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Effect of Antibiotic Stewardship Program Intensity and Outpatient Antibiotic Prescribing Rates on the Variability in Prevalence of Antibiotic-Resistant Phenotypes between U.S. States

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Bachelor of Science
Whitworth University
2016

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ABSTRACT

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CHAPTER I: BACKGROUND

The introduction of antibiotics has forever shifted the paradigm of modern medicine. Deadly bacterial diseases that were once incurable are now easily treated with a strict antibiotic regimen. However, bacteria have adapted over time to withstand the effects of the antibiotics that were once used to destroy them. This phenomenon is called antibiotic resistance, and it has become a worldwide public health concern within the past decade.

Mechanisms of Antibiotic Resistance

Bacteria can develop resistance to antibiotics by one or more of the following biological mechanisms: (1) intrinsic resistance, (2) genetic mutation, and (3) transfer of genetic material (1, 2). Bacteria with intrinsic resistance have the innate ability to survive exposure to an antibiotic due to the bacteria's inherent structure or functional properties. Bacteria with intrinsic resistance typically lack a susceptible target for the antibiotic, rendering the antibiotic useless against the bacteria (1). Bacteria can also develop resistance through genetic mutation. Upon reproduction, natural mutations occur at various intervals, and occasionally provide the bacteria with new genetic code that produce a mechanism to survive exposure to an antibiotic or class of antibiotics. Most antibiotic-resistant bacteria that develop resistance through mutation obtain properties to minimize intracellular concentrations of antibiotics, modify the antibiotic target or antibiotic pathway, or inactivate the antibiotic all together (2). Bacteria can also transfer their resistance genes to other bacteria. The most common forms of genetic transfer are conjugation, a form of horizontal gene transfer in which genetic material is transferred between bacterial cells through either direct or indirect contact, injection of resistance

genes from a virus into bacteria, or acquisition of free DNA with resistance genes from their environment (1, 2). Bacteria with these properties may live in small numbers within any population of bacteria living in humans. However, in the setting of antibiotic exposure, these small populations of resistant bacteria can proliferate, become the predominant strain, and potentially cause infection or be transmitted to other humans.

Multidrug-Resistant Pseudomonas Aeruginosa Infections

Pseudomonas aeruginosa are Gram-negative rod-shaped bacteria that are a common cause of healthcare-associated infections (HAIs) in the United States (3). The emergence of the multidrug-resistant (MDR) phenotype of *P. aeruginosa* has hindered the standard treatment for HAIs caused by *P. aeruginosa* and is strongly associated with worsening clinical outcomes, including increased morbidity and mortality, longer hospital stays, and increased requirements for procedures (4). Multidrug resistance for *P. aeruginosa* has been attributed to several mechanisms, such as the low permeability of the bacterial cellular envelope, the presence of encoded resistant genes, and the use of multidrug efflex pumps (5). Although multidrug resistance can occur from a variety of sources, the consensus among the medical community is that the MDR phenotype of *P. aeruginosa* is most attributable to de novo genetic mutations more so than genetic transfer (6).

Prevalence of MDR *P. aeruginosa* in the hospital setting significantly increased from 8% in the early 1990s to 14% in 2010 (6, 7), with intensive care units (ICUs) and infectious disease wards reporting higher prevalence of MDR *P. aeruginosa* than other hospital wards (8). MDR *P. aeruginosa* can be isolated from a variety of sources in hospitals, such as respiratory equipment, antiseptics, soaps, and mops, and are thus

strongly associated with ventilator-associated pneumonia and sepsis in the hospital setting (9). Prominent risk factors for MDR *P. aeruginosa* include prior use of antibiotics (particularly carbapenems, quinolones, and fluoroquinolones), length of ICU stay, and use of mechanical ventilation, but other factors such as presence of invasive devices, comorbidities, age, and movement ability have been shown to increase the risk of MDR *P. aeruginosa* infection (4, 10, 11).

Extended-Spectrum Beta-Lactamase Producing Escherichia Coli Infections

Extended-spectrum beta-lactamases (ESBLs) are complex enzymes that complicate antibiotic therapies for hospitalized patients and are a major cause of HAIs. (12). Typically found within Gram-negative bacteria, these enzymes can hydrolyze extended-spectrum cephalosporins and confer resistance to these antibiotics. ESBL-producing bacteria generate antibiotic resistance via genetic mutation, mainly by modifying the permeability barrier, modifying the antibiotic target to lower the affinity for the antibiotic, producing more beta-lactamases, or inhibiting the release of autolytic enzymes (13).

During the 1990s, strains of *Escherichia coli* were found to produce ESBLs. ESBL-producing *E. coli* is strongly associated with urinary tract infections (UTIs) and cause between 44% and 86% of ESBL-related UTIs in the hospital setting (14, 15). Incidence of ESBL-producing *E. coli* isolates has significantly increased within the United States, ranging from a 0.2% to 5.5% increase in isolates per year (16). However, the incidence may even be higher due to inconsistencies in reporting caused by a lack of consensus over the definition of ESBL-producing bacteria (17). Prominent risk factors for ESBL-producing *E. coli* include prior use of antibiotics (particularly fluoroquinoloes), previous hospitalization, length of hospital stay, inadequate antibiotic therapy, and

presence of a urinary catheter (14-16, 18-20). Additional but less significant risk factors for ESBL-producing *E. coli* include immunosuppression, use of gastric and suppressive agents, tube feeding, non-ambulatory status, and previous healthcare-associated UTI (15, 18).

