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Assessment of Antibiotic Use and Interhospital Variability in Antibiotic Resistant Gram-Negative Pathogens in U.S. Acute Care Hospitals, 2012-2017

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Assessment of Antibiotic Use and Interhospital Variability in Antibiotic Resistant Gram-Negative Pathogens in U.S. Acute Care Hospitals, 2012-2017

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Abstract

Assessment of Antibiotic Use and Interhospital Variability in Antibiotic Resistant Gram-Negative Pathogens in U.S. Acute Care Hospitals, 2012-2017

By Shae Duka

Background: Antibiotic resistance (AR) is a growing threat in the United States, and Gram-negative pathogens such as Carbapenem-resistant Enterobacteriaceae (CRE), Carbapenem-resistant (CR) *Acinetobacter* spp. and Multi-drug resistant *Pseudomonas aeruginosa* (MDR *P. aeruginosa*) have become resistant to nearly all first-line antibiotics. This study assessed drivers of antibiotic-resistant infections by examining interhospital variability, specifically in antibiotic use (AU), of these three pathogens and combined, at the hospital level.

Methods: Clinical microbiology and discharge data from U.S. hospitals in the Premier Healthcare Database from 2012 -2017 were analyzed. The primary exposure, total AU, was measured in days of therapy (DOT) per 1,000 patient days. Rates of antibiotic resistant (AR) infections were measured as the number of specimens that tested resistant (R) to specified antibiotics for each pathogen, per 1,000 discharges. AU and AR were reported descriptively by year, and the unadjusted relationship was examined through scatterplots. Twelve Poisson regression models assessed the association between total AU and AR infection rates of each pathogen and type (all, hospital-onset (HO), community-onset (CO)), adjusting for hospital characteristics and covariates.

Results: Unadjusted results showed very low combined infection rates (all pathogens of interest) across all years (median hospital level rate=1.68 per 1,000 discharges). MDR *P. aeruginosa* had the highest median hospital-level rate of 1.17, followed by CRE (median=0.22) and CR *Acinetobacter* spp. (median=0.07). Scatterplots of unadjusted total AU and unadjusted AR rates showed no relationship between pathogens, except for CR *Acinetobacter* spp. which displayed a weak but positive linear relationship. In the adjusted models, no association was found between total AU and AR infection rates except for the CR *Acinetobacter* spp. models where AU was significantly associated with each type (all, HO, CO) (IRR=1.06, 1.12, 1.04, respectively). Significant associations between urban/rural status and census divisions (specifically the Middle Atlantic, East North Central and East South Central) appeared frequently across models.

Conclusion: These findings suggest variability in AR may be associated with total antibiotic use in CR *Acinetobacter* spp.; however, future studies should examine antibiotic class-specific associations. Additionally, significant associations between AR infection rates and urban/rural status and census divisions were found – highlighting focus areas for future research.

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Introduction

Antibiotic Resistance as a Public Health Threat

The emergence and spread of antibiotic resistant pathogens have been a growing threat in the United States and become one of the greatest public health challenges facing the globe over the past decade. Antibiotic resistance began to develop as early as the 1940s, and resistance has been seen toward nearly all antibiotics today (1). Resistance to antibiotics occurs when pathogens (typically bacteria and fungi) are no longer responsive to the antibiotics designed to kill them. This crisis has been attributed to overuse and inappropriate prescribing of antibiotics, in addition to lack of novel drug development in the pharmaceutical pipeline (1).

In 2013, the Centers for Disease Control and Prevention (CDC) published *Antibiotic Resistance Threats in the United States, 2013* which presented initial estimates of the burden and trends of antibiotic resistant pathogens in U.S. hospitals (2). In this report, the CDC estimated that at least two million people were infected with antibiotic resistant pathogens each year, contributing to at least 23,000 deaths (2). Since then, new data sources allowed for a more complete antibiotic resistant profile in the United States, and an updated report titled *Antibiotic Resistant Threats in the United States, 2019* was released by the CDC in late 2019 (3). Within these reports, the CDC classified each antibiotic resistant threat as “urgent”, “serious”, or “concerning” threat status based upon level of concern for human health (2, 3). The updated data sources from the 2019 report projected the 2013 estimates to show more than 2.6 million infections and nearly 44,000 deaths per year, almost doubling the initial death estimate (3). The 2019 report included

data for the years 2012 through 2017 and estimated that over 2.8 million antibiotic resistant infections and greater than 35,000 deaths occur each year in the U.S., an 18% decrease since the 2013 report (3). This decrease is suggestive that U.S. efforts to prevent infections and improve antibiotic use are working. However, infections are still high and new threats continue to emerge with ever-changing resistance profiles of pathogens (3).

Antibiotic resistant pathogens can spread in both the community ("community-acquired" or "community-onset") and in healthcare settings ("healthcare-acquired" or "hospital-onset"). Healthcare settings can include but are not limited to inpatient acute care hospitals, ambulatory care, outpatient care (e.g. a physician's office), long-term care facilities (e.g. nursing homes), and dialysis facilities. Patients in healthcare settings are a highly vulnerable population due to comorbidities such as hypertension or diabetes, weakened immunity (due to cancer, organ transplant, etc.), common exposure to antibiotics, and frequent contact with healthcare personnel and other vulnerable individuals, allowing for some of the most deadly and resistant pathogens to spread (3). Three antibiotic resistant Gram-negative bacteria commonly found in the healthcare setting that are resistant to nearly all antibiotics are: Carbapenem-resistant Enterobacteriaceae (CRE) and Carbapenem-resistant (CR) *Acinetobacter* spp.– classified as urgent threats – and Multi-drug resistant *Pseudomonas aeruginosa* (MDR *P. aeruginosa*) – classified as a serious threat. These three pathogens, though rarer than others, have high rates of mortality and are difficult to treat (4). A major contributor to these growing threats is the increased use of inpatient antibiotics.

Antibiotic Use in United States Hospitals

Inpatient prescribing of antibiotics in U.S. hospitals is commonplace and often inappropriate (5, 6). Antibiotic use has been a focal point since the United States identified antibiotic resistance as a national priority in 2014 and established the *U.S. National Strategy for Combating Antibiotic-Resistant Bacteria* and the accompanying *U.S. National Action Plan for Combating Antibiotic-Resistant Bacteria* (6, 7). Overprescribing of antibiotics and inappropriate prescribing can lead to increased antibiotic resistance, and complications such as *Clostridium difficile* infections (6). Studies have shown that approximately 30-50% of antibiotic prescribing might be incorrect (5).

In order to encourage and maintain proper antibiotic prescribing, hospitals across the U.S. have implemented antibiotic stewardship programs, with an estimated 84% of U.S. hospitals reported to have a stewardship program that meets all seven of CDC's *Core Elements of Hospital Antibiotic Stewardship* as of fiscal years 2016-2019 according to the 2019 threat report (3). Despite this, trends in antibiotic use have remained stable through the years, and class-specific and hospital-level variability have been noted (6). In a temporal study utilizing administrative data of 300 hospitals from 2006-2012, antibiotic usage estimates decreased over time for aminoglycosides, first and second generation cephalosporins, fluoroquinolones, sulfa, metronidazole and penicillins, with the greatest decrease in fluroquinolones (6). However, in this same study, macrolides, third and fourth generation cephalosporins, glycopeptides, β-lactam/ β-lactamase inhibitor combinations, carbapenems, tetracyclines, and other types of antibacterials all increased (6). Hospital characteristics such as geographic location, teaching status, and the proportion of

inpatient-days that are billed with an infectious disease diagnosis code ("bacterial infection patient-days") have also been found to be associated with hospital antibiotic use (8). Multiple studies have found variation in antibiotic use across geographic location, specifically in the South (6, 8, 9). A crucial component to maintaining decreasing trends in cases of antibiotic resistance is appropriate antibiotic usage, especially for highly resistant Gram-negative bacteria such as CRE, CR *Acinetobacter* spp., and MDR *P. aeruginosa*.

Significant Gram-Negative Resistant Pathogens in U.S. Hospitals

Carbapenem-resistant Enterobacteriaceae (CRE)

Enterobacteriaceae are a family of different types of bacteria, that commonly cause infections in the healthcare setting, typically targeting the urinary tract, lungs, blood and other areas (10). When Enterobacteriaceae test resistant to at least one of the carbapenem antibiotics or produce carbapenemase, they are considered Carbapenem-resistant (10). Carbapenemase is an enzyme that can make these bacteria resistant to carbapenem, and approximately 30% of CRE carry it (10). CRE are transmitted person-to-person via healthcare personnel or environmentally through medical equipment or surfaces such as sink drains and toilets (10). CRE are difficult to treat as they typically do not respond to commonly used antibiotics and are occasionally resistant to nearly all available antibiotics. These attributes combined with high rates of mortality, are why CRE are often referred to as "nightmare bacteria" (3, 10).

Healthy people usually do not acquire a CRE infection, making community spread unlikely (10). Patients have a greater risk of acquisition when they are hospitalized

or in long-term care facilities as ventilators, catheters, intravenous catheters, long courses of antibiotics and weakened immune systems greatly increase a person's risk of a CRE infection (10, 11). The most recent estimates and trends based upon the 2019 threat report show CRE infections have been stable, with annual estimates falling between 11,400 and 13,100 cases per year in hospitalized patients between 2012 and 2017. In 2017 alone, 1,100 deaths and approximately $130 million in healthcare costs were attributable to CRE (3).

Carbapenem-resistant Acinetobacter spp.

Acinetobacter spp. is a group of bacteria commonly found in wet environments (i.e. soil and water). There are many types of Acinetobacter, however *Acinetobacter baumanii* (*A. baumanii*) accounts for most Acinetobacter infections in humans, typically causing blood, urinary tract, lung and wound infections (12). Non-baumanii Acinetobacter such as *A. lwoffii* colonize and are part of the normal flora in approximately a quarter of healthy individuals, meaning they are present on the body's surface without causing infection (13). In general, HIV or transplant patients rarely acquire Acinetobacter infections, however, in patients with acute pulmonary disease, who require mechanical ventilation or devices such as catheters, have open wounds, a weakened immune system, are in the intensive care unit or have longer hospitals stays, these colonized Acinetobacter pathogens can cause sepsis, pneumonia, meningitis, urinary tract, skin and wound infections (12, 13). *Acinetobacter* spp. have an extended lifespan on surfaces, therefore transmission typically occurs through fomites such as environmental surfaces and equipment or through contaminated hands. Similar to CRE, when *Acinetobacter* spp. develop resistance to carbapenems, they become carbapenem-

resistant. Carbapenem-resistant *Acinetobacter* spp. are usually multi-drug resistant and although rare, this makes an infection extremely dangerous (12).

In the U.S. carbapenem-resistant *Acinetobacter* spp. infections rarely occur outside of healthcare settings, with one multi-state surveillance study finding that nearly all documented cases of carbapenem-resistant *Acinetobacter* spp. were in patients who stayed overnight in a healthcare facility (i.e. hospital onset) or had indwelling devices (14). Trends in the national estimates of carbapenem-resistant *Acinetobacter* spp. infections in U.S. hospitals appears to be decreasing from 11,700 cases in 2012 to 8,500 cases in 2017. In 2017 alone, the attributable deaths related to carbapenem-resistant Acinetobacter spp. were 700, with healthcare costs of approximately $281 million (3).

Multi-drug resistant Pseudomonas aeruginosa (MDR P. aeruginosa)

Commonly found in the environment (i.e. soil and water), *Pseudomonas aeruginosa* may cause infection in the blood, lungs, at the surgical site, or other parts of the body (15). The most at-risk patients are those on mechanical ventilators, using devices such as catheters, or with wounds from surgery or burns as each of these circumstances prolong hospital stays and require extensive care and treatment (15). Similar to carbapenem-resistant *Acinetobacter* spp. and CRE, *Pseudomonas aeruginosa* can spread person-to-person through contaminated hands, equipment or surfaces (15). Multi-drug resistance occurs when *Pseudomonas aeruginosa* develops resistance to several antibiotics, with some types resistant to nearly all antibiotics (3, 15).

Since 2012, the trend in multi-drug resistant *Pseudomonas aeruginosa* infections has decreased from 46,000 cases to approximately 32,600 cases in 2017. In 2017 alone, there were 2,700 attributable deaths and a staggering healthcare cost of $767 million (3).

Measuring Antibiotic Resistance in Large Healthcare Databases

CDC's 2019 threat report measured trends and estimates for CRE, carbapenem-resistant *Acinetobacter* spp., and MDR *P. aeruginosa* infections using three large healthcare databases. These electronic health databases included the Premier Healthcare Database, Cerner Health Facts, and BD Insights Research Database, each containing data on any inpatient visit in acute care hospitals between January 1, 2012 and December 31, 2017 (3). Electronic health databases house comprehensive hospital-based healthcare history of each patient in a healthcare system, using multiple sources such as electronic medical records and claims (16). Electronic health databases allow users to access real-world, readily available data for research and surveillance. The databases used in the 2019 threat report contained a dynamic cohort of short-term acute care hospitals in the U.S. Hospitals were included if they reported at least one positive result from a microbiology culture with associated antimicrobial susceptibility testing data (3). The total sample size of the 2012-2017 dynamic cohort was 722 hospitals accounting for 7.4 million discharges annually (3).

