
Home	CRE mono-detection	-	-	-
LTACH/LTCF/SNF	**Co-detection**	**3.199**	**1.674**	**6.112**
Home	Co-detection	-	-	-
LTACH/LTCF/SNF	**CRE mono-detection**	**3.901**	**3.072**	**4.954**
Home	CRE mono-detection	-	-	-
Age	**Co-detection**	**1.014**	**1.001**	**1.027**
Age	**CRE mono-detection**	**1.009**	**1.004**	**1.014**
Female	Co-detection	1.051	0.648	1.706
Male	Co-detection	-	-	-
Female	CRE mono-detection	0.920	0.762	1.112
Male	CRE mono-detection	-	-	-
White	Co-detection	0.902	0.354	2.297
White	CRE mono-detection	1.033	0.749	1.426
Black	**Co-detection**	**3.095**	**1.275**	**7.514**
Black	**CRE mono-detection**	**2.501**	**1.826**	**3.424**
Asian	Co-detection	3.070	0.599	15.732
Asian	CRE mono-detection	1.759	0.829	3.733

CRE – carbapenem-resistant Enterobacteriaceae, LTACH – long-term acute care hospital, LTCF – long-term care facility, SNF – skilled nursing facility. Reference group for model is *C. difficile* mono-detection, – indicates covariate reference group.

Table 6: Evaluation of the effect of modified Charlson comorbidity index (CCI) score, controlling for age, sex, and race.

Effect	Detection Group	OR	95% Wald Confidence Limits	
CCI	**Co-detection**	**1.482**	**1.369**	**1.605**
CCI	**CRE mono-detection**	**1.589**	**1.534**	**1.646**
Age	Co-detection	0.989	0.975	1.004
Age	CRE mono-detection	0.972	0.967	0.977
Female	Co-detection	1.078	0.665	1.748
Male	Co-detection	-	-	-
Female	CRE mono-detection	0.972	0.797	1.185
Male	CRE mono-detection	-	-	-
White	Co-detection	0.987	0.427	2.284
White	**CRE mono-detection**	**2.269**	**1.588**	**3.241**
Black	**Co-detection**	**4.368**	**2.062**	**9.255**
Black	**CRE mono-detection**	**4.999**	**3.529**	**7.081**
Asian	Co-detection	4.313	0.898	20.716
Asian	CRE mono-detection	0.972	0.797	1.185

CRE – carbapenem-resistant Enterobacteriaceae, LTACH – long-term acute care hospital, LTCF – long-term care facility, SNF – skilled nursing facility. Reference group for model is *C. difficile* mono-detection, – indicates covariate reference group.

Figure 6: 90-day survival estimates for patients with *C. difficile* (CDI) or carbapenem-resistant Enterobacteriaceae (CRE) mono-detection or CDI and CRE co-detection in metropolitan Atlanta, 2011-2015.