Methicillin-Resistant Staphylococcus Aureus Infections

Staphylococcus aureus are Gram-positive bacteria that are a leading cause of pneumonia, surgical site infections, and bloodstream infections within the hospital (9). Methicillin-resistant *S. aureus* (MRSA) is of great concern; historically, beta-lactams such as methicillin were highly effective in the treatment and prevention of *S. aureus* infections in hospitalized patients. *S. aureus* can develop resistance to beta-lactams either through expressing the PC1 beta-lactamase enzyme that hydrolyzes and inactivates beta-lactams, or by acquiring a gene containing a penicillin-binding protein that is resistant to beta-lactams (21).

Prevalence of MRSA in the United States (U.S.) has significantly increased since the 1990s, with an estimated prevalence between 11% and 37% (22-24). MRSA bacteremia prevalence has drastically improved since 2005; however, progress in preventing MRSA bacteremia has slowed in recent years (25). Prominent risk factors for MRSA include prior antibiotic therapy (particularly fluoroquinolones and macrolides), African American race, presence of a ventilator or catheter, inadequate antibiotic therapy, previous hospitalization, and length of hospital stay. Immunosuppression, enteral feedings, surgery, and non-ambulatory status are also shown to increase the risk for MRSA in the hospital setting (23, 26-28).

Intensity of Antibiotic Stewardship

Antibiotic stewardship involves interventions that monitor and improve proper antibiotic use in a healthcare setting, and is one method hospitals can use to combat antibiotic resistance. Many U.S. hospitals implement antibiotic stewardship programs (ASPs) in order to identify whether an inappropriate regimen, duration of therapy, or dose for an antibiotic is being used. The CDC has identified seven core elements that should be incorporated into a successful hospital ASP; these elements include leadership commitment, accountability, drug expertise, action, tracking, reporting, and education (29). Recent research suggests that a higher intensity of antibiotic stewardship (i.e. an ASP that includes all seven core elements) is strongly associated with a reduction in incidence of antibiotic resistance, with an estimated reduction of resistant isolates between 28.9% and 54% (30, 31). Therefore, intensity of antibiotic stewardship is an appropriate predictor of antibiotic resistance among inpatients with an infection.

Outpatient Antibiotic Prescribing Rates

Most antibiotics used for human health in the U.S. are distributed within the outpatient setting. Approximately 266.1 million courses of antibiotics were dispensed in the outpatient setting in 2014, but at least 30% of these courses of antibiotics were either inappropriate or unnecessary for the patient's condition (32). Outpatient antibiotic prescribing rates also differ by state and region. Outpatient antibiotic prescribing rates are significantly higher in the Southern regions of the U.S., where there are higher proportions of obese persons, young children, and prescribers per capita compared to other U.S. regions (33). Recent research has shown that increased outpatient prescribing contributes to increased incidence of resistant isolates among community-based

infections with bacterial pneumonia (*Streptococcus pneumonia*) (34). Thus, outpatient antibiotic prescribing rate is an appropriate predictor of antibiotic resistance among community pathogens, but unclear if it will predict resistance among inpatients with a hospital-onset infection.

CHAPTER II

Effect of Antibiotic Stewardship Program Intensity and Outpatient Antibiotic Prescribing Rates on the Variability in Prevalence of Antibiotic-Resistant Phenotypes between U.S. States

Julianne N. Kubes, Scott K. Fridkin, and Lindsey M. Weiner

ABSTRACT

Antibiotic resistant bacteria are major causes of morbidity and mortality in the United States. Despite the presence of national recommendations to reduce the prevalence of antibiotic resistant bacteria, there is significant variability in resistance prevalence between U.S. states. The purpose of this study was to determine whether the variability in prevalence for multidrug-resistant (MDR) *P. aeruginosa*, extended-spectrum beta lactamase-producing (ESBL) *E. coli*, and methicillin-resistant *Staphylococcus aureus* (MRSA) healthcare-associated infection (HAI) prevalence between U.S. states can be explained by differences in the extent of hospital antibiotic stewardship programs and outpatient antibiotic prescribing rates. Multivariate logistic regression was used to build models for each antibiotic-resistant phenotype. Pearson's partial correlation coefficients (R^2) and respective p-values were calculated to determine direction and strength of correlations. Intensity of antibiotic stewardship did not explain the geographic variability in MDR *P. aeruginosa*, ESC-R *E. coli*, or MRSA prevalence. Outpatient fluoroquinolone and cephalosporin prescribing rates explained some of the geographic variability in ESC-R *E. coli* prevalence between U.S. states. Outpatient fluoroquinolone prescribing rate explained some of the geographic variability in MRSA prevalence; this correlation was slightly elevated in states with a higher population of

African-Americans. Future research should focus on racial differences in antibiotic use or the temporal relationship between timing of antibiotic stewardship implementation and antibiotic-resistant prevalence.