The use of large, administrative healthcare databases allows for a higher level of detail in the analysis through the use of administrative and billing data, including transaction charges for medications and procedures, and capture a greater proportion of U.S. hospitals (>20% of U.S. hospital discharges/admissions) compared to retrospective

and surveillance studies (3). In addition, the accrual of data is from a large geographically diverse population, allowing for rare outcomes and long-term effects to be studied (16). The Premier Healthcare Database (PHD) is one of the most comprehensive electronic healthcare databases, comprising a large, U.S. hospital-based, service-level, all-payer database containing information on inpatient discharges from geographically diverse non-profit, non-governmental and community and teaching hospitals and health systems (16). Accounting for over 10 million inpatient admissions per year since 2012, the PHD represents approximately twenty-five percent of annual U.S. inpatient admissions (16). Hospital characteristics are categorized by geographic location – based upon four geographic regions and divisions defined by the U.S. Census – and include bed size, teaching status, and population served (16). Data is collected at both the hospital-level and hospital-encounter (patient) level, creating a more granular scope. Since its origination in 2000, the PHD has appeared in 621 publications and counting (16).

Literature Findings and Gaps in Research

In the United States, few studies exist that measure trends and estimates in national antibiotic use. However, a 2016 study utilizing the Truven Health MarketScan Hospital Drug Database analyzed trends in adult and pediatric inpatient antibiotic use from January 1, 2006 to December 31, 2012 (6). Approximately 300 acute care hospitals and over 34 million discharges were included in the sample (6). Overall, 55% of patients discharged received at least one dose of an antibiotic during their hospital visit, with the overall rate of antibiotic use for all study years of 755 DOT per 1,000 patient-days (6). In other words, for every 10 days of hospitalization, about 7 included receipt of an antibiotic. Variability was found in both the facility-specific proportion of discharges

during which an antibiotic was received, and the days of therapy per 1,000 patient-days. In addition, interhospital variability was found in antibiotic usage in critical care locations, by geographic location, and teaching status. Although overall antibiotic use in U.S. hospitals did not change significantly between 2006 and 2012, important class-specific and regional differences were found, which could have implications on differences in antibiotic resistance by region (6).

Upon review of the literature, while patient-level analyses have often documented the relationship between antibiotic consumption and antibiotic resistance, few studies have successfully documented hospital level antibiotic use and its association with resistance. Of the hospital level studies reviewed, two were in the United States (4, 17), and five were international (18-22). Although not directly measuring the association between use and resistance, a retrospective cohort study utilizing the Premier Healthcare Database from 2009 to 2013 sought to determine the magnitude of difficult-to-treat antibiotic resistant (DTR) pathogens by determining the prevalence, predictors and outcomes of these pathogens to first-line agents (4). This study concluded that urban healthcare and higher baseline illness were predictors of DTR infections (4). A retrospective study conducted from 2005 to 2012 of health care beneficiaries of the Department of Defense, examined the correlation of carbapenem and fluoroquinolone usage and CRE (17). Findings of this study included an incidence of CRE as under 1 case per 100,000 person-years, an increase of CRE incidence relative to baseline, and that antibiotic resistance and use were strongly correlated (17). In addition, incident proportions of carbapenem resistance differed significantly across years, geographical regions, and bacterial species (17). International studies found increases in the inpatient

consumption of broad-spectrum and antibiotics against MDR pathogens, in addition to increases in overall antibiotic resistance (18). In a French-based study, a statistically significant relationship was found between the inpatient rate of fluoroquinolone use and the rate of resistance among *Staphylococcus aureus* and *P. aeruginosa* isolates (19). A different French study of both inpatients and outpatients, found that the incidence of quinolone resistant *Escherichia Coli* (*E. Coli)* isolates was independently associated with consumption of tetracyclines, cephalosporins, and quinolones (20). A multicenter ecological study in Canada found that increased inpatient and outpatient antibiotic consumption was associated with decreased antibiotic susceptibility for *P. aeruginosa* but had an inverse relationship with the other six pathogens (21). Similarly, in Australia a retrospective study of 12 hospitals of both inpatient and outpatient data, did not find a relationship between ertapenem usage and carbapenem-resistant (CR) *P. aeruginosa* but did find an association between greater usage of aPCs (antipseudomonal carbapenems) and CR *P. aeruginosa* (22). These international studies suggest a relationship may exist between antibiotic consumption and rates of antibiotic resistance at a larger, hospital level, where the relationship is harder to demonstrate.

Similar studies have also been conducted examining the relationship between outpatient antibiotic prescribing and antibiotic resistance. A Belgium-based study found resistance in *E. coli* was higher when more antibiotics were prescribed prior to isolation of the sample, and a dose-response relationship existed between antibiotic use and resistance in *E. Coli* (23). Finally, using Truven MarketScan data from 2011 to 2014 a study sought to examine outpatient antibiotic use and population antibiotic resistance. After examining 72 pathogen-antibiotic combinations, and determining use across all

four years, it was found that intense antibiotic use had a weaker association with resistance than extensive use (24).

Purpose and Thesis Statement

These literature findings are indicative that few studies exist in the United States examining the association between antibiotic use and antibiotic resistance at a hospital level. The studies that do exist are largely international, and focus on either one or a few specific antibiotics, or one or a few specific pathogens. There is a clear gap in knowledge assessing whether or not interhospital variability in antibiotic resistance exists, specifically in carbapenem-resistant Enterobacteriaceae, carbapenem-resistant *Acinetobacter* spp., and multi-drug resistant *Pseudomonas aeruginosa*, and if this variability exists, if it can be explained by the difference in facility level antibiotic use. Antibiotic use has been identified as one of many potential drivers for antibiotic resistance. This research aims to potentially quantify the association between antibiotic use and rates of resistant infections at an ecologic level within a hospital. Thus, these findings may be able to inform how hospital antibiotic stewardship programs may have the potential to reduce antibiotic resistant infection rates and make a public health impact. Prevention of antibiotic resistant threats may decrease incidence, morbidity, and mortality of resistant infections and attributable healthcare costs.

Thus, the knowledge gaps we aim to address in this study are to assess the association between hospital-level antibiotic use and hospital-level rates of three antibiotic resistant threats – carbapenem-resistant Enterobacteriaceae, carbapenem-resistant *Acinetobacter* spp., multi-drug resistant *Pseudomonas aeruginosa* – in US acute

care hospitals, based off of the 2019 antibiotic resistance threat report released by the CDC. This aim will be achieved through the following objectives:

1. Assess interhospital variability in antibiotic resistant infection rates for each threat individually and as a combined rate of all three pathogens.
2. Determine if an association exists between rates of antibiotic use and rates of antibiotic resistant infections at the hospital level, adjusting for hospital and/or threat characteristics.

Methods

Study Design, Population and Data Source

This study is a hospital-level cross-sectional study of all adult hospitalizations (≥ 18 years of age) in acute care hospitals included in the Premier Healthcare Database (PHD) between January 1, 2012 and December 31, 2017.

Hospitals included in the study were limited to those with available microbiology lab sensitivity, charge, and provider data at any point for 2012-2017. Hospitals were included for any month they reported at least one positive result from a microbiology culture with associated antibiotic susceptibility results between 2012 and 2017. Hospitals were excluded if they were children's hospitals and had no adult discharges, or were missing antibiotic usage data (e.g. days of therapy). In the PHD, microbiology tables were used to identify clinical culture specimens that were positive for the three pathogens of interest – carbapenem resistant Enterobacteriaceae, carbapenem resistant *Acinetobacter* spp., and multi-drug resistant *Pseudomonas aeruginosa* and had the necessary associated antimicrobial susceptibility testing. For hospitalizations with more than one positive culture type, cultures from a blood specimen were chosen over those with other specimen sources within 14 days (3). Encounter tables provided information surrounding patients' hospitalizations and discharges.

Exposure, Outcomes, and Covariates

The primary exposure in this study was hospital-level antibiotic use, measured in days of therapy (DOT). One DOT represents the administration of a single agent on a given service day, regardless of dosage or number of doses (6). For example, if a patient

is administered two doses of cefazolin 8 hours apart, this is equivalent to 1 DOT, whereas a patient receiving one dose of vancomycin and one dose of ceftazidime would be equivalent to 2 DOTs (6). Antibiotics were categorized into 1 of 15 classes: aminoglycosides, first- and second-generation cephalosporins, third- and fourth-generation cephalosporins, lincosamides, fluoroquinolones, macrolides, glycopeptides, sulfonamides, B-lactam/B-lactamase inhibitor combinations, carbapenems, penicillins, tetracyclines, metronidazoles, and other antibacterial agents. Hospital-level antibiotic use was calculated as the sum of all DOTs for all discharges in a given year per 1,000 patient days (DOTs/1,000 PDs) and reported as the mean across all hospitals. A total annual antibiotic use rate was calculated for each hospital for each year participating and as a total rate across all years.

The outcome of interest was the rate of three antibiotic resistant pathogens. Rates of resistance were measured as the number of specimens that test resistant (R) to specified antibiotics for each pathogen per 1,000 discharges. Rates are reported as three distinct measures for each individual pathogen, and an overall combined infection rate. Our case definitions for the pathogens of interest were the same as those used in the CDC's 2019 antibiotic threat report:

1. Carbapenem-resistant Enterobacteriaceae (CRE): Any isolate with at least 1 resistant result (R) to imipenem, meropenem, doripenem, ertapenem.
2. Carbapenem-resistant *Acinetobacter* spp.: Any isolate with at least 1 non-susceptible result (I or R) to: cefotaxime, ceftriaxone, ceftazidime, cefepime.

3. Multidrug-resistant (MDR) *Pseudomonas aeruginosa*: Any isolate that tested either (I) or (R) to at least 1 drug in at least 3 of the medication categories: (1) extended-spectrum cephalosporins, (2) fluoroquinolones, (3) aminoglycosides, (4) carbapenems, (5) piperacillins (3).

Clinical cultures were further classified as hospital- or community-onset by date of specimen collection. A positive culture obtained on day four or later of admission was classified as hospital-onset (HO), and a positive culture obtained within the first three days of admission was classified as community-onset (CO).

Hospital covariates included in our analyses from the Premier database were the hospital's U.S. census division, bed size, population served (urban/rural), and teaching status. In addition, the hospital-level annual proportion of discharges that were categorized into various age categories (18-<55, 55-<65, 65-<75, ≥75), that were surgical, and that had an infection, were calculated and included. Annual hospital-level average length of stay (LOS), and patient case mix index (CMI) were also included as covariates. Patient CMI represents the average diagnosis-related group weight for a hospital and is calculated as the sum of the weights of the facility's DRGs divided by the number of admissions during the time period of interest (e.g. quarter, year) (25, 26). CMI has been used as an indicator of facility-level disease severity, as DRGs are based upon diagnosis and procedure codes, the presence of complications or comorbidity, age, gender, and discharge status, with each DRG having a relative assigned weight (25, 26).

Analytic Methods

All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC). For statistical tests, $p < 0.05$ (two-tailed) were considered statistically significant.

Descriptive statistics were calculated for the exposure, outcome, and covariates of interest. Categorical variables (e.g. U.S. census division, bed size, population served, bed size) were described with frequencies and proportions. Continuous variables were described using the mean and standard deviation, unless found to be skewed, then the median and interquartile range were used instead. Annual rates of hospital-level antibiotic use were described by the number of DOTs/1,000 PDs. Rates of hospital-level antibiotic resistance were described by the median and interquartile range (IQR).

Objective One

To assess interhospital variability in rates of antibiotic resistant infections, unadjusted infection rates (for all three pathogens individually and combined) were calculated and reported as an overall rate by hospital and stratified by HO and CO. These hospital-level unadjusted rates were then calculated across all years (2012-2017) and stratified by year.

Objective Two

To determine if an association exists between rates of antibiotic use and rates of antibiotic resistant infections at the hospital level, a table of mean hospital-level annual total and class-specific antibiotic use (DOT/1,000 PDs) across all years and per year from 2012 to 2017 were reported. To examine the association between antibiotic use and antibiotic resistant infections, multivariate regression models using generalized

estimating equations (GEE) were used. An analytic model finds the curve that best fits the data to approximate the true (but unknown) relationship between X (the independent variable) and Y (the dependent variable) (27). These models can be a simple regression analysis (one independent and one dependent variable) or a multiple regression analysis (multiple independent variables and one dependent variable) depending upon your research question. The nature of the dependent variable – whether it is nominal, binary, continuous, etc., will change the type of model that can be used to fit the data.

