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Concise Communication

Factors affecting the geographic variability of antibiotic-resistant healthcare-associated infections in the United States using the CDC Antibiotic Resistance Patient Safety Atlas

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Abstract

We utilized publicly available data from the Centers for Disease Control to explore possible causes of state-to-state variability in antibiotic-resistant healthcare-associated infections. Outpatient antibiotic prescribing rates of fluoroquinolones and cephalosporins explained some variability in extended-spectrum cephalosporin-resistant *Escherichia coli* after adjusting for differences in age and healthcare facility composition.

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The Centers for Disease Control (CDC) estimates that ~2 million people develop antibiotic-resistant infections per year in the United States.[1] A major contributor to antibiotic resistance includes excessive use of antibiotics in both inpatient and outpatient settings.[1,2] The proportion of healthcare-associated infections (HAIs) caused by antibiotic-resistant pathogens can be viewed geospatially on a relatively new database hosted by CDC.[3] We explored possible causes of state-to-state variability in prevalence of multidrug-resistant (MDR) *Pseudomonas aeruginosa*, extended-spectrum cephalosporin resistant (ESC-R) *Escherichia coli*, and methicillin-resistant *Staphylococcus aureus* (MRSA) HAIs. We included population characteristics considering historical associations with resistance, such as race and age.[4]

Methods

The primary source of data used in this study was the CDC Antibiotic Resistance Patient Safety Atlas,[3] which contains state-level datasets on outpatient antibiotic prescriptions per 1,000 population stratified by age group and agent classification, prevalence of antibiotic stewardship programs in acute-care hospitals, and summary data on pathogens associated with HAIs tested and testing resistant to select antibiotics reported to the National Healthcare Safety Network (NHSN). State-level summary data on aspects of state HAI programs are also available in the database. The Centers for Medical and Medicare Services (CMS) Hospital Compare, Long-Term Hospital Compare, and Nursing Home Compare datasets were utilized for state-level characteristics on acute-care facilities (ACFs), long-term acute-care facilities (LTACFs), and skilled nursing facilities (SNFs).[5–7] State population estimates were obtained from the US Census Bureau. Only data from 2011–2014 were included in the analysis.

Primary outcomes included state-level prevalence, defined as the total number of *E. coli*, *S. aureus*, or *P. aeruginosa* reported as resistant aggregated across all hospitals in the state divided by the total number of each pathogen reported. MDR *P. aeruginosa* was defined as *P. aeruginosa* testing intermediate or resistant to at least 1 drug in 3 of the following classes: extended-spectrum cephalosporin, fluoroquinolone, aminoglycoside, carbapenem, or piperacillins/tazobactam. ESC-R *E. coli* was defined as *E. coli* testing resistant to ceftriaxone, ceftazidime, cefepime, or cefotaxime. MRSA was defined as *S. aureus* testing resistant to methicillin, oxacillin, or cefoxitin.[8] States that had <10 isolates tested for each pathogen were excluded.

Predictors of resistance included inpatient antibiotic stewardship (measured as the percentage of hospitals in the state incorporating all 7 CDC Core Elements into their program) and state-level outpatient antibiotic prescription rates by antibiotic class (referred to as "outpatient prescribing"). Potential confounders included number and types of healthcare facilities, population characteristics (eg, population >65 years or African-American population greater than the national percentage), having a state-specific requirement to report HAI data to the NHSN or a state-program to validate NHSN data. Validation programs indicate that the state health department had access to NHSN data, performed an assessment of missing or implausible values on at least 6 months of the year's data, and contacted identified facilities.

A Wilcoxon ranked-sum test was used to examine differences in distribution of HAI antibiotic resistance prevalence between states with and without NHSN mandate and validation standards. Multivariable logistic regression with events/trials and forward selection method was utilized to fit models for each outcome and to identify confounders to retain for further evaluation. Events were the number of isolates resistant and trials were the number of isolates tested; this method accounts for the sizeable

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Table 1. Demographic Characteristics of Key State-Level Antibiotic Resistance Indicators, 2011–2014

Characteristics (n = 51)[a]	Median	IQR
Staphylococcus aureus isolates resistant to methicillin (n = 46)	82.0	34.0–121.5
MRSA, %	45.6	37.9–53.6
Escherichia coli isolates resistant to extended-spectrum cephalosporins (n = 49)	28.0	9.0–50.0
ESC-resistant, %	12.5	8.6–16.1
Pseudomonas aeruginosa isolates resistant to multiple antibiotics (n = 42)	12.0	7.3–28.0
MDR %	13.6	8.4–16.1
Hospitals with all 7 CDC Core Elements per state, no.	22.0	10.0–37.0
Hospitals with all 7 CDC Core Elements, %	36.0	28.0–48.5
Outpatient antibiotic prescription rate per 1,000 population		
Fluoroquinolones	106.0	78.0–117.0
Macrolides	159.0	132.0–177.0
Cephalosporins	110.0	89.5–136.5
Penicillins	193.0	166.0–215.5
Acute-care facilities per state, no.	53.0	24.0–92.0
Long-term acute-care facilities per state, no.	5.0	2.0–9.5
Skilled nursing facilities per state, no.	181.5	64.8–341.5
Skilled nursing facility bed days per state, no.	6,001,600	1,948,384–12,713,369
Total population per state	4,413,457	1,742,395–6,903,465

Note. MRSA, methicillin-resistant *S. aureus*; CDC, Centers for Disease Control and Prevention; MDR, multidrug resistant; IQR, interquartile range.
[a]All 50 states plus the District of Columbia had data on all the predictors; however, some states had <10 isolates tested and thus were dropped from specific analysis.

differences in the number of isolates tested between US states. A Wald test was used to determine inclusion in the model. Significant confounders were then included to evaluate the Pearson partial correlation coefficients and *P* values of the main predictors (ie, stewardship and outpatient prescribing), this method was chosen to better reflect the state-level summary metrics as ecologic data. All statistical analyses were performed using SAS version 9.4 software (SAS Institute, Cary, NC).