INTRODUCTION

Antibiotic resistance is a critical public health issue. Although antibiotic resistance has spread worldwide within the past decade, a great burden lies within developed countries such as the United States (U.S). An estimated 2 million US residents develop life-threatening infections that are resistant to at least one antibiotic used to treat the infection and more than 20,000 US residents die each year with antibiotic-resistant infections (35). Antibiotic resistance also overburdens the U.S. healthcare system with costlier treatments and production of new antibiotics.

Several bacterial pathogens are of major public health concern due to their ability to cause dangerous healthcare-associated infections (HAIs) that are difficult to treat. *Pseudomonas aeruginosa* is a pathogen that accounts for approximately 8% of serious HAIs, and approximately 13% of these infections are multidrug-resistant (MDR) which account for more than 400 deaths per year in the US (36). Extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli* accounts for 14% of *E. coli* HAIs, totaling 9,000 yearly infections among hospitalized patients and 600 deaths in the U.S. (35). Methicillin-resistant *Staphylococcus aureus* (MRSA) causes infections both inside and outside of hospitals and is one of the leading causes of HAIs. The Centers for Disease Control and Prevention (CDC) estimates that MRSA is associated with more than 80,000 severe infections and 11,000 deaths per year in the US (35). There is an obvious need to

combat these drug resistant microbes, as they are associated with high morbidity and mortality across the country.

The CDC has identified major contributors to antibiotic resistance: two of these include lack of antibiotic stewardship and increased outpatient antibiotic use. The CDC developed the Core Elements of Hospital Antibiotic Stewardship Programs, which describe important components of a successful hospital antibiotic stewardship program (28). Additionally, the CDC recommends reducing the number of antibiotic prescriptions in the outpatient setting, since at least 30% of oral antibiotics prescribed in the outpatient setting are unnecessary (37). Previous research supports the CDC's recommendations by finding that targeted antibiotic stewardship and reduction of outpatient antibiotic use reduces prevalence of antibiotic resistance in the U.S. (38, 39). However, despite CDC's national recommendations, wide variability in the prevalence of antibiotic resistance exists between US states when evaluated by the limited measures publicly available to evaluate state-specific antibiotic resistance (i.e. among hospital-onset infections) (40). There are differences in intensity of antibiotic stewardship programs and rates of outpatient antibiotic prescribing between U.S. states, which may explain the geographical variability in antibiotic resistance. This study examined whether the variability in prevalence for MDR *P. aeruginosa*, ESBL-producing *E. coli*, and MRSA HAIs between US states can be explained by differences in the extent of hospital antibiotic stewardship programs and outpatient antibiotic prescribing practices between U.S. states.

METHODS

Study Design

This study utilized an ecological secondary analysis of publicly available datasets to test the null hypothesis that the extent of hospital antibiotic stewardship programs and outpatient antibiotic prescribing practices do not explain the variability in prevalence of MDR *P. aeruginosa*, ESBL-producing *E. coli*, and MRSA HAIs between U.S. states.

Population and Data Sources

The primary source of data used in this study was the CDC's Antibiotic Resistance Patient Safety Atlas (AR Atlas). The AR Atlas contains several datasets that were utilized. The first dataset includes pathogen and resistance data on elements such as central-line associated bloodstream infections (CLABSIs), catheter-associated urinary tract infections (CAUTIs), and surgical site infections (SSIs). The second dataset provides state-level outpatient antibiotic prescription rates. These data are from oral antibiotic prescriptions dispensed to outpatients in U.S. community pharmacies between 2011 and 2015, supplied to CDC from QuintileIMS as the Xponent database (Danbury, Connecticut). The third dataset contains information about antibiotic stewardship programs within all acute care hospitals in the U.S., as reported to the annual survey required for all hospitals participating in CDC's National Healthcare Safety Network (NHSN). In addition, state-level data regarding basic characteristics of acute care facilities (ACFs), long-term acute care facilities (LTACFs), and skilled nursing facilities (SNFs) were obtained from the Centers for Medicaid and Medicare Services Hospital Compare and Nursing Home Compare datasets. Finally, state population estimates were obtained from the U.S. Census Bureau.

Because all datasets are publicly available and do not contain any protected health information, Institutional Review Board approval was not required. In order to simplify data analysis, data reported from long-term care facilities and inpatient rehabilitation facilities were excluded. Additionally, only data reported during 2014 was included in the analysis.