The model used in this analysis was Poisson regression. Poisson regression is used for modeling a dependent variable that is typically a count of the number of occurrences of an event of interest that occurs over a given follow-up time, obtained for each of a number of subgroups that are described by a set of predictor (independent) variables (27). The Poisson model assumes that the underlying distribution of the dependent variable is Poisson and is useful when the dependent variable (outcome) is rare. However, under a Poisson distribution the mean and variance are assumed to be equal, and it is possible to observe count data for which sample variances are larger than the sample means, otherwise referred to as over-dispersion (27). In the case of over-dispersion, a Negative Binomial model is more appropriate as this does not assume the sample variance and sample mean are equal.

As mentioned, to examine the second objective of this study – the association between antibiotic use and antibiotic resistant infection rates – multivariate regression models using generalized estimating equations (GEE) were used. GEE allow for analysis of repeated measurement and are commonly used in public health to find a population

average (in this study, the parameter would be change in antibiotic resistant infection rates across all hospitals observed) (28). The analytic approach for this objective was to use a Poisson model to fit the data first, and if over-dispersion was found, the Negative Binomial model would be used instead. However, there was no indication of over-dispersion in our models and each of our models converged using Poisson regression.

In total there were twelve models in this analysis assessing the association between hospital-level annual total antibiotic use and hospital-level resistant infection rates for the four threat groups (i.e. carbapenem-resistant *Enterobacteriaceae*, carbapenem-resistant *Acinetobacter* spp., multi-drug resistant *Pseudomonas aeruginosa*, and combined across all three) of interest per 1,000 discharges, with a separate model for each type (all, HO, and CO). In other words, one model assessed the relationship between total antibiotic use and all types of CRE, a second model assessed the relationship between total antibiotic use and HO CRE, and a third model assessed the relationship between total antibiotic use and CO CRE, repeated for all of the threats of interest. Each model adjusted for all covariates of interest including discharge year, teaching status, urban/rural, bed size, census division, and the proportion of discharges in various age categories, proportion of discharges that were surgical, proportion of discharges with an infection, average length of stay and patient case mix index.

Ethics Approval

Since this study is a secondary analysis of de-identified data, it was deemed to not meet the requirements for Human Subjects Research and therefore did not require IRB approval.

Results

Characteristics of Hospitals

A total of 253 Premier hospitals were included in a dynamic cohort between 2012 and 2017, ranging from 161 – 192 hospitals reporting annually. Hospitals reported a median of 51 months of data during the study period, representing over 1.5 million discharges annually. The largest number of hospitals were in the South Atlantic (68, 26.9%) and East North Central (56, 22.1%) census divisions. The majority of hospitals had less than 300 beds (166, 65.6%), 184 (72.7%) served urban communities, and 188 (74.3%) were non-teaching. The mean proportion of discharges in the designated age groups were as follows: 36.7% in 18-<55, 16.9% in 55-<65, 18.8% in 65-<75, and 27.7% greater than 75 years of age. The mean proportion of surgical discharges was 28.2%, likewise the mean proportion of discharges with an infection was 22.7%. In addition, the average case mix index was 1.3 and average length of stay (LOS) was 3.8 days.

Unadjusted Rates of Antibiotic Resistant Infections

Combined

Median hospital-level AR infection rates for all pathogens combined (i.e., CRE, CR *Acinetobacter* spp., MDR *P. aeruginosa*) for all types was 2.11/1,000 discharges in 2012 and 1.39/1,000 discharges in 2017. The median hospital-level rate per 1,000 discharges for all pathogens combined across all years was 1.68. The median hospital-level rate per 1,000 discharges for HO infections was lower (0.41) than CO (1.23), across all years. Rates of combined HO infections were highest in 2012 (0.59) and lowest (0.29) in 2017. However, rates of combined CO infections were highest in 2013 (1.38) and lowest in 2017 (1.01) (Table 2A, Figure 1A).

CRE

Median hospital-level antibiotic resistant infection rates for CRE for all types was 0.20/1,000 discharges in 2012 and 0.20/1,000 discharges in 2017 and across all years was 0.22/1,000 discharges. The median rate across all years per 1,000 discharges for HO CRE infections was lower than CO (0.00 vs 0.13, respectively). Rates of HO CRE were 0.00 in each year from 2012 to 2017. However, CO CRE infections were highest in 2015 (0.17) and lowest in 2014 (0.10) (Table 2B, Figure 1B).

CR Acinetobacter spp.

Median hospital-level antibiotic resistance rates for carbapenem-resistant *Acinetobacter* spp. infections for all types was 0.13/1,000 discharges in 2012 and 0.00/1,000 discharges in 2017, and across all years was 0.07/1,000 discharges. Across all years, the median hospital-level rate for HO carbapenem-resistant *Acinetobacter* spp. infections was the same as CO, with a rate less than 1 per 100,000 discharges. Hospital-level rates of HO were less than 1 per 100,000 discharges in each year from 2012 to 2017, while CO rates were highest in 2012 (0.06) followed by 2014 (0.04), and lowest in all other years (less than 1 per 100,000 discharges) (Table 2C, Figure 1C).

MDR P. aeruginosa

Multi-drug resistant *Pseudomonas aeruginosa* had the highest rates of resistant infections compared to the two other Gram-negative pathogens studied (CRE, CR *Acinetobacter* spp.). The median hospital-level rate for all types was 1.52/1,000 discharges in 2012 and 0.79/1,000 discharges in 2017, and across all years was 1.17/1,000 discharges. Across all years, the median rates per 1,000 discharges for HO

MDR *P. aeruginosa* (0.27) was lower than CO which was 0.82. Median rates of HO were highest in 2013 (0.40) and lowest in 2017 (0.13). CO infection rates were highest in 2012 (1.01) and lowest in 2017 (0.58) (Table 2D, Figure 1D).

Antibiotic Use

Mean hospital-level total antibiotic use for all years was 970.3 DOT/1,000 PDs and was highest in 2017 (1005.9) and lowest in 2012 (936.9). Across all years, the most frequently used antibiotics in this dynamic cohort were third and fourth generation cephalosporins (mean hospital-level rate: 163.6 DOT/1,000 PDs), fluroquinolones (144.0), glycopeptides (137.5), and β-Lactam/β-lactamase inhibitor combinations (133.6). The mean hospital-level rate of third and fourth generation cephalosporins was lowest in 2012 (139.5 DOT/1,000 PDs) and highest in 2017 (195.4). Likewise, the mean hospital-level rate of glycopeptides and β-Lactam/β-lactamase inhibitor combinations were lowest in 2012 (125.0 and 124.4, respectively) and highest in 2017 (148.7 and 146.8, respectively). However, the mean rate of fluoroquinolone use was highest in 2012 (167.0) and lowest in 2017 (106.7). Other notable antibiotics including aminoglycosides, first and second generation cephalosporins, carbapenems, and penicillins had a mean hospital-level rate of 14.0, 93.2, 44.0, and 18.3 DOT/1,000 PDs across all years. Mean hospital-level rates of aminoglycosides and penicillins were lowest in 2017. In contrast, first and second generation cephalosporins and carbapenems had higher mean rates in 2017 compared to previous years (Table 3).

Association Between Antibiotic Use and Antibiotic Resistant Infection Rates

Combined

Scatter plots identify little to no relationship between unadjusted rates of all types of combined antibiotic resistant infection rates (i.e., combined CRE, CR *Acinetobacter* spp., MDR *P. aeruginosa)* and total antibiotic use (Pearson's r =-0.063 to 0.0793) (Figure 2A). Furthermore, antibiotic use was not significantly associated with combined rates of infection in adjusted Poisson regression models for all types or stratified by HO and CO infections (Table 4A). However, there were covariates significantly associated with combined rates of infection within each model. For all, HO, and CO combined infections, urban versus rural location, census division, and discharge year were significantly associated with combined rates of infection. Lower adjusted rates of combined all, HO, and CO infections were observed for rural areas compared to urban, and the discharge years of 2014, 2015, 2016, and 2017 compared to 2012. The adjusted rate for combined infections of all types were significantly higher for hospitals in the Middle Atlantic, East North Central, and East South Central divisions compared to hospitals in the New England division are (IRR=1.86, 95% CI (1.26, 2.74), 1.77, 95% CI (1.23, 2.55), and 1.75, 95% CI (1.06, 2.88), respectively). These findings were also consistent for HO and CO. Other significant covariates for combined rates of infection were model specific. The proportion of discharges that were an infection and the average LOS were significantly associated with increased combined infection rates for all types; for every 10% increase in discharges that were an infection, the rate of combined resistant infection rates for all types was expected to increase by 1.31 (95% CI (1.07, 1.60)), and for every one-day increase in average LOS, the rate of combined resistant infection rates for all types was

expected to increase by 1.21 (95% CI (1.07, 1.38)). The average LOS was also significantly associated with higher rates of HO combined infections (IRR=1.62, 95% CI (1.30, 2.00)). The average CMI and proportion of discharges that were an infection were significantly associated with increased rates of CO combined infections (IRR=1.51, 95% CI (1.03, 2.22) for CMI, and IRR=1.34, 95% CI (1.12, 1.61) for infection proportion). However, lower adjusted rates of combined CO infections were observed for the proportion of surgical discharges; for every 10% increase in the proportion of surgical discharges, the rate of combined CO infections was expected to decrease by 0.83 (95% CI (0.74, 0.93)) (Table 4A).

CRE

There was no correlation observed between unadjusted total antibiotic use and unadjusted all CRE infection rates of all types in the scatterplots (Pearson's r=-0.106 to -0.002) (Figure 2B). Likewise, total antibiotic use was not significantly associated with rates of CRE infections in adjusted Poisson regression models for all types or stratified HO and CO infections (Table 4B). However, there were covariates significantly associated with CRE rates of infection within each model. For all, HO, and CO models, urban vs rural location and census division were significantly associated with CRE rates of infection. Lower adjusted rates of CRE all, HO and CO infections were observed for rural areas compared to urban. The adjusted rates for all CRE infections were significantly higher for hospitals in the Middle Atlantic, East North Central, and Pacific census divisions compared to hospitals in the New England division (IRR=3.25, 95% CI (1.56, 6.77), 2.11, 95% CI (1.01, 4.40) and 3.25, 95% CI (1.56, 6.77), respectively). These findings change slightly for HO and CO infections. The Middle Atlantic division

was the only division significantly associated with higher rates of HO CRE (IRR=2.62, 95% CI (1.25, 5.56) while the Middle Atlantic, East North Central, and Mountain division were significantly associated with higher rates of CO CRE (IRR=3.60, 95% CI (1.67, 7.76), 2.54, 95% CI (1.19, 5.43) and 3.21, 95% CI (1.06, 9.67), respectively). Other covariates that were significantly associated with CRE infection rates were model specific. Average LOS was significantly associated with increased all and HO CRE infection rates; for every one-day increase in average LOS, the rate of CRE was expected to increase by 1.28 for all types (95% CI (1.03, 1.59) and 1.52 for HO (95% CI (1.14, 2.04)). The proportion of surgical discharges was significantly associated with lower rates of CO CRE infections (IRR=0.70, 95% CI (0.55, 0.90)). The proportion of discharges in the age category 55-<65 and ≥75 was significantly associated with higher rates of CO CRE infections; for every 10% increase in the proportion of discharges that were age 55-65 and ≥75 compared to age 18-55, the rate of CO CRE was expected to increase by 1.69 (95% CI (1.07, 2.68) and 1.40 (95% CI (1.01, 1.96)), respectively (Table 4B).

CR Acinetobacter spp.

Scatter plots identified a very weak positive relationship between unadjusted rates of all CR *Acinetobacter* spp. infections with total antibiotic use (Pearson's r=0.0406 to 0.1097) (Figure 2C). Furthermore, total antibiotic use was significantly associated with rates of CR *Acinetobacter* spp. in adjusted Poisson regression models for all types and stratified by HO and CO (Table 4C). When increased by 50 DOTs/1,000 PDs, the models estimate the rate of CR *Acinetobacter* spp. would increase by 1.06 (95% CI (1.02, 1.09)) (all), 1.12 (95% CI (1.05, 1.20)) (HO), and 1.04 (95% CI (1.01, 1.07)) (CO). In addition,

there were other covariates that were significantly associated with rates of CR *Acinetobacter* spp. infections that were model specific. In the model of all CR *Acinetobacter* spp., discharge year, census division and average LOS were significantly associated with rates of infection. Lower adjusted rates of all CR *Acinetobacter* spp. infections were observed for rural areas compared to urban, and the discharge years 2014, 2015, 2016, 2017 compared to 2012. For every one-day increase in average LOS, the rate of all CR *Acinetobacter* spp. infections was expected to increase by 1.39 (95% CI (1.08, 1.79)). In addition, every census division with the exception of the South Atlantic and West North Central, were significantly associated with increased rates of all types of infection compared to hospitals in the New England division, with the Mountain division expected to have increased rates of 8.06 (95% CI (2.15, 30.18)). Results of the HO CR *Acinetobacter* spp. model were similar to the model of all types, except the discharge year of 2016 was not significant. In addition, only the East North Central, East South Central, West South Central, and Mountain divisions were significantly associated with increased rates of HO CR *Acinetobacter* spp. compared to New England. This is again most notable in the Mountain division (IRR=8.11, 95% CI (2.63, 24.98)). When modeling CO CR *Acinetobacter* spp., results were nearly identical to the model of all types except the discharge year of 2013 was also significantly associated with lower adjusted rates of CO infections, however average LOS was not significantly associated with CO infection rates. The adjusted rate for CO infections was significantly higher for hospitals in every census division with the exception of the South Atlantic compared to hospitals in the New England division (Table 4C).