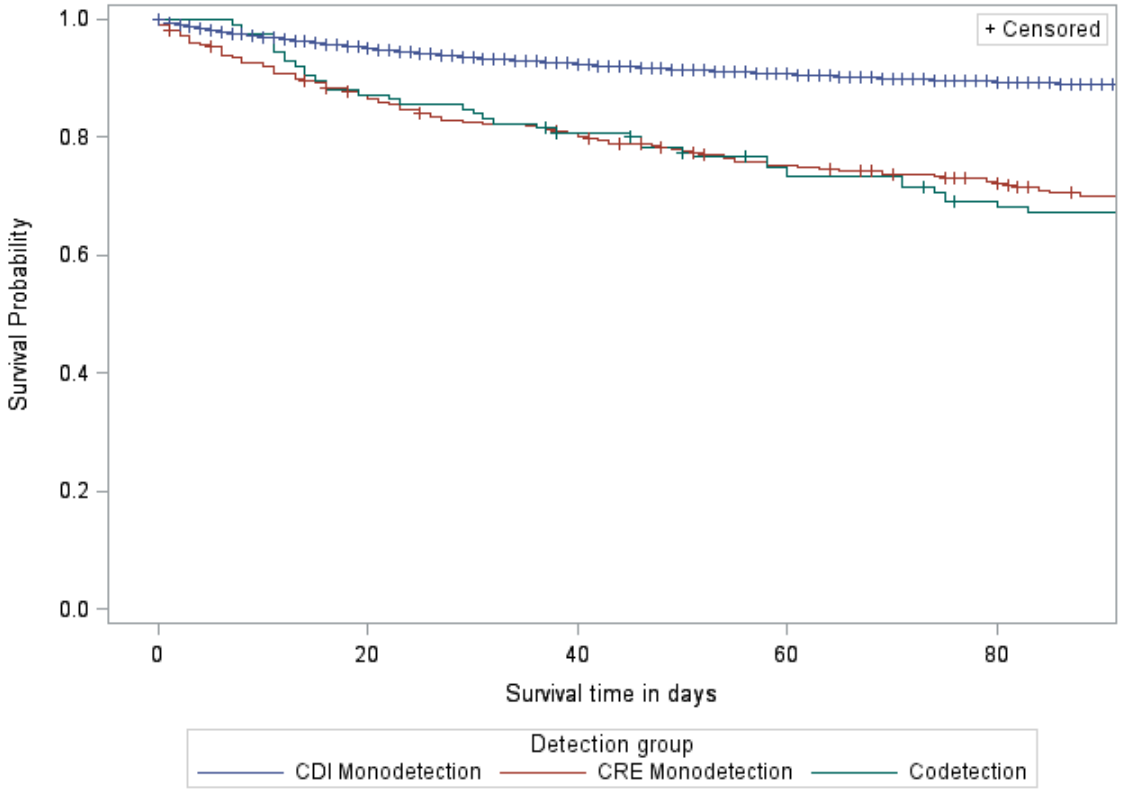

Figure 7: 90-day survival estimates for CRE detection in urine vs invasive sterile-site cultures among patients with CRE mono-detection in metropolitan Atlanta, 2011-2015.

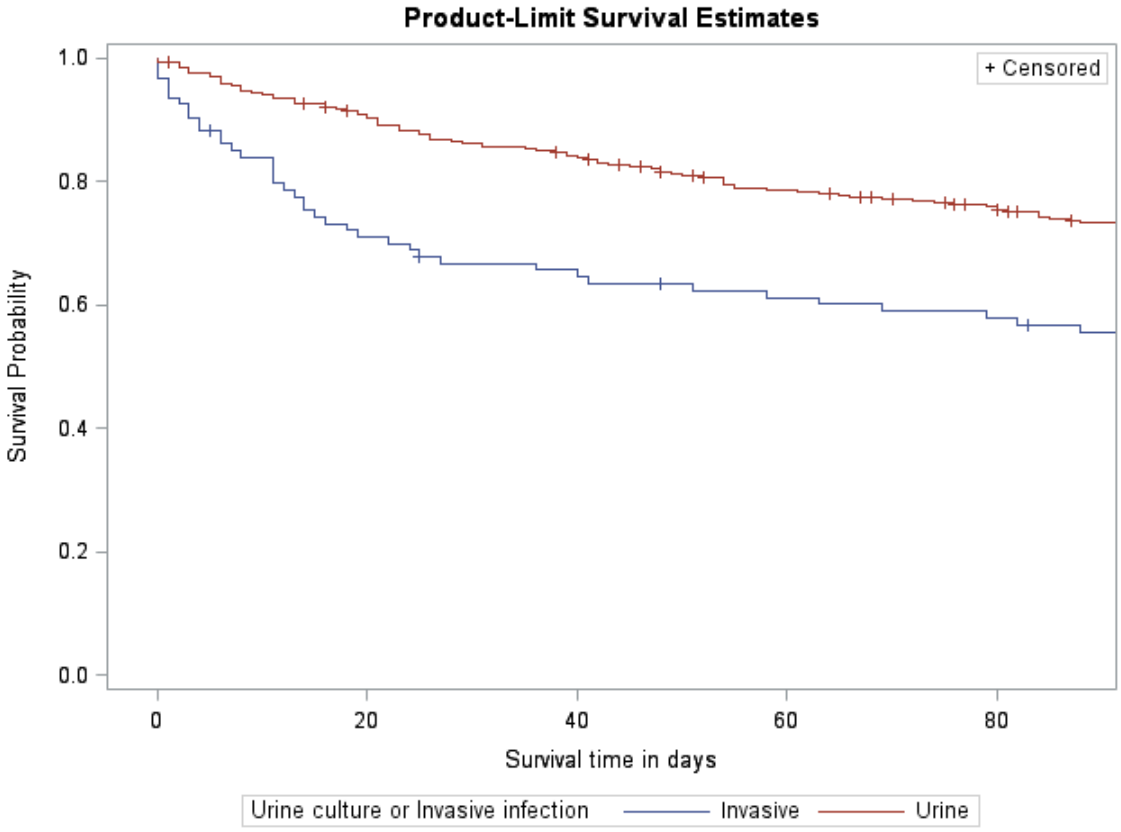

Figure 8: 90-day survival estimates for CRE detection in urine vs invasive sterile-site cultures among patients with *C. difficile* and CRE co-detection in metropolitan Atlanta, 2011-2015.