Phenotype Definitions

MDR *P. aeruginosa* was defined as any *P. aeruginosa* isolate that tested either intermediate or resistant to at least one drug in at least three of the following classes of antibiotics (categories): extended-spectrum cephalosporins, fluoroquinolones, aminoglycosides, carbapenems, and piperacillins/tazobactam. Since NHSN does not collect data on presence of ESBLs in bacteria, extended-spectrum cephalosporin-resistant (ESC-R) *E. coli* was used as a proxy to measure ESBL-producing *E. coli* (41). ESC-R *E. coli* was further defined as any *E. coli* isolate that tested resistant to ceftriaxone, ceftazidime, cefepime or cefotaxime. MRSA was defined as any *S. aureus* isolate that tested resistant to methicillin, oxacillin, or cefoxitin (hereafter, referred to as methicillin).

Statistical Analysis

The study examined three state-level outcomes: percentage of *S. aureus* isolates resistant to methicillin, percentage of *E. coli* isolates resistant to extended-spectrum cephalosporins, and percentage of *P. aeruginosa* isolates resistant to multiple drugs. The primary predictors were intensity of antibiotic stewardship, which was measured as the percentage of hospitals per state that incorporated all 7 CDC Core Elements into their antibiotic stewardship program, and state-level outpatient antibiotic prescription rates,

both overall and by class of antibiotics: fluoroquinolones, penicillins, cephalosporins, and macrolides. Potential confounders included number of ACFs, number of LTACFs, number of SNFs, number of SNF bed-days, total population, percentage of the population older than 65 years of age, percentage of the population African-American (categorized into two subgroups: states with ≤ 11.3% of the population African-American and states with > 11.3% of the population African-American), validation, and NHSN mandate. The cutoff of 11.3% for categorizing percentage of the population African-American was chosen because that was the national percentage of the population African-American in 2014. Validation indicates that the state health department reported the completion of all of the following validation activities for NHSN data during 2014: state health department had access to NHSN data, state health departments performed an assessment of missing or implausible values on at least six months of the year's data prior to the freeze date of July 1st, 2015, and state health department contacted identified facilities. NHSN mandate indicates that a legislative or regulatory requirement for acute care hospitals to report data for the given HAI type to the state health department or hospital association via NHSN was in effect at the beginning of 2014.

Multivariate logistic regression with events/trials and forward selection method was utilized to fit models for each outcome. Events was defined as the number of isolates resistant while trials was defined as the number of isolates tested. Events/trials was used in order to balance the sizable differences in the number of isolate tested between U.S. states. An alpha level of 0.05 was used to determine inclusion in the model. In order to observe the correlation between each predictor and outcome, percentage of hospitals with all 7 CDC Core Elements and outpatient prescribing rates for

penicillins, fluoroquinolones, cephalosporins, and macrolides were forced into each model regardless of statistical significance. Likelihood ratio tests were used to determine presence of interaction. Because prevalences for all three outcomes were normally distributed, Pearson's partial correlation coefficients (R^2) and p-values were calculated to determine direction and strength of correlations between predictors and outcomes adjusted for confounding. Additionally, a Wilcoxon ranked sum test was performed to examine difference in distribution of MDR *P. aeruginosa*, ESC-R *E. coli*, and MRSA prevalence between states with and without NHSN mandate and validation standards. All statistical analyses were performed using SAS v 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

Demographics

Demographic characteristics of the U.S. in 2014 are reported in Table 1. All 50 U.S. states and District of Columbia were included in the analysis. Puerto Rico was removed from the analysis because it was an outlier for all three antibiotic-resistant phenotypes. Hawaii, North Dakota, South Dakota, Vermont, and Wyoming had fewer than 10 *S. aureus* isolates tested and thus were dropped from MRSA analysis. North Dakota and Wyoming had fewer than 10 *E. coli* isolates tested and thus were dropped from ESC-R *E. coli* analysis. Alaska, Maine, Montana, New Hampshire, North Dakota, South Dakota, Utah, Vermont, and Wyoming had fewer than 10 *P. aeruginosa* isolates tested and thus were dropped from MDR *P. aeruginosa* analysis.

Approximately 45% of *S. aureus* isolates were resistant to methicillin, 12.7% of *E. coli* isolates were resistant to extended-spectrum cephalosporins, and 12.8% of *P. aeruginosa* isolates were resistant to multiple drugs. In 2014, the overall U.S. outpatient antibiotic prescription rate was 860.3 per 1000 population and 36.2% of hospitals incorporated all 7 CDC Core Elements into their antibiotic stewardship programs. Approximately 14.8% of the population was older than 65 years of age and 11.3% of the population was African-American. Nearly 71% of states incorporated data validation standards and nearly 65% of states had an NHSN reporting mandate.

MDR P. aeruginosa

Pearson's partial correlation coefficients for each predictor on MDR *P. aeruginosa* prevalence are reported in Table 2. There was a slight positive correlation between outpatient fluoroquinolone prescribing rate and MDR *P. aeruginosa* prevalence that was borderline significant (Figure 1; $p = 0.09$). There were no other statistically significant or impressive correlations between the predictors or confounders and MDR *P. aeruginosa* prevalence.

Wilcoxon ranked-sum test results for MDR *P. aeruginosa* prevalence are reported in Table 3. States without NHSN mandate standards had similar prevalence of MDR *P. aeruginosa* to states with NHSN mandate standards (23.5% vs. 17.6%; $p = 0.26$); states without validation standards also had similar prevalence of MDR *P. aeruginosa* to states with validation standards (21.7% vs. 18.7%; $p = 0.41$).