MDR Pseudomonas aeruginosa

In the scatter plots, there is little to no relationship between unadjusted rates of all MDR *P. aeruginosa* infections and total antibiotic use (Pearson's r=-0.111 to 0.1297) (Figure 2D). Likewise, total antibiotic use was not significantly associated with MDR *P. aeruginosa* rates in adjusted Poisson regression models all types or stratified by HO and CO infections (Table 4D). However, there were covariates significantly associated with MDR *P. aeruginosa* rates of infection within each model. Lower adjusted rates of all, HO, and CO infections were observed for the discharges years of 2014, 2015, 2016, and 2017 compared to 2012. The adjusted rate for all MDR *P. aeruginosa* infections was significantly higher for hospitals in the Middle Atlantic, East North Central, and East South Central census divisions compared to hospitals in the New England division (IRR=1.41, 95% CI (1.04, 1.92), 1.43, 95% CI (1.09, 1.88) and 1.69, 95% CI (1.01, 2.82), respectively). These findings were consistent with the CO model, with the addition of West South Central (IRR 1.56, 95% CI (1.10, 2.23)). However, no census division was significantly associated with HO MDR *P. aeruginosa* rates of infection when compared to hospitals in the New England division. The proportion of discharges that were an infection and the average LOS were significantly associated with increased MDR *P. aeruginosa* rates of all types; for every 10% increase in the proportion of discharges with an infection, the rate was expected to increase by 1.47 (95% CI (1.14, 1.88)) and for every one-day increase in average LOS, the rate was expected to increase by 1.24 (95% CI (1.06, 1.44)). These findings were also consistent in the HO model. The proportion of discharges that were an infection and CMI were significantly associated with higher CO

MDR *P. aeruginosa* rates of infection (IRR=1.43, 95% CI (1.13, 1.82) for infection proportion and IRR=1.63, 95% CI (1.05, 2.53) for CMI) (Table 4D).

Discussion

This cross-sectional study of a dynamic cohort of over 200 acute care hospitals in the Premier Healthcare Database between 2012-2017 is one of the largest examining interhospital variability and the association between antibiotic use and antibiotic resistant infections for three Gram-negative pathogens. Total antibiotic use measured in DOT per 1,000 patient-days, was not significantly associated with antibiotic resistant infection rates in any of the adjusted Poisson regression models for combined, CRE, or MDR *P. aeruginosa*. However, significant associations were identified between total antibiotic use and rates of all, HO, and CO CR *Acinetobacter* spp. infection rates.

Adjusted models identified hospital characteristics such as urban location and census division (i.e., Middle Atlantic, East North Central or East South Central) to frequently be associated with increased rates of these important resistant infections. Hospital-level rates of all pathogens were lowest in 2017 compared to previous years, except for CRE. Total hospital-level mean antibiotic use was highest in 2017 compared to previous years. First and second generation cephalosporins, third and fourth generation cephalosporins, glycopeptides, β-Lactam/β-lactamase inhibitor combinations and carbapenems had higher usage in 2017 compared to previous years. Aminoglycosides and penicillins had slightly lower usage in 2017 compared to previous years. Fluroquinolone use changed the greatest; 106.7 DOT per 1,000 PDs in 2017 compared to 167.0 in 2012. These inverse findings contrast the argument that antibiotic use drives resistance.

Few studies have previously examined hospital-level antibiotic use and rates of antibiotic resistant infections in acute care hospitals, though limited findings have found

associations between class-specific antibiotic use and resistant infections for select pathogens. However, these results were varied in their studies (i.e. only one antibiotic-resistance combination was significant, but others had an inverse relationship). The studies closest in profile to ours were a 2015 study of the Department of Defense (DoD) (17) and a 2017 study of acute care hospitals in Ontario, Canada (21). In the DoD study, antibiotic use and resistant infection rates were found to be correlated, but several "bug-drug" combinations were not significant at the national or facility level, and inpatient consumption of fluoroquinolones was only significantly correlated with CRE when they combined two major referral centers (17). The Ontario-based study of 37 acute care hospitals found that increased antibiotic consumption was associated with decreased antibiotic susceptibility for *P. aeruginosa*, but an inverse relationship was found for *E. Coli*, *Klebsiella* spp., *Enterobacter* spp., and *Enterococcus* spp., which coincide with the results of our study (21). Our lack of associations found between total antibiotic use and rates of resistant infections of our combined, CRE, and MDR *P. aeruginosa* infections, may be because we did not assess antibiotic class-specific associations or that we were unable to account for outpatient (community) antibiotic use. One study of 42 Spanish hospitals compared community antibiotic usage through retail pharmaceutical sales and antibiotic susceptibility of *E. Coli* isolates in hospitals and found that the rate of ciprofloxacin nonsusceptibility in these *E. Coli* isolates was strongly and significantly correlated with the outpatient (community) consumption of levofloxacin, moxifloxacin, and amoxicillin (29). A second study supports this finding, which found a significant association between community fluoroquinolone use and fluoroquinolone-resistant *E. coli* infections in 17 U.S. hospitals (30). Furthermore, a study utilizing the CDC

Antibiotic Resistance Patient Safety Atlas, found that outpatient antibiotic prescribing rates of fluoroquinolones and cephalosporins explained some geographic variability in extended-spectrum cephalosporin-resistant *E. coli* prevalence when adjusting for age and healthcare facility characteristics, thus suggesting that outpatient antibiotic prescribing frequency may have a direct impact on the resistance phenotypes of hospital-onset infection pathogens (31).

However, we did find a significant association between total antibiotic use and rates of all, HO, and CO carbapenem-resistant *Acinetobacter* spp. infections. In comparison to the literature, this is a novel finding and a pathogen that is understudied in this respect. One study conducted in Korea from six university hospitals examined correlations between *A. baumanii* and class-specific antibiotics (18). This study concluded that *A. baumanii* resistance to ciprofloxacin was significantly correlated with increasing consumption of FQs, and resistance to imipenem was significantly correlated with increasing consumption of carbapenems. Further investigation in our data is needed to see if associations between CR *Acinetobacter* spp. infections are similar when looking at more specific antibiotic classes.

Previous research suggested that geographical variation in antibiotic resistance and usage may exist and is corroborated by the significance of factors such as urban/rural status and census region in our models (6, 8, 9, 17). Additionally, our finding that hospitals serving rural areas were associated with lower rates of resistant infections agree with previous findings that urban healthcare was a predictor of difficult-to-treat resistant infections (4).

Limitations

Our study has several limitations. This study is a cross-sectional ecologic study, and limitations are inherent in ecologic findings such as ecological bias or what is often referred to as the "ecologic fallacy". As such, we cannot determine linkage between risk and disease within individuals (i.e., specific antibiotic usage and antibiotic resistance within the same individual) (32). A second limitation is that we assessed total antibiotic use as our primary exposure and did not examine class-specific associations between antibiotic use and resistance. Assessment of class-specific associations could potentially reveal more granular results and insight than total antibiotic use. Third, we did not take into consideration a lag time or seasonality between antibiotic usage and the development of resistance, which are important in understanding the true relationship between this exposure and outcome since antibiotic resistance takes time to develop. Due to limitations within our dataset we did not include additional confounders such as the proportion of patients that had a hematology, oncology, or transplant diagnosis, which are known drivers of antibiotic use. Finally, we were unable to include any metrics of hospital infection control measures, variability in community-level resistance rates, or other metrics of inter-facility transmission of antibiotic resistant infections.

Strengths

This study is one of few studies that exist examining the relationship between hospital-level antibiotic usage and resistance in the United States. Our study is one of the largest to date, including over 200 hospitals from a geographically dispersed set of hospitals nationwide, which increases the external validity of our study (16).

Future Directions

This study begins to address the gap in knowledge regarding the association between hospital-level antibiotic use and hospital-level rates of three antibiotic resistant pathogens, by extending the findings from the 2019 antibiotic resistance threat report released by the CDC. This study serves as a hypothesis generating study that identifies several key areas for future research. However, future research should examine antibiotic class-specific associations between antibiotic use and resistance. In addition, this study cited a need for further analysis into the variability of antibiotic resistance in census divisions and between urban/rural populations.

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Tables

Table 1. Characteristics of Acute Care Hospitals by Year in the Premier Healthcare Database 2012-2017

Hospital Characteristics	All Years	2012	2013	2014	2015	2016	2017
No. of Hospitals	253	162	190	183	161	169	192
	N (%)	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
U.S. Census Division							
New England	12 (4.7)	7 (4.3)	8 (4.2)	7 (3.8)	7 (4.4)	7 (4.1)	9 (4.7)
Middle Atlantic	31 (12.3)	13 (8.0)	16 (8.4)	13 (7.1)	13 (8.1)	20 (11.8)	22 (11.5)
South Atlantic	68 (26.9)	34 (21.0)	42 (22.1)	43 (23.5)	38 (23.6)	38 (22.5)	56 (29.2)
East North Central	56 (22.1)	35 (21.6)	50 (26.3)	48 (26.2)	49 (30.4)	51 (30.2)	52 (27.1)
East South Central	12 (4.7)	8 (4.9)	8 (4.2)	8 (4.4)	7 (4.4)	9 (5.3)	9 (4.7)
West North Central	14 (5.5)	11 (6.8)	12 (6.3)	10 (5.5)	9 (5.6)	5 (3.0)	6 (3.1)
West South Central	32 (12.7)	26 (16.1)	26 (13.7)	26 (14.2)	19 (11.8)	20 (11.8)	21 (10.9)
Mountain	3 (1.2)	3 (1.9)	3 (1.6)	3 (1.6)	3 (1.9)	3 (1.8)	1 (0.5)
Pacific	25 (9.9)	25 (15.4)	25 (13.2)	25 (13.7)	16 (9.9)	16 (9.5)	16 (8.3)
Bed Size							
<300	166 (65.6)	96 (59.3)	116 (61.1)	113 (61.8)	101 (62.7)	105 (62.1)	129 (67.2)
≥300	87 (34.4)	66 (40.7)	74 (39.0)	70 (38.3)	60 (37.3)	64 (37.9)	63 (32.8)
Population Served							
Urban	184 (72.7)	124 (76.5)	141 (74.2)	136 (74.3)	120 (74.5)	123 (72.8)	139 (72.4)
Rural	69 (27.3)	38 (23.5)	49 (25.8)	47 (25.7)	41 (25.5)	46 (27.2)	53 (27.6)
Teaching Status							
Teaching	65 (25.7)	45 (27.8)	52 (27.4)	49 (26.8)	49 (30.4)	49 (29.0)	50 (26.0)
Non-teaching	188 (74.3)	117 (72.2)	138 (72.6)	134 (73.2)	112 (69.6)	120 (71.0)	142 (74.0)
Age							

Group[a] (mean (SD))							
18-55	36.7 (9.9)	39.2 (9.0)	37.6 (9.6)	37.6 (9.8)	36.2 (9.8)	35.8 (9.7)	33.8 (10.3)
55-65	16.9 (2.8)	16.0 (2.4)	16.5 (2.8)	16.9 (3.0)	17.1 (2.9)	17.3 (2.7)	17.3 (2.8)
65-75	18.8 (3.3)	17.3 (2.8)	18.1 (3.0)	18.4 (3.2)	18.9 (3.1)	19.5 (3.3)	20.2 (3.6)
≥75	27.7 (7.6)	27.4 (7.5)	27.9 (7.9)	27.0 (7.5)	27.8 (7.8)	27.4 (7.4)	28.7 (7.7)
% Surgical[a] (mean (SD))	28.2 (10.0)	28.7 (8.7)	29.0 (9.5)	28.3 (9.8)	27.3 (10.3)	28.6 (10.8)	27.2 (10.7)
% Infection[a] (mean (SD)	22.7 (6.3)	21.1 (5.2)	22.0 (5.7)	22.5 (6.0)	23.6 (6.4)	23.4 (6.7)	23.4 (7.2)
Case Mix Index (mean (SD))	1.3 (0.4)	1.3 (0.3)	1.4 (0.3)	1.3 (0.4)	1.3 (0.4)	1.4 (0.4)	1.2 (0.5)
Length of Stay (mean (SD))	3.8 (1.2)	4.1 (1.0)	4.0 (1.0)	3.9 (1.2)	3.9 (1.1)	3.8 (1.1)	3.4 (1.4)

