Regional Escherichia coli antibiotic resistance among outpatients in Washington state from 2013-2019

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Abstract

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Escherichia coli is a predominant pathogen of urinary tract infections (UTIs) in the United States. Understanding regional patterns of uropathogenic *E. coli* antimicrobial resistance (AMR) may help further antibiotic stewardship by creating region-specific antibiograms. We analyzed regional patterns of uropathogenic *E. coli* AMR among outpatients in Washington state.

Deidentified results from antibiotic susceptibility tests performed by Quest Diagnostics on Washington state outpatient isolates from 2013 through 2019 were analyzed. Only the first *E. coli* isolate from each patient was included in the analyses. We conducted logistic regressions with robust standard errors for five antibiotics, with isolates classified as “susceptible” or “non-susceptible” for each antibiotic and adjusted for sex, year of isolate collection, and age group (0-18, 19-50, >50). The state’s nine Public Health Emergency Preparedness Regions (PHEPRs), served as the exposures for the analysis.

We included 40,217 isolates in the study (93% female, mean age 47 years). Compared to the Central PHEPR (containing Seattle), most other regions had significantly lower adjusted

prevalence ratios (aPR) of AMR; no regions had significantly higher aPR of resistance for any of the five antibiotics. Differences in resistance between the Central and other regions varied by antibiotic. Regional AMR differences were largest for ceftriaxone (low aPRs in other regions compared to Central) and smallest for ampicillin.

The regional variation of AMR calls for more specific outpatient antibiograms to enable healthcare providers to take a precision medicine approach to antibiotic prescribing and stewardship. Importantly, this will improve health outcomes and mitigate emerging resistance among outpatients with uropathogenic *E. coli* UTIs.

Introduction

The global threat of antimicrobial resistance (AMR) is growing in scale and severity. The World Health Organization estimates that 10 million people globally will die each year due to antibiotic resistance by 2050.[1] Bacteria are considered resistant to an antibiotic when the minimum inhibitory concentration (MIC) threshold set by organizations such as the Clinical and Laboratory Standards Institute (CLSI) is met, meaning it takes more concentrated antibiotics (or a switch to a different antibiotic) to treat an infection by either inhibiting bacterial growth or causing bacterial cell death.[2]

Escherichia coli is a common uropathogenic bacteria and is currently the leading cause of urinary tract infections (UTIs) in the United States. *E. coli* is also one of the most common bacterial infections in the United States, totaling an estimated $5 billion in direct and indirect costs annually.[3] Recurrent UTIs occur in 20-30% of females within months of the first infection.[3,4] The frequency of infection within the population, with up to 50% of females experiencing a UTI in their lifetimes, and recurrent nature allows for high potential that the pathogen develops AMR and highlights the importance of monitoring and preventing AMR in common infections.[5] Better understanding of the resistance patterns of *E. coli*, including risk factors for resistance, will allow for more timely and effective treatment.

AMR genes can be passed along vertically and horizontally through the transfer of genes between bacteria or through random advantageous mutations in their genome.[6] There is a spatial component to the reproduction and transference of AMR genes wherein proximity is necessary to transfer resistance promoting genes, and the environmental conditions necessary to make the AMR genes beneficial and drive population dynamics exist locally.[7,8] Antibiotic prescribing and use patterns may vary by geography due to variation in access to care and community standards of care, emphasizing that history of antibiotic use could be regionally distinct and is a critical risk factor for the acquisition of antibiotic resistant bacteria.[9,10] Furthermore, anthropogenic factors in the environment, such as contamination of water and soil from antibiotic application to orchards and use of antibiotics in commercial animal farm operations, can influence the evolution of bacterial AMR genome in the environment and risk to humans in the area,[7,11–16] On top of anthropogenic factors, abiotic factors such as the composition of soils are associated with different AMR persistence in environments,[17–19] demonstrating the importance of geography and the environment in understanding the distribution of AMR.

While many studies have discovered spatial and temporal associations between antibiotic resistance in the environment and in inpatient settings, addressing human AMR through a spatial lens in an outpatient setting is less researched.[20–22] Applying the known differences in AMR due to a multitude of factors comes down to appropriately creating and using antibiograms. Antibiograms are a tool used by prescribers to help prescribe more effective antibiotics for their patients using aggregate summaries of resistance patterns in a specific setting, such as a hospital or geographic area. While these tools exist, studies have found a gap in the utilization of antibiograms by prescribers[23,24]. There have been successes in implementing computer programs to help prescribers access and use antibiograms effectively which changed prescribing habits.[25,26] Educating prescribers, making antibiograms more accessible, and creating more accurate antibiograms could help tailor the practice of antibiotic stewardship by prescribers. Should there be significant spatial patterns of resistance, local antibiograms could be created to provide the most regionally accurate information to prescribers.