ESC-R E. coli

Pearson's partial correlation coefficients for each predictor on ESC-R *E. coli* prevalence are reported in Table 2. Outpatient fluoroquinolone and cephalosporin prescribing rates were positively and significantly correlated with ESC-R *E. coli* prevalence, respectively (Figure 1; $p < 0.01$; $p < 0.001$). There were no other statistically significant or impressive correlations between the predictors or confounders and ESC-R *E. coli* prevalence.

Wilcoxon ranked-sum test results for ESC-R *E. coli* prevalence are reported in Table 3. States without NHSN mandate standards had similar prevalence of ESC-R *E. coli* to states with NHSN mandate standards (26.9% vs. 19.5%; $p = 0.06$); states without validation standards also had similar prevalence of ESC-R *E. coli* to states with validation standards (23.9% vs. 27.5%; $p = 0.26$).

MRSA

Pearson's partial correlation coefficients for each predictor on MRSA prevalence are reported in Table 2. Outpatient fluoroquinolone prescribing rate was positively and significantly correlated with MRSA prevalence for states with both a low and high population of African-Americans; this correlation was slightly elevated in states with a high population of African-Americans ($p < 0.05$). There were no other statistically significant or impressive correlations between the predictors or confounders and MRSA prevalence.

Wilcoxon ranked-sum test results for MRSA prevalence are reported in Table 3. States without NHSN mandate standards had similar prevalence of MRSA to states with NHSN mandate standards (23.1% vs. 27.8%; $p = 0.23$); states without validation standards also

had similar prevalence of MRSA to states with validation standards (21.3% vs. 31.5%; p = 0.07).

Final Models and Parameters

Results from forward selection, including final parameter estimates and p-values for each outcome, are shown in Tables 4-6. Confounders for MDR *P. aeruginosa* prevalence were the percentage of the population older than 65 years of age, the number of LTACFs, and validation. Confounders for ESC-R *E. coli* prevalence were the percentage of the population older than 65 years of age, the percentage of the population African-American, and the total population size. Confounders for MRSA prevalence were the percentage of the population African-American, the number of SNF bed-days, validation, and NHSN mandate. Due to statistical significance, an interaction term between outpatient fluoroquinolone prescription rate and percentage of the population African-American was included in the model for MRSA prevalence.

DISCUSSION

This ecological analysis found that intensity of antibiotic stewardship within a state, as measured by the NHSN survey, did not explain the geographic variability in MDR *P. aeruginosa*, ESC-R *E. coli*, or MRSA prevalence. Conversely, outpatient fluoroquinolone and cephalosporin prescribing rates explained some of the geographic variability in ESC-R *E. coli* prevalence. Outpatient fluoroquinolone prescribing rate also explained some of the geographic variability in MRSA prevalence; this variability was slightly elevated in states with a higher population of African-Americans. There was no significant difference in MDR *P. aeruginosa*, ESC-R *E. coli*, or MRSA prevalence

between U.S. states with and without NHSN validation standards. There was also no significant difference in MDR *P. aeruginosa*, ESC-R *E. coli*, and MRSA prevalence between U.S. states with and without the NHSN mandate.

There may be several reasons why intensity of antibiotic stewardship was not a major predictor of resistance prevalence. One prominent reason may include the poor accuracy in the assessment of effective stewardship programs as measured by the NHSN survey tool. A systematic review by Akpan et al. concluded that studies that utilized rates of inpatient antibiotic usage as a proxy for antibiotic stewardship compared to survey data observed significant reductions in antibiotic resistant prevalence after implementation of the antibiotic stewardship program (42). Representing antibiotic stewardship as a proportion of hospitals with all 7 CDC Core Elements may not be a sensitive measure to detect differences in stewardship efforts and thus a significant relationship between antibiotic stewardship and resistance prevalence was not observed. Another reason for this observation could be that the NHSN survey only captured hospitals that incorporated all 7 of CDC's Core Elements, whereas hospitals that incorporate 5 or 6 of CDC's Core Elements may contribute to reducing antibiotic-resistant phenotype prevalence but are not being included in a state's overall percentage of antibiotic stewardship. Additional reasons for this observation may include the lack of any time-series component of this assessment preventing any temporal relationship between timing of stewardship implementation and changes in prevalence of the target antibiotic-resistant phenotypes, or lack of any infection control assessment.

One major finding of the ecologic assessment is the relationship between outpatient antibiotic prescribing and prevalence of the antibiotic-resistant phenotypes

among HAIs reported to NHSN. This was somewhat surprising. Some significant associations were anticipated, notably that outpatient extended-spectrum cephalosporin use was anticipated to influence community-based UTIs resistance patterns, with potential to spill over that effect to HAIs identified early in patients' hospital stay (16). However, the association was profound; one of the most significant independent predictors for ESC-R *E. coli*, outpatient cephalosporin prescribing rate, had no significant interactions. The additional observation that outpatient fluoroquinolone prescribing was associated with higher resistance percentages for ESC-R *E. coli* suggests that perhaps the outpatient prescribing frequency may be indicative of other general behaviors that influence resistant *E. coli* among HAIs, such as promotion or alteration of the gastrointestinal tract flora among outpatients. In addition, outpatient prescription data may be reflecting recently discharged patients, or serving as a proxy measure for how antibiotics are prescribed among inpatients.