SD=standard deviation

[a]Age group, % surgical and % infection, are calculated as the proportion of discharges within the designated age groups, that were surgical, or that had an infection

Table 2A. Hospital-level Unadjusted Combined Infection Rates per 1,000 Discharges in the Premier Healthcare Database (2012-2017)

		Unadjusted Combined Rate (All)[a]	Unadjusted Combined Rate (HO)[a]	Unadjusted Combined Rate (CO)[a]
All Years	**Pooled**	2.74	0.96	1.78
	Median	1.68	0.41	1.23
	Q1	0.84	0.00	0.59
	Q3	3.07	0.95	2.19
2012	**Pooled**	3.34	1.27	2.06
	Median	2.11	0.59	1.37
	Q1	1.03	0.14	0.77
	Q3	3.92	1.49	2.56
2013	**Pooled**	3.10	1.14	1.96
	Median	2.03	0.56	1.38
	Q1	1.20	0.24	0.77
	Q3	3.56	1.19	2.49
2014	**Pooled**	2.67	0.90	1.77
	Median	1.61	0.37	1.20
	Q1	0.74	0.00	0.56
	Q3	2.98	0.92	2.24
2015	**Pooled**	2.59	0.87	1.71
	Median	1.71	0.42	1.25
	Q1	0.84	0.12	0.67
	Q3	2.83	0.85	2.17
2016	**Pooled**	2.46	0.80	1.65
	Median	1.59	0.37	1.22
	Q1	0.79	0.00	0.55
	Q3	2.60	0.82	2.03
2017	**Pooled**	2.16	0.69	1.47
	Median	1.39	0.29	1.01
	Q1	0.51	0.00	0.39
	Q3	2.35	0.61	1.77

Q1=First Quartile; Q3=Third Quartile; HO=Hospital-onset; CO=Community-onset

[a]Combined, CRE, CR *Acinetobacter* spp. and MDR *P. aeruginosa* rates are the number of resistant (R) infections per 1,000 discharges

Table 2B. Hospital-level Unadjusted CRE Infection Rates per 1,000 Discharges in the Premier Healthcare Database (2012-2017)

		Unadjusted CRE Rate (All)[a]	Unadjusted CRE Rate (HO)[a]	Unadjusted CRE Rate (CO)[a]
All Years	**Pooled**	0.54	0.19	0.36
	Median	0.22	0.00	0.13
	Q1	0.00	0.00	0.00
	Q3	0.58	0.16	0.42
2012	**Pooled**	0.58	0.20	0.38
	Median	0.20	0.00	0.13
	Q1	0.00	0.00	0.00
	Q3	0.48	0.15	0.36
2013	**Pooled**	0.57	0.22	0.35
	Median	0.24	0.00	0.14
	Q1	0.00	0.00	0.00
	Q3	0.66	0.22	0.41
2014	**Pooled**	0.54	0.17	0.36
	Median	0.19	0.00	0.10
	Q1	0.00	0.00	0.00
	Q3	0.46	0.15	0.36
2015	**Pooled**	0.54	0.17	0.37
	Median	0.22	0.00	0.17
	Q1	0.00	0.00	0.00
	Q3	0.59	0.16	0.47
2016	**Pooled**	0.54	0.19	0.35
	Median	0.24	0.00	0.12
	Q1	0.00	0.00	0.00
	Q3	0.73	0.15	0.55
2017	**Pooled**	0.48	0.16	0.32
	Median	0.20	0.00	0.13
	Q1	0.00	0.00	0.00
	Q3	0.57	0.13	0.41

Q1=First Quartile; Q3=Third Quartile; HO=Hospital-onset; CO=Community-onset

[a]Combined, CRE, CR *Acinetobacter* spp. and MDR *P. aeruginosa* rates are the number of resistant (R) infections per 1,000 discharges

Table 2C. Hospital-level Unadjusted CR *Acinetobacter* spp. Infection Rates per 1,000 Discharges in the Premier Healthcare Database (2012-2017)

		Unadjusted CR *Acinetobacter* spp. Rate (All)[a]	Unadjusted CR *Acinetobacter* spp. Rate (HO)[a]	Unadjusted CR *Acinetobacter* spp. Rate (CO)[a]
All Years	**Pooled**	0.45	0.17	0.28
	Median	0.07	0.00	0.00
	Q1	0.00	0.00	0.00
	Q3	0.44	0.14	0.29
2012	**Pooled**	0.61	0.25	0.36
	Median	0.13	0.00	0.06
	Q1	0.00	0.00	0.00
	Q3	0.61	0.27	0.39
2013	**Pooled**	0.49	0.18	0.30
	Median	0.08	0.00	0.00
	Q1	0.00	0.00	0.00
	Q3	0.60	0.18	0.37
2014	**Pooled**	0.45	0.16	0.29
	Median	0.10	0.00	0.04
	Q1	0.00	0.00	0.00
	Q3	0.47	0.15	0.32
2015	**Pooled**	0.41	0.15	0.25
	Median	0.12	0.00	0.00
	Q1	0.00	0.00	0.00
	Q3	0.40	0.13	0.30
2016	**Pooled**	0.38	0.13	0.25
	Median	0.06	0.00	0.00
	Q1	0.00	0.00	0.00
	Q3	0.38	0.10	0.22
2017	**Pooled**	0.33	0.11	0.21
	Median	0.00	0.00	0.00
	Q1	0.00	0.00	0.00
	Q3	0.22	0.00	0.15

Q1=First Quartile; Q3=Third Quartile; HO=Hospital-onset; CO=Community-onset

[a]Combined, CRE, CR *Acinetobacter* spp. and MDR *P. aeruginosa* rates are the number of resistant (R) infections per 1,0000 discharges

Table 2D. Hospital-level Unadjusted MDR *P. aeruginosa* Infection Rates per 1,000 Discharges in the Premier Healthcare Database (2012-2017)

		Unadjusted MDR *P. aeruginosa* Rate (All)[a]	Unadjusted MDR *P. aeruginosa* Rate (HO)[a]	Unadjusted MDR *P. aeruginosa* Rate (CO)[a]
All Years	**Pooled**	1.75	0.61	1.15
	Median	1.17	0.27	0.82
	Q1	0.54	0.00	0.37
	Q3	2.02	0.60	1.42
2012	**Pooled**	2.15	0.83	1.32
	Median	1.52	0.38	1.01
	Q1	0.66	0.00	0.51
	Q3	2.76	0.97	1.77
2013	**Pooled**	2.05	0.74	1.31
	Median	1.45	0.40	0.99
	Q1	0.75	0.11	0.54
	Q3	2.37	0.74	1.61
2014	**Pooled**	1.68	0.57	1.11
	Median	1.20	0.26	0.84
	Q1	0.47	0.00	0.37
	Q3	1.95	0.56	1.42
2015	**Pooled**	1.64	0.55	1.08
	Median	1.16	0.26	0.81
	Q1	0.65	0.00	0.43
	Q3	1.94	0.55	1.40
2016	**Pooled**	1.54	0.48	1.05
	Median	0.99	0.21	0.75
	Q1	0.48	0.00	0.25
	Q3	1.77	0.47	1.32
2017	**Pooled**	1.35	0.42	0.94
	Median	0.79	0.13	0.58
	Q1	0.11	0.00	0.00
	Q3	1.58	0.42	1.17

Q1=First Quartile, Q3=Third Quartile; HO=Hospital-onset; CO=Community-onset

[a]Combined, CRE, CR *Acinetobacter* spp. and MDR *P. aeruginosa* rates are the number of resistant (R) infections per 1,000 discharges

Table 3. Total and Class Specific Mean Hospital-level Antibiotic Use by Discharge Year in the Premier Healthcare Database (2012-2017)

	All Years (N=253)	**2012 (N=162)**	**2013 (N=190)**	**2014 (N=183)**	**2015 (N=161)**	**2016 (N=169)**	**2017 (N=192)**
Antibiotic Class DOT/1,000 PDs (mean (SD))							
Total (All Classes)	970.3 (234.6)	936.9 (205.7)	952.7 (209.8)	971.9 (224.1)	981.2 (234.3)	969.3 (254.3)	1005.9 (267.9)
Aminoglycosides	14.0 (12.9)	14.3 (10.8)	15.0 (13.3)	14.6 (12.8)	14.0 (13.7)	13.3 (14.0)	12.5 (12.7)
1st and 2nd Cephalosporins	93.2 (43.7)	89.8 (31.1)	89.1 (40.1)	90.9 (38.5)	91.4 (40.4)	96.9 (51.1)	100.5 (54.5)
3rd and 4th Cephalosporins	163.6 (71.9)	139.5 (56.1)	151.2 (59.5)	154.2 (61.0)	170.8 (69.8)	168.0 (72.9)	195.4 (91.4)
Lincosamide	26.8 (16.5)	24.8 (14.3)	25.7 (14.9)	27.4 (16.6)	28.3 (17.1)	28.2 (17.6)	26.8 (18.1)
Fluoroquinolones	144.0 (67.3)	167.0 (63.6)	162.7 (63.6)	157.8 (68.2)	145.7 (66.6)	126.8 (64.1)	106.7 (56.6)
Macrolides	64.5 (42.3)	59.3 (35.0)	63.5 (39.4)	60.7 (38.2)	64.8 (41.3)	62.7 (40.1)	75.0 (54.3)
Glycopeptides	137.5 (45.7)	125.0 (42.1)	128.2 (42.7)	136.4 (44.0)	141.8 (45.3)	144.5 (47.3)	148.7 (47.9)
Sulfa	11.9 (6.3)	12.5 (6.6)	12.9 (6.5)	12.3 (6.5)	11.6 (5.7)	11.1 (5.8)	10.9 (6.5)
β-Lactam/β-lactamase inhibitor combinations	133.6 (54.9)	124.4 (54.6)	126.3 (50.5)	136.5 (50.6)	127.6 (50.7)	138.2 (59.5)	146.8 (59.6)
Carbapenems	44.0 (30.2)	42.9 (27.8)	42.2 (29.2)	44.9 (30.5)	45.5 (29.8)	44.0 (30.0)	44.6 (33.8)
Penicillins	18.3 (10.2)	19.5 (10.9)	18.2 (10.1)	18.2 (9.6)	18.4 (9.8)	17.9 (10.0)	17.7 (10.6)
Tetracyclines	22.4 (18.7)	20.2 (13.6)	18.9 (14.9)	19.8 (19.4)	22.3 (16.4)	23.0 (17.1)	29.6 (25.5)
Metronidazole	61.5 (25.7)	62.5 (23.6)	62.9 (25.2)	62.3 (25.1)	64.3 (27.7)	60.1 (27.9)	57.5 (24.2)
Other	34.9 (19.2)	35.2 (18.8)	35.8 (19.7)	35.9 (19.3)	34.9 (18.5)	34.6 (19.6)	33.1 (19.1)

SD=standard deviation; DOT=Days of Therapy; PDs=Patient-Days

Table 4A. Poisson Regression Results for Hospital-level Combined Infection Rates per 1,000 Discharges in the Premier Healthcare Database (2012-2017)