Results

Across all states, 5,322 MDR isolates were MRSA (45% of *S. aureus* tested), 2,333 were ESC-R *E. coli* (12.7% of tested), and 1,066 were MDR *P. aeruginosa* (12.8% of tested) (Table 1). There was no statistical difference in the median resistance rates between states based on presence of NHSN mandates or validation programs (data not shown). Potential confounders of isolates found to be resistant were identified (for each resistant phenotype) as follows: proportion of the state's population being >65 years (MDR *P. aeruginosa*, ESC-R *E. coli*), large African-American population (ESC-R *E. coli* and MRSA), having a state-validation program (MDR *P. aeruginosa*, MRSA), number of LTACFs (MDR *P. aeruginosa*) or number of SNF bed-days (MRSA), and the state's

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

Predictor	MRSA[a]	*P* Value	ESC-R *E. coli*[b]	*P* Value	MDR *P. aeruginosa*[c]	*P* Value
Antibiotic stewardship	0.11	.50	−0.06	.72	0.08	.65
Fluoroquinolones	. . .	. . .	0.44	.003	0.29	.09
Large African-American population	0.35	.03	. . .	. . .	. . .	. . .
Small African-American population	0.33	.04	. . .	. . .	. . .	. . .
Cephalosporins	0.13	.45	0.57	<.0001	−0.09	.61
Penicillins	−0.18	.43	0.18	.42	0.17	.41
Macrolides	0.04	.72	−0.07	.71	−0.15	.46

Note. MRSA, methicillin-resistant *Staphylococcus aureus*; ESC-R *E. coli*, extended-spectrum cephalosporin resistant *Escherichia coli*; MDR, multidrug resistant.
[a]Adjusted for number of SNF bed days, % of the population that was African American, validation, and mandate.
[b]Adjusted for % of the population that was African American, total population, and percent of the population ≥65 years of age.
[c]Adjusted for % of the population ≥65 years of age, number of long-term acute-care facilities, and validation.

population (ESC-R *E.coli*). Due to statistical significance, an interaction term between outpatient fluoroquinolone prescribing and largeAfrican-American population was included in the model for MRSA prevalence.

Adjusting for the observed confounding, the partial Pearson correlation coefficients of the associations between resistance and either inpatient stewardship or outpatient prescribing were calculated (Table 2). Outpatient fluoroquinolone and cephalosporin prescribing were positively and significantly correlated with ESC-R *E. coli* prevalence. For MRSA, only outpatient fluoroquinolone prescribing was positively and significantly correlated prevalence; however, the magnitude of the correlation was slightly elevated in states with a large population of African Americans. Correlation between outpatient prescribing and inpatient MDR *P. aeruginosa* prevalence was only of appreciable magnitude but not significant (P = 0.09).

Discussion

Intensity of antibiotic stewardship did not explain geographic variability in inpatient MDR *P. aeruginosa*, ESC-R *E. coli*, or MRSA prevalence. Conversely, outpatient fluoroquinolone and cephalosporin prescribing explained some geographic variability in ESC-R *E. coli* prevalence. Outpatient fluoroquinolone prescribing also explained some geographic variability in MRSA prevalence that was slightly elevated in states with a larger population of African Americans. These observations suggest that outpatient prescribing frequency may have a direct impact on the resistance phenotypes of hospital-onset infection pathogens[8] or have indirect effects such as promotion or alteration of the gastrointestinal tract flora among outpatients. Other explanations may include outpatient prescription data reflecting recently discharged patients or serving as a proxy measure for how antibiotics are prescribed among inpatients.

We did not observe any association between stewardship intensity among inpatient setting and inpatient HAI resistance

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metrics. One prominent reason is that the NHSN survey data available only reported frequency of hospitals that incorporated all 7 of the CDC Core Elements, whereas hospitals that incorporate fewer CDC Core Elements may contribute to reducing antibiotic-resistant phenotype prevalence but are not included in the percentage of antibiotic stewardship programs in place. Additionally, even those with all 7 components may vary in effectiveness, and no validation of inpatient stewardship data is available. Additional reasons for this observation may include lack of any time-series component preventing any temporal relationship between timing of stewardship implementation and prevalence of the target antibiotic-resistant phenotypes or lack of infection control assessment. Notably, the resistance data were limited to only 3 types of NHSN-defined HAIs; therefore, they do not reflect the majority of HAIs nor community or nursing-home–onset infections. Regardless, these data do suggest that stewardship in the outpatient setting could have an impact on inpatient resistance phenotypes and should be studied in more detail. In conclusion, we observed interesting associations with some biologic plausibility using publicly available data summarized at the state-level from both CMS[5–7] and CDC.[3] More granular data would allow for more conclusive analysis in the future should it become publicly available.

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