Another interesting finding of the ecologic assessment was the difference in MRSA prevalence predicted by outpatient fluoroquinolone prescribing between states with high and low populations of African-Americans. There are a couple of reasons for this observation. A study conducted by Milstone et al. found that African-American children have higher rates of MRSA colonization, which could lead to a higher prevalence of MRSA as adults (43). Risk for MRSA infection would then be further elevated among African-Americans taking fluoroquinolones since fluoroquinolones alone are already a prominent risk factor for MRSA infection (22). Another reason for this observation could be that African-Americans are more likely to develop illnesses

requiring the use of antibiotics, such as tuberculosis, septicemia, and bacterial meningitis (44).

States with validation standards did not differ in prevalence of the target antibiotic-resistant phenotypes to states without validation standards. This observation is likely seen because data validation from state health departments would likely include review of both the numerator and the denominator of the antibiotic resistance prevalence metric. Thus, it makes sense that stronger data validation efforts would not lead to significantly different antibiotic resistance percentages compared to states without a validation program (40). Similarly, states with the NHSN mandate did not differ in prevalence of the target antibiotic-resistant phenotypes to states without the NHSN mandate. Because the infections analyzed in this report are all included in the Centers for Medicare and Medicaid (CMS) federal quality reporting programs, almost all hospitals in all states are reporting these data to NHSN. The presence or absence of an additional reporting mandate from the state did not lead to statistically significant differences in the proportion of isolates with a resistant phenotype.

There are several strengths to this ecological study. To our knowledge, this study was the first to examine state differences in the context of antibiotic use and resistance prevalence. The study also utilized a newly compiled national dataset that was released by NHSN in 2016. Furthermore, the data were comprehensive, with approximately 4000 hospitals contributing to the dataset, and each state provided robust data. The study also controlled for differences in state legislation and reporting by using validation and NHSN mandate as proxies for intensity of surveillance across states. Finally, the analysis is representative of almost all hospitals in the county since almost all healthcare facilities

are reporting CLABSIs, CAUTIs, and select SSIs into NHSN due to the CMS quality reporting programs.

Nonetheless, this study was not without its limitations, particularly surrounding the dataset used for analysis. First, the study captured only a subset of HAI events, as the dataset only contained 25% of the 721,800 HAIs that are expected to occur each year in the U.S.; therefore the results may not be representative of other infection types not captured by this analysis (40). There is also the possibility of misclassification of resistant isolates within the dataset. NHSN requires reporting of the final interpretation of the isolate (either susceptible or resistant), and interpretation of an isolate may vary across laboratories. Another significant limitation is that the antibiotic prescribing dataset was restricted to outpatient healthcare settings, while the infections, resistance, and stewardship datasets were all limited to inpatient healthcare facilities. The data for this study were also lacking in measures of infection control programs within each state, so the impact of infection control on resistance prevalence could not be observed.

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TABLES

Table 1. Demographic Characteristics of the United States, 2014.

Variable (number of states)[a]	
OUTCOMES	**No. (%)**
S. aureus isolates resistant to methicillin (n=46)	5,322 (45%)
E. coli isolates resistant to extended-spectrum cephalosporins (n=49)	2,333 (12.7%)
P. aeruginosa isolates resistant to multiple drugs (n=42)	1,066 (12.8%)
PREDICTORS (n=51)	
Hospitals with all 7 CDC Core Elements	1,642 (36.1%)
Outpatient antibiotic prescription rate per 1000 population	Mean (SD)
Fluoroquinolones	103.8 (29.3)
Macrolides	157.5 (36.1)
Cephalosporins	117.5 (35.8)
Penicllins	192.3 (36.2)
COVARIATES (n=51)	
No. of acute care facilities per state (Mean (SD))	71.5 (69.1)
No. of long-term acute care facilities per state (Mean (SD))	8.3 (11.4)
No. of skilled nursing facilities per state (Mean (SD))	238.8 (236.0)
No. of skilled nursing facility bed-days per state (Mean (SD))	8,893,906 (9,453,406)
Total U.S. population (Median (IQR))	4,413,457 (5,427,066)
Number of people ≥ 65 years	46,243,211 (14.8%)
Number of people African-American	40,380,578 (11.3%)
Number of states performing data validation	36 (70.6%)
Number of states with an NHSN mandate	33 (64.7%)

[a]All 50 states + DC had data on all the predictors; however, some states had fewer than 10 isolates tested and thus were dropped from specific analysis

Table 2. Pearson's Partial Correlation Coefficients (R^2) for Intensity of Antibiotic Stewardship and Outpatient Prescription Rates on Prevalence of MRSA, ESC-R *E.coli*, and MDR *P. aeruginosa*