Hospital Characteristics	Combined Rate (All) IRR (95% CI)	Combined Rate (HO) IRR (95% CI)	Combined Rate (CO) IRR (95% CI)
Total Antibiotic Use[a]	1.00 (0.97, 1.02)	1.02 (0.98, 1.06)	0.99 (0.97, 1.01)
Discharge Year			
2012	REF	REF	REF
2013	0.95 (0.89, 1.01)	0.93 (0.85, 1.03)	0.95 (0.89, 1.02)
2014	0.79 (0.72, 0.87)	0.72 (0.63, 0.83)	0.84 (0.76, 0.91)
2015	0.75 (0.68, 0.83)	0.70 (0.62, 0.80)	0.77 (0.69, 0.87)
2016	0.73 (0.64, 0.83)	0.66 (0.55, 0.80)	0.76 (0.67, 0.87)
2017	0.63 (0.55, 0.72)	0.57 (0.47, 0.68)	0.66 (0.58, 0.76)
U.S. Census Division			
New England	REF	REF	REF
Middle Atlantic	1.86 (1.26, 2.74)	1.66 (1.13, 2.44)	2.01 (1.32, 3.07)
South Atlantic	1.07 (0.76, 1.52)	0.88 (0.61, 1.27)	1.25 (0.85, 1.85)
East North Central	1.77 (1.23, 2.55)	1.43 (0.98, 2.09)	1.99 (1.33, 2.98)
East South Central	1.75 (1.06, 2.88)	1.45 (0.95, 2.23)	2.03 (1.16, 3.56)
West North Central	1.00 (0.64, 1.55)	0.74 (0.49, 1.11)	1.16 (0.70, 1.93)
West South Central	1.49 (1.00, 2.22)	1.09 (0.75, 1.58)	1.79 (1.13, 2.85)
Mountain	1.50 (0.62, 3.65)	1.63 (0.68, 3.92)	1.55 (0.65, 3.70)
Pacific	1.22 (0.72, 2.04)	0.94 (0.53, 1.67)	1.38 (0.81, 2.38)
Bed Size			
<300	0.81 (0.63, 1.04)	0.77 (0.57, 1.03)	0.85 (0.67, 1.08)
≥300	REF	REF	REF
Population Served			
Urban	REF	REF	REF
Rural	0.72 (0.54, 0.96)	0.70 (0.51, 0.95)	0.73 (0.54, 0.98)
Teaching Status			
Teaching	REF	REF	REF
Non-teaching	0.96 (0.76, 1.21)	0.92 (0.73, 1.15)	1.00 (0.78, 1.29)
Age Group[b, c]			
18-55	REF	REF	REF
55-65	1.07 (0.75, 1.51)	1.15 (0.73, 1.81)	1.03 (0.72, 1.47)
65-75	1.01 (0.76, 1.32)	1.10 (0.72, 1.68)	0.92 (0.70, 1.21)
≥75	1.04 (0.85, 1.26)	1.05 (0.85, 1.31)	1.06 (0.87, 1.30)
% Surgical[b, c]	0.92 (0.82, 1.03)	1.06 (0.89, 1.27)	0.83 (0.74, 0.93)
% Infection[b, c]	1.31 (1.07, 1.60)	1.17 (0.85, 1.61)	1.34 (1.12, 1.61)
Case Mix Index	1.07 (0.70, 1.64)	0.70 (0.32, 1.56)	1.51 (1.03, 2.22)
Length of Stay	1.21 (1.07, 1.38)	1.62 (1.30, 2.00)	1.04 (0.93, 1.16)

IRR=Incidence Rate Ratio; CI=Confidence Interval; HO=Hospital-onset; CO=Community-onset

[a]The IRR and corresponding 95% CI represent a change in rate of 50 DOT/1,000 PDs

[b]Age group, % surgical and % infection, are calculated as the proportion of discharges within the designated age groups, that were surgical, or that had an infection

[c]The IRR and corresponding 95% CI for age group, % surgical and % infection represent a 10% change in the proportion of discharges

Table 4B. Poisson Regression Results for Hospital-level CRE Infection Rates per 1,000 Discharges in the Premier Healthcare Database (2012-2017)

Hospital Characteristics	CRE Rate (All) IRR (95% CI)	CRE Rate (HO) IRR (95% CI)	CRE Rate (CO) IRR (95% CI)
Total Antibiotic Use[a]	1.02 (0.98, 1.06)	1.03 (0.99, 1.07)	1.01 (0.97, 1.06)
Discharge Year			
2012	REF	REF	REF
2013	1.01 (0.91, 1.13)	1.18 (0.98, 1.43)	0.92 (0.81, 1.05)
2014	0.95 (0.81, 1.10)	0.95 (0.76, 1.18)	0.95 (0.79, 1.15)
2015	0.93 (0.76, 1.13)	0.92 (0.72, 1.18)	0.93 (0.73, 1.18)
2016	0.97 (0.79, 1.20)	1.07 (0.83, 1.37)	0.92 (0.71, 1.20)
2017	0.83 (0.65, 1.07)	0.87 (0.65, 1.16)	0.80 (0.60, 1.06)
U.S. Census Division			
New England	REF	REF	REF
Middle Atlantic	3.25 (1.56, 6.77)	2.62 (1.24, 5.56)	3.60 (1.67, 7.76)
South Atlantic	1.52 (0.73, 3.16)	1.27 (0.58, 2.77)	1.72 (0.81, 3.65)
East North Central	2.11 (1.01, 4.40)	1.48 (0.71, 3.10)	2.54 (1.19, 5.43)
East South Central	0.90 (0.29, 2.74)	0.73 (0.24, 2.26)	1.19 (0.40, 3.50)
West North Central	0.91 (0.36, 2.27)	0.47 (0.20, 1.10)	1.20 (0.46, 3.13)
West South Central	1.00 (0.43, 2.31)	0.64 (0.28, 1.46)	1.24 (0.51, 3.00)
Mountain	2.91 (0.92, 9.22)	2.42 (0.67, 8.76)	3.21 (1.06, 9.67)
Pacific	3.25 (1.56, 6.77)	0.96 (0.38, 2.43)	1.64 (0.67, 4.06)
Bed Size			
<300	0.86 (0.54, 1.36)	0.74 (0.47, 1.17)	0.99 (0.61, 1.60)
≥300	REF	REF	REF
Population Served			
Urban	REF	REF	REF
Rural	0.52 (0.29, 0.91)	0.43 (0.20, 0.91)	0.59 (0.35, 0.98)
Teaching Status			
Teaching	REF	REF	REF
Non-teaching	0.70 (0.46, 1.06)	0.70 (0.45, 1.08)	0.68 (0.44, 1.05)
Age Group[b, c]			
18-55	REF	REF	REF
55-65	1.49 (0.97, 2.30)	1.18 (0.58, 2.40)	1.69 (1.07, 2.68)
65-75	0.90 (0.52, 1.54)	1.04 (0.48, 2.25)	0.80 (0.44, 1.46)
≥75	1.28 (0.92, 1.79)	1.11 (0.73, 1.69)	1.40 (1.01, 1.96)
% Surgical[b, c]	0.80 (0.64, 0.99)	0.92 (0.66, 1.26)	0.70 (0.55, 0.90)
% Infection[b, c]	1.09 (0.81, 1.47)	0.95 (0.59, 1.55)	1.04 (0.75, 1.45)
Case Mix Index	0.71 (0.33, 1.51)	0.60 (0.21, 1.65)	0.98 (0.43, 2.22)
Length of Stay	1.28 (1.03, 1.59)	1.52 (1.14, 2.04)	1.12 (0.88, 1.42)

IRR=Incidence Rate Ratio; CI=Confidence Interval; HO=Hospital-onset; CO=Community-onset

[a]The IRR and corresponding 95% CI represent a change in rate of 50 DOT/1,000 PDs

[b]Age group, % surgical and % infection, are calculated as the proportion of discharges within the designated age groups, that were surgical, or that had an infection

[c]The IRR and corresponding 95% CI for age group, % surgical and % infection represent a 10% change in the proportion of discharges

Table 4C. Poisson Regression Results for Hospital-level CR *Acinetobacter* spp. Infection Rates per 1,000 Discharges in the Premier Healthcare Database (2012-2017)

Hospital Characteristics	CR *Acinetobacter* spp. Rate (All) IRR (95% CI)	CR *Acinetobacter* spp. Rate (HO) IRR (95% CI)	CR *Acinetobacter* spp. Rate (CO) IRR (95% CI)
Total Antibiotic Use[a]	1.06 (1.02, 1.09)	1.12 (1.05, 1.20)	1.04 (1.01, 1.07)
Discharge Year			
2012	REF	REF	REF
2013	0.85 (0.73, 1.00)	0.85 (0.66, 1.08)	0.85 (0.74, 0.99)
2014	0.75 (0.60, 0.94)	0.71 (0.52, 0.96)	0.77 (0.64, 0.94)
2015	0.70 (0.57, 0.87)	0.74 (0.55, 0.99)	0.67 (0.55, 0.82)
2016	0.72 (0.57, 0.91)	0.71 (0.50, 1.02)	0.71 (0.57, 0.87)
2017	0.57 (0.43, 0.75)	0.57 (0.40, 0.82)	0.55 (0.42, 0.73)
U.S. Census Division			
New England	REF	REF	REF
Middle Atlantic	3.32 (1.36, 8.10)	1.93 (0.94, 3.97)	4.03 (1.70, 9.59)
South Atlantic	1.65 (0.61, 4.44)	1.13 (0.48, 2.68)	1.94 (0.75, 5.03)
East North Central	5.00 (2.06, 12.17)	2.83 (1.34, 5.99)	5.81 (2.50, 13.48)
East South Central	4.42 (1.65, 11.87)	3.63 (1.63, 8.07)	4.29 (1.56, 11.83)
West North Central	2.55 (0.90, 7.17)	1.12 (0.45, 2.80)	3.43 (1.27, 9.30)
West South Central	3.12 (1.30, 7.49)	2.19 (1.02, 4.68)	3.36 (1.46, 7.75)
Mountain	8.06 (2.15, 30.18)	8.11 (2.63, 24.98)	6.96 (1.68, 28.84)
Pacific	3.24 (1.18, 8.88)	1.65 (0.63, 4.32)	4.01 (1.54, 10.42)
Bed Size			
<300	0.78 (0.48, 1.27)	0.67 (0.41, 1.09)	0.84 (0.51, 1.39)
≥300	REF	REF	REF
Population Served			
Urban	REF	REF	REF
Rural	0.43 (0.18, 1.02)	0.50 (0.21, 1.19)	0.46 (0.19, 1.10)
Teaching Status			
Teaching	REF	REF	REF
Non-teaching	0.87 (0.52, 1.46)	0.95 (0.57, 1.60)	0.85 (0.49, 1.48)
Age Group[b, c]			
18-55	REF	REF	REF
55-65	0.71 (0.31, 1.59)	1.21 (0.47, 3.13)	0.59 (0.26, 1.36)
65-75	0.98 (0.50, 1.94)	0.58 (0.25, 1.35)	1.29 (0.67, 2.47)
≥75	0.99 (0.67, 1.48)	1.45 (0.96, 2.19)	0.82 (0.54, 1.26)
% Surgical[b, c]	0.86 (0.64, 1.15)	0.82 (0.55, 1.23)	0.82 (0.63, 1.07)
% Infection[b, c]	0.94 (0.65, 1.35)	0.55 (0.32, 0.95)	1.17 (0.82, 1.69)
Case Mix Index	0.80 (0.36, 1.78)	0.73 (0.19, 2.82)	1.03 (0.48, 2.21)
Length of Stay	1.39 (1.08, 1.79)	1.64 (1.14, 2.35)	1.20 (0.95, 1.52)

IRR=Incidence Rate Ratio; CI=Confidence Interval; HO=Hospital-onset; CO=Community-onset

[a]The IRR and corresponding 95% CI represent a change in rate of 50 DOT/1,000 PDs

[b]Age group, % surgical and % infection, are calculated as the proportion of discharges within the designated age groups, that were surgical, or that had an infection

[c]The IRR and corresponding 95% CI for age group, % surgical and % infection represent a 10% change in the proportion of discharges

Table 4D. Poisson Regression Results for Hospital-level MDR *Pseudomonas aeruginosa* Infection Rates per 1,000 Discharges in the Premier Healthcare Database (2012-2017)

Hospital Characteristics	MDR *P. aeruginosa* Rate (All) IRR (95% CI)	MDR *P. aeruginosa* Rate (HO) IRR (95% CI)	MDR *P. aeruginosa* Rate (CO) IRR (95% CI)
Total Antibiotic Use[a]	0.99 (0.95, 1.02)	1.00 (0.95, 1.05)	0.99 (0.96, 1.01)
Discharge Year			
2012	REF	REF	REF
2013	0.96 (0.89, 1.03)	0.90 (0.81, 0.99)	0.99 (0.92, 1.07)
2014	0.77 (0.69, 0.85)	0.67 (0.57, 0.79)	0.82 (0.75, 0.91)
2015	0.72 (0.64, 0.81)	0.64 (0.56, 0.75)	0.77 (0.68, 0.87)
2016	0.67 (0.58, 0.78)	0.56 (0.46, 0.69)	0.75 (0.65, 0.86)
2017	0.60 (0.51, 0.71)	0.50 (0.40, 0.62)	0.66 (0.56, 0.78)
U.S. Census Division			
New England	REF	REF	REF
Middle Atlantic	1.41 (1.04, 1.92)	1.41 (0.97, 2.05)	1.42 (1.06, 1.90)
South Atlantic	0.97 (0.75, 1.26)	0.82 (0.57, 1.17)	1.12 (0.85, 1.47)
East North Central	1.43 (1.09, 1.88)	1.21 (0.82, 1.79)	1.58 (1.20, 2.08)
East South Central	1.69 (1.01, 2.82)	1.37 (0.85, 2.21)	1.98 (1.13, 3.44)
West North Central	0.85 (0.63, 1.14)	0.74 (0.51, 1.06)	0.93 (0.66, 1.31)
West South Central	1.33 (0.95, 1.85)	1.00 (0.67, 1.51)	1.56 (1.10, 2.23)
Mountain	0.98 (0.49, 1.94)	0.97 (0.47, 2.01)	1.10 (0.56, 2.14)
Pacific	0.93 (0.62, 1.37)	0.74 (0.44, 1.25)	1.02 (0.69, 1.50)
Bed Size			
<300	0.83 (0.68, 1.02)	0.82 (0.63, 1.07)	0.85 (0.70, 1.03)
≥300	REF	REF	REF
Population Served			
Urban	REF	REF	REF
Rural	0.86 (0.67, 1.10)	0.84 (0.64, 1.10)	0.85 (0.66, 1.10)
Teaching Status			
Teaching	REF	REF	REF
Non-teaching	1.09 (0.90,1.31)	1.00 (0.81, 1.24)	1.16 (0.96, 1.41)
Age Group[b, c]			
18-55	REF	REF	REF
55-65	1.05 (0.73, 1.52)	1.12 (0.67, 1.89)	0.97 (0.67, 1.41)
65-75	1.01 (0.74, 1.40)	1.14 (0.73, 1.80)	0.88 (0.64, 1.21)
≥75	1.01 (0.86, 1.19)	0.99 (0.81, 1.22)	1.05 (0.89, 1.24)
% Surgical[b, c]	1.02 (0.89, 1.17)	1.18 (0.97, 1.45)	0.93 (0.81, 1.07)
% Infection[b, c]	1.47 (1.14, 1.88)	1.44 (1.00, 2.07)	1.43 (1.13, 1.82)
Case Mix Index	1.18 (0.71, 1.97)	0.86 (0.33, 2.24)	1.63 (1.05, 2.53)
Length of Stay	1.24 (1.06, 1.44)	1.72 (1.38, 2.15)	1.05 (0.92, 1.20)

IRR=Incidence Rate Ratio; CI=Confidence Interval; HO=Hospital-onset; CO=Community-onset

[a]The IRR and corresponding 95% CI represent a change in rate of 50 DOT/1,000 PDs

[b]Age group, % surgical and % infection, are calculated as the proportion of discharges within the designated age groups, that were surgical, or that had an infection

[c]The IRR and corresponding 95% CI for age group, % surgical and % infection represent a 10% change in the proportion of discharges

Figures

Figure 1A. Box Plots of Unadjusted Combined Antibiotic Resistant Rates of Infection per 1,000 Discharges by Discharge Year

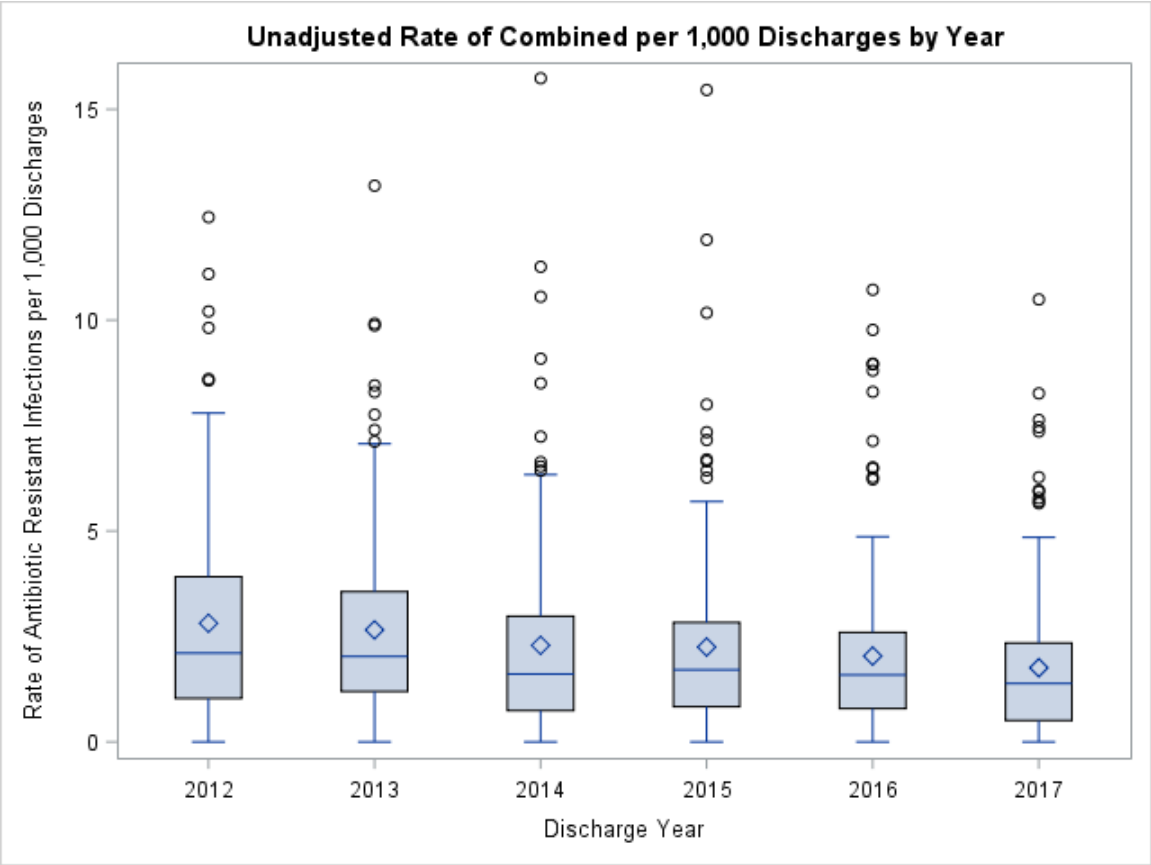

Figure 1B. Box Plots of Unadjusted CRE Antibiotic Resistant Rates of Infection per 1,000 Discharges by Discharge Year

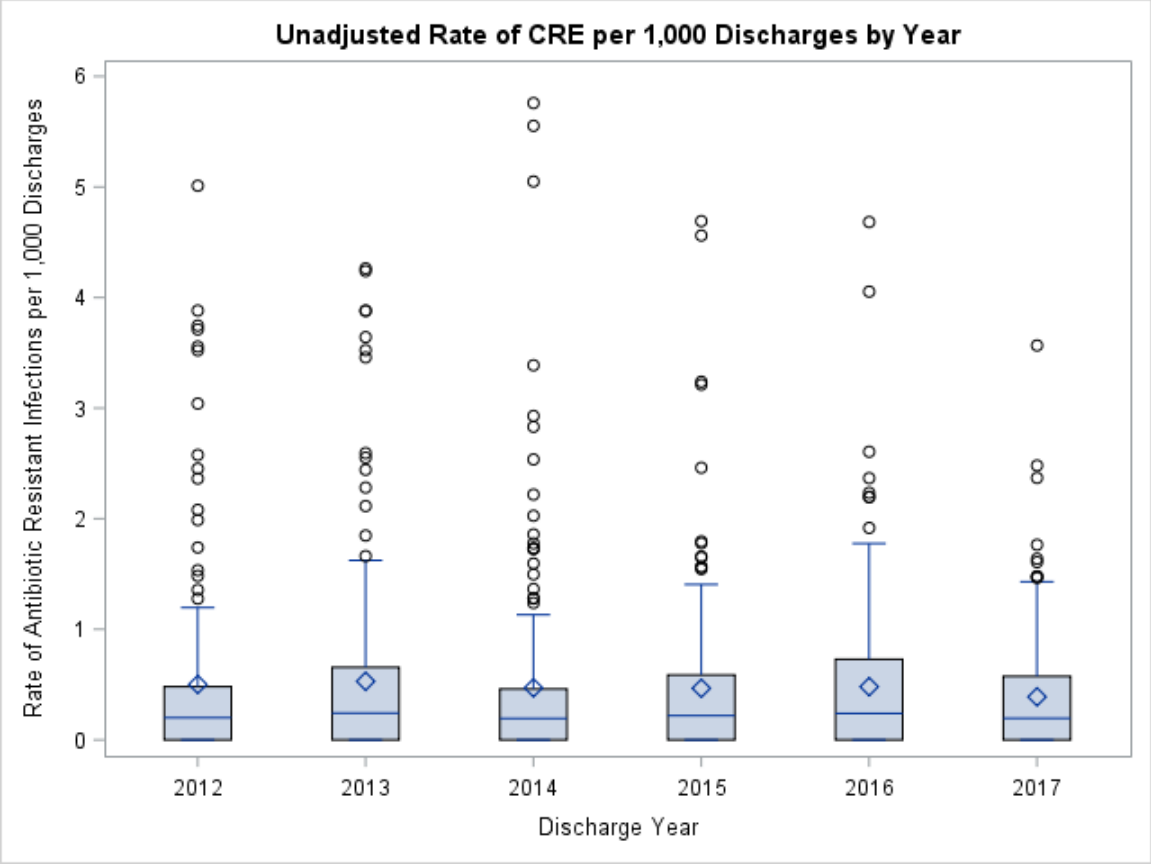

Figure 1C. Box Plots of Unadjusted CR *Acinetobacter* spp. Antibiotic Resistant Rates of Infection per 1,000 Discharges by Discharge Year

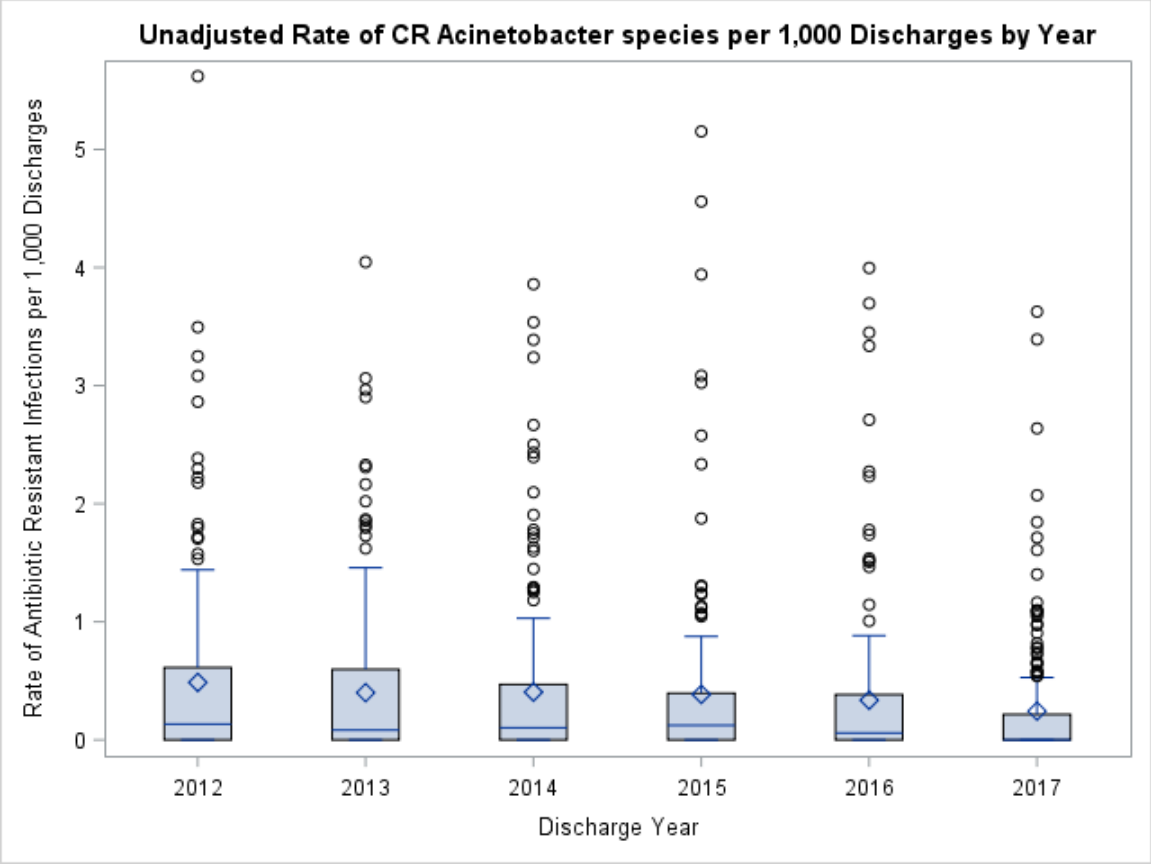

Figure 1D. Box Plots of Unadjusted MDR *Pseudomonas aeruginosa* Antibiotic Resistant Rates of Infection per 1,000 Discharges by Discharge Year