	Pearson's Partial Correlation Coefficient (R^2)		
Predictor	**MRSA[a]**	**ESC-R *E.coli*[b]**	**MDR *P. aeruginosa*[c]**
Antibiotic Stewardship	0.1134	-0.057	0.0803
Fluoroquinolones	-	0.4417**	0.2876
High African-American	0.3499*	-	-
Low African-American	0.3333*	-	-
Cephalosporins	0.1268	0.566***	-0.089
Penicillins	-0.182	0.1813	0.1705
Macrolides	0.0381	-0.07	-0.153

[a] Adjusted for number of SNF bed-days, percent of the population African-American, validation, and mandate

[b] Adjusted for percent of the population African-American, total population, and percent of the population ≥ 65 years of age

[c] Adjusted for percent of the population ≥ 65 years of age, number of LTACFs, and validation

* $p < 0.05$

** $p < 0.01$

*** $p < 0.001$

Table 3. Comparison on Antibiotic Resistance Prevalence between States with NHSN Reporting Mandates or Validation to those without for each Antibiotic Resistance Phenotype using Wilcoxon Ranked Sum Test

		Median (Range) of % Resistance		
Variable	**Response**	**MRSA**	**ESC-R *E.coli***	**MDR *P. aeruginosa***
Mandate	Yes	27.8 (4.9 - 47.1)	19.5 (1.7 - 45.1)	17.6 (3.4 - 40.8)
	No	23.1 (1.6 - 44.9)	26.9 (5.1 - 49.5)	23.5 (1.1 - 41.9)
	p-value	0.2338	0.0637	0.2612
Validation	Yes	31.5 (7.8 - 49.6)	27.5 (3.1 - 45.1)	18.7 (1.5 - 41.8)
	No	21.3 (1.8 - 46.5)	23.9 (1.7 - 49.5)	21.7 (1.6 - 40.0)
	p-value	0.0652	0.2557	0.4173

Table 4. Final Model Parameter Estimates and Adjusted Odds Ratios (OR) for MDR *P. aeruginosa*

Variable	Parameter Estimate	p-value	Adjusted OR (95% CI)
% hospitals with all 7 CDC Core Elements	0.00339	0.4415	1.003 (0.995, 1.012)
Outpatient penicillin prescribing rate	0.00297	0.2396	1.003 (0.998, 1.008)
Outpatient cephalosporin prescribing rate	-0.00263	0.2955	0.997 (0.992, 1.002)
Outpatient fluoroquinolone prescribing rate	0.016	< 0.0001	1.016 (1.008, 1.024)
Outpatient macrolide prescribing rate	-0.00462	0.2053	0.995 (0.998, 1.003)
Percentage ≥ 65 years	-0.1029	< 0.0001	0.902 (0.864, 0.942)
Number of long-term acute care facilities	0.00514	0.0088	1.005 (1.001, 1.009)
Validation	-0.3417	< 0.0001	0.711 (0.604, 0.835)

Table 5. Final Model Parameter Estimates and Adjusted Odds Ratios (OR) for ESC-R *E. coli*