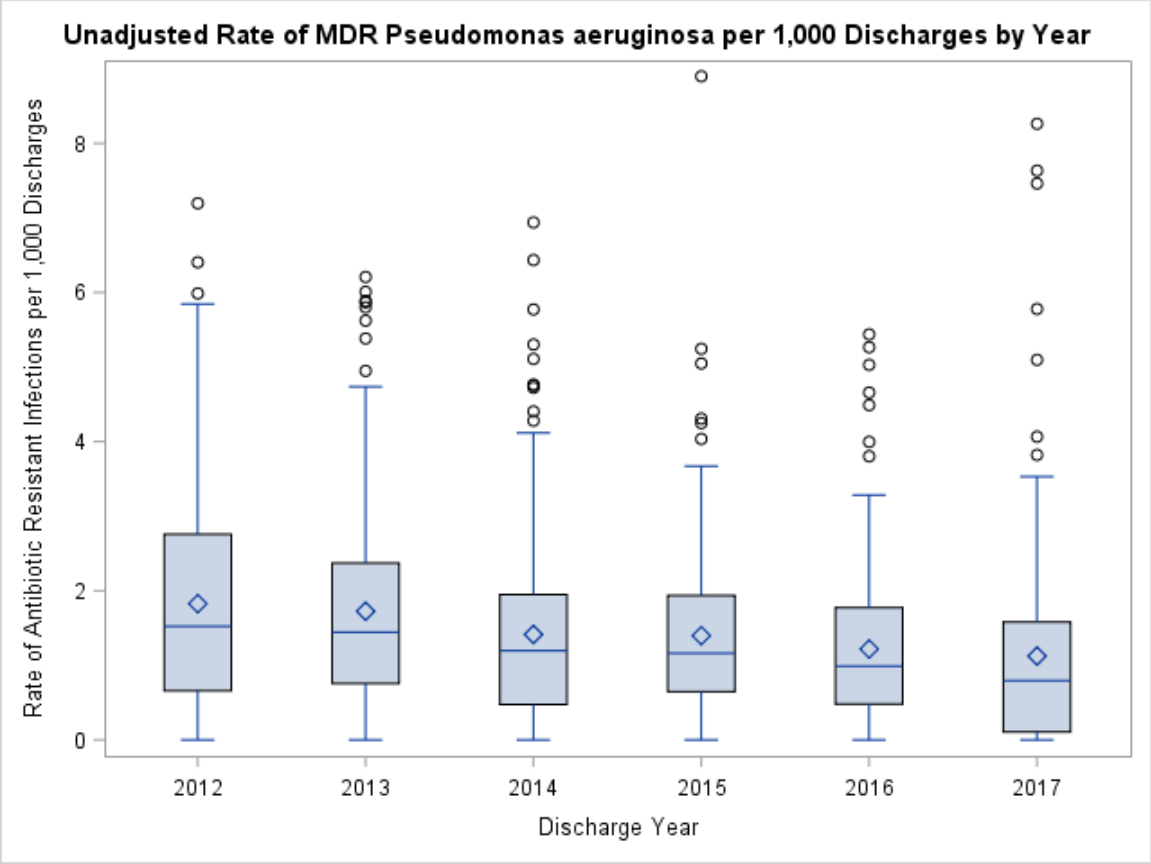

Figure 2A. Scatterplots of Antibiotic Use (DOT/1,000 PDs) and Combined Antibiotic Resistant Rates of Infection per 1,000 Discharges by Year

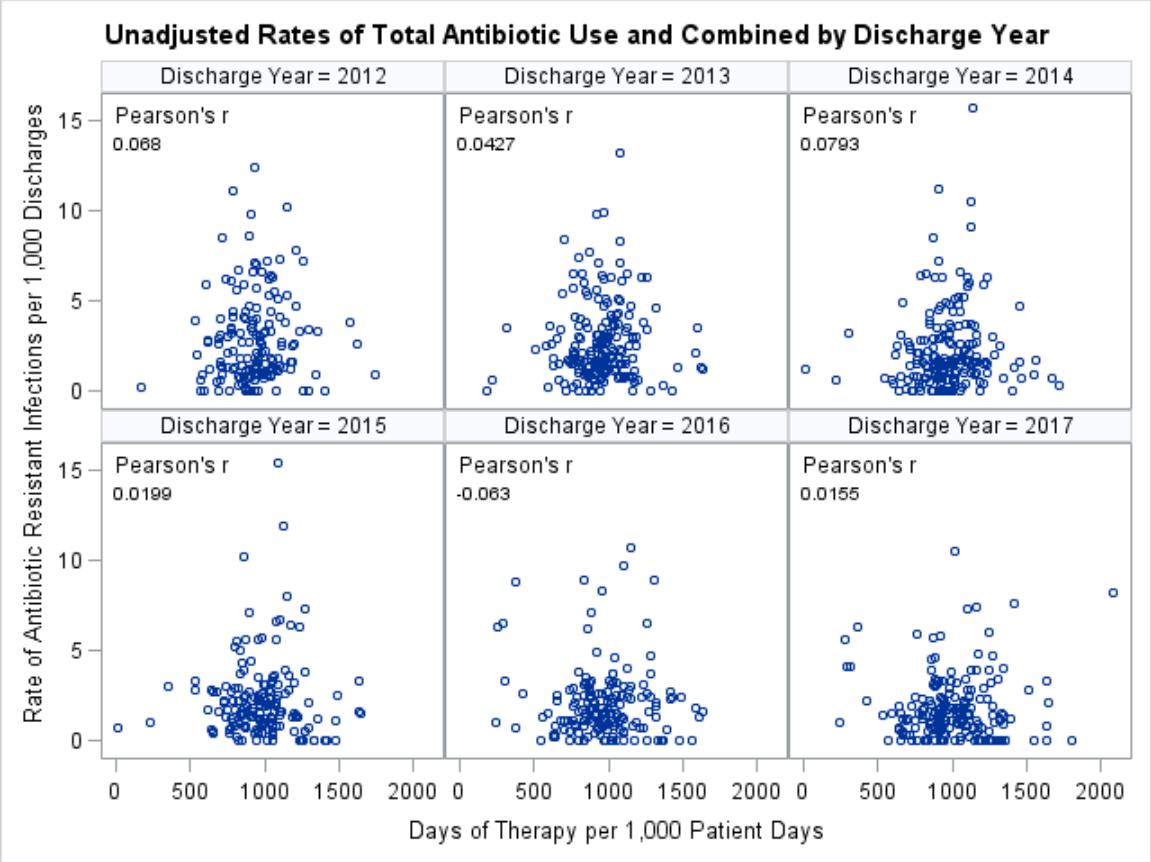

Figure 2B. Scatterplots of Antibiotic Use (DOT/1,000 PDs) and CRE Antibiotic Resistant Rates of Infection per 1,000 Discharges by Year

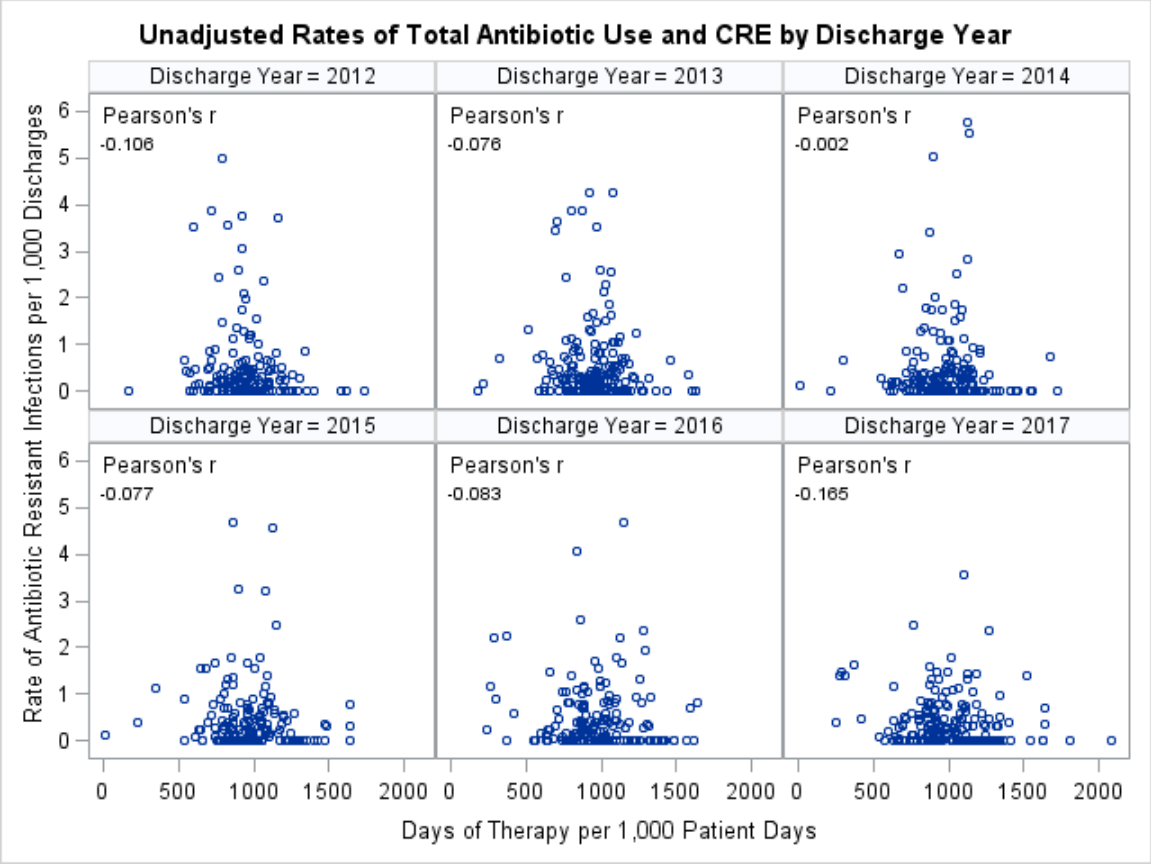

Figure 2C. Scatterplots of Antibiotic Use (DOT/1,000 PDs) and CR *Acinetobacter* spp. Antibiotic Resistant Rates of Infection per 1,000 Discharges by Year

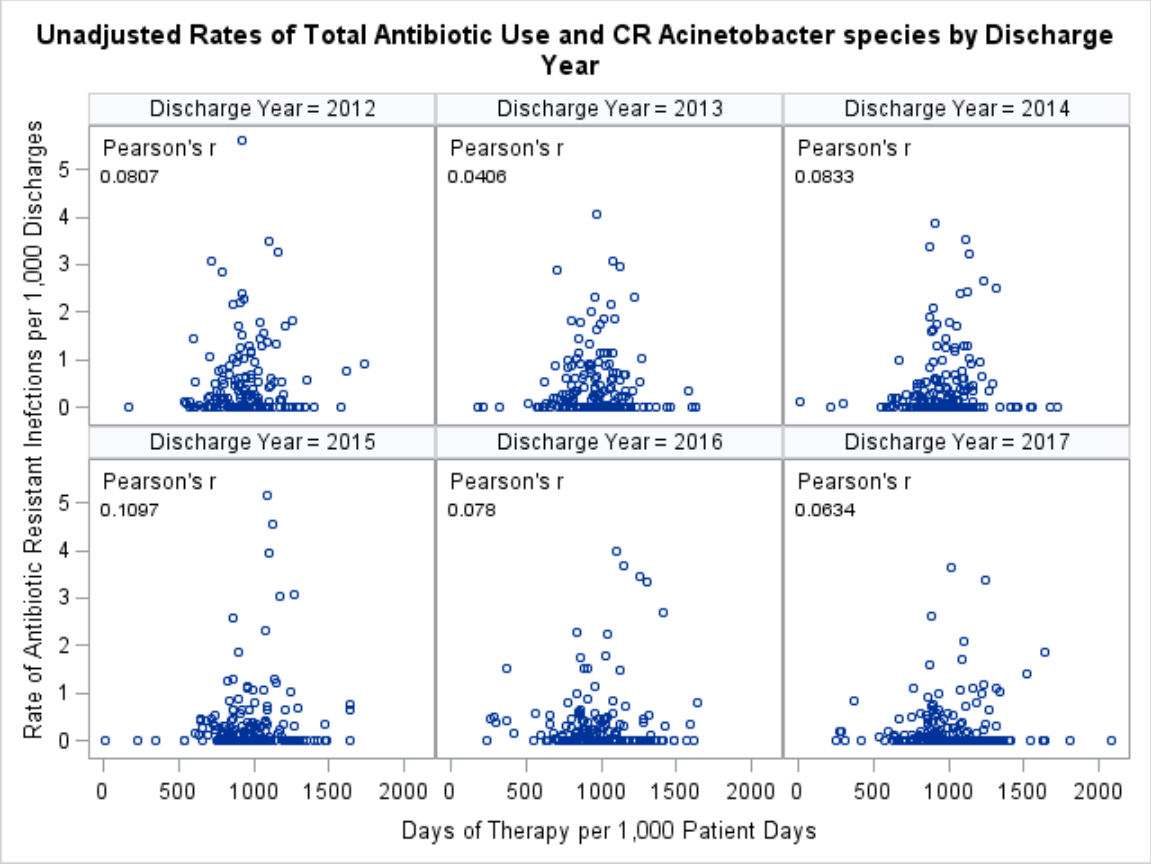

Figure 2D. Scatterplots of Antibiotic Use (DOT/1,000 PDs) and MDR *P. aeruginosa* Antibiotic Resistant Rates of Infection per 1,000 Discharges by Year