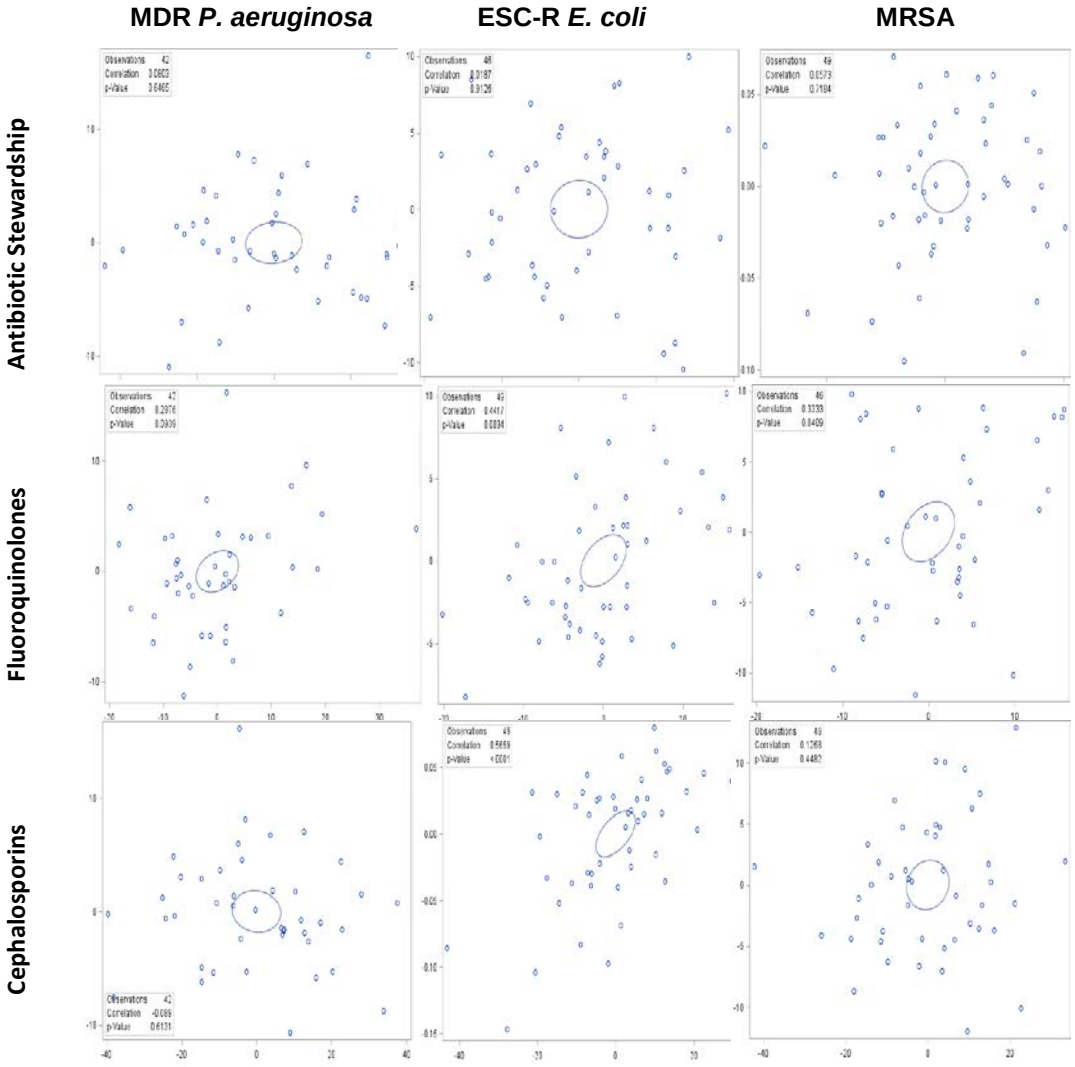
Variable	Parameter Estimate	p-value	Adjusted OR (95% CI)
% hospitals with all 7 CDC Core Elements	0.00396	0.2106	1.004 (0.998, 1.010)
Outpatient penicillin prescribing rate	-0.00229	0.1979	0.998 (0.994, 1.001)
Outpatient cephalosporin prescribing rate	0.0162	< 0.0001	1.016 (1.012, 1.021)
Outpatient fluoroquinolone prescribing rate	0.0202	< 0.0001	1.020 (1.012, 1.029)
Outpatient macrolide prescribing rate	0.00271	0.3025	1.003 (0.998, 1.008)
Percentage ≥ 65 years	0.0794	< 0.0001	1.083 (1.042, 1.125)
Percentage African-American	0.0282	< 0.0001	1.029 (1.018, 1.039)
Total population	7.08E-09	0.0204	1.000 (1.000, 1.000)

Table 6. Final Model Parameter Estimates and Adjusted Odds Ratios (OR) for MRSA

Variable	Parameter Estimate	p-value	Adjusted OR (95% CI)
% hospitals with all 7 CDC Core Elements	0.00761	0.0029	1.008 (1.003, 1.013)
Outpatient penicillin prescribing rate	-0.00472	0.0009	0.995 (0.993, 0.998)
Outpatient cephalosporin prescribing rate	0.00323	0.0498	1.004 (1.001, 1.007)
Outpatient fluoroquinolone prescribing rate	0.00837	0.0036	1.008 (1.003, 1.014)
Outpatient macrolide prescribing rate	0.0017	0.4571	1.002 (0.997, 1.006)
Percentage African-American	0.0122	0.0005	1.012 (1.005, 1.019)
Skilled nursing facility bed-days	5.90E-09	0.0019	1.000 (1.000, 1.000)
Validation	-0.1635	0.0072	0.849 (0.754, 0.957)
NHSN mandate	-0.1881	0.0016	0.829 (0.737, 0.931)
Fluoroquinolone*African-American	0.00165	0.0006	1.002 (1.001, 1.003)

FIGURES

Figure 1. Scatterplots of Pearson's Partial Correlation Coefficients for Intensity of Antibiotic Stewardship, Outpatient Fluoroquinolone Prescribing Rate, and Outpatient Cephalosporin Prescribing Rate on MDR *P. aeruginosa*, ESC-R *E.coli*, and MRSA Prevalence



CHAPTER III: PUBLIC HEALTH IMPLICATIONS

This ecological assessment emphasized the strength of the relationship between outpatient antibiotic prescribing and inpatient prevalence of antibiotic-resistant phenotypes. Hence, public health policy should pursue interventions or changes that combat unnecessary outpatient antibiotic prescribing in addition to antibiotic stewardship programs. However, development of new or improvement of existing antibiotic stewardship measuring tools is essential to determining an accurate measurement of the relationship between antibiotic stewardship and inpatient prevalence of antibiotic-resistant phenotypes. Future research on prevalence of antibiotic-resistant phenotypes should focus on racial differences in antibiotic use or the temporal relationship between timing of antibiotic stewardship implementation and antibiotic-resistant prevalence.