The ever evolving situation surrounding AMR calls for additional resource allocation and more specific and timely guidance for healthcare providers to improve health outcomes and mitigate further resistance to antibiotics of clinical importance. While educating providers about current AMR trends can reduce the morbidity of AMR, larger systemic changes, such as reevaluating the antibiotic use of multiple industries, will be necessary to mitigate further resistance.

Methods

Study design: The study was a retrospective cross-sectional analysis of antibiotic resistance data across the state of Washington from 2012-2019 for outpatient urinary *E. coli* isolates using clinical data from Quest Diagnostics, a major clinical laboratory provider for the Washington state.

Study subjects: *E. coli* isolates from Quest patients throughout the state of Washington were included in the analysis if they were obtained from a urine sample from the years 2013-2019. The first isolate from each individual in the dataset was used in the analysis and any subsequent tests for that individual were excluded, as recommended by the CLSI for the creation of antibiograms[27]. The Quest dataset included 56,022 E. coli isolates confirmed through a urine sample, of which 15,157 isolates were excluded due to not being the first E. coli isolate for the patient and another 648 isolates were not included due to missing data for age, sex, or county of residence. The final dataset used for the analyses contained 40,217 unique patient isolates.

Data collection: Antibiotic susceptibility tests were performed at Quest laboratories in Seattle, WA to determine the susceptibility of the isolates. VITEK* 2 (Biomérieux, North Carolina, USA) methods delivered results for the genus and species for identification of the pathogen and additionally the MIC values for each antibiotic tested. MIC value and "Susceptible", "Intermediate" and "Resistant" interpretations were based on breakpoints established by the CLSI Subcommittee on Antibiotic Susceptibility Testing.[2] Antibiotic resistance values were binarized to be either "susceptible" if categorized as susceptible or "nonsusceptible", meaning resistant, if categorized as resistant or intermediate.[2] Through a research collaboration between Quest Diagnostics (Secaucus, New Jersey, USA) and the University of Washington, a deidentified dataset was supplied for analysis. Additional metadata included date tested, type of sample, age, and sex. This study assessed the results of susceptibility testing for five antibiotics, each representing a different class of antibiotics: ceftriaxone (cephalosporins), gentamicin (aminoglycosides), ampicillin (penicillins), ciprofloxacin (quinolones), trimethoprim-sulfa (sulfonamides).

Exposure classification: Public Health Emergency Preparedness Regions (PHEPRs) were created by the Washington State Department of Health to coordinate regional resources during times of public health need.[28] A local health jurisdiction in the region coordinates regional emergency response and leads the development of preparedness plans for the region. There are nine regions in Washington.

Regression analysis: Logistic regression, performed in R[29], was used with the PHEPRs for the state as the predictors and binomial resistance as the outcome. Robust standard errors and 95% confidence intervals with prevalence odds ratio (PR) estimates for the fully adjusted regressions are presented. Sex (male and female binary), categorical age groups (0-18, 19-50, >50), year of specimen collection (factor) were included in the model as covariates as indicated *a priori*. The Central PHEPR was selected as the reference group because it had the largest number of isolates in the analysis and it contains Seattle, the largest metropolitan area in the state.

Ethical approval: This study was approved by the Human Subjects Review Committee of the University of Washington (STUDY00008443).

Results

There were 40,217 *E. coli* isolates from unique individuals used in the analyses (Table 1). The Central PHEPR, the reference group, had the most isolates and the top three regions (Central, North, and Pierce) with the most data collectively represented more than 50% of the isolates (Figure 1). There were three regions that jointly had less than 10% of the isolates: North Central, Northwest, and South Central. A great majority of the isolates were from females (93.6%) and persons over 18 years of age (19-50: 44.8%; >50: 44.3%).

The overall resistance rates for each antibiotic varied greatly, ranging from 3.2% for ceftriaxone (CRO) to 37.0% for ampicillin (Table 2). There were significant differences in resistance between the Central PHEPR and other regions for all antibiotics, controlling for year of isolate collection, sex, and age group. *E. coli* antibiotic resistance was significantly lower in nearly all PHEPRs compared to the Central region. aPRs for antibiotic resistance for ampicillin, ciprofloxacin and trimethoprim-sulfa were consistently 10-35% less in all the non-Central regions, and all regions were significantly different than the Central region. Compared to the Central region, aPRs varied the most for ceftriaxone (aPR ranged from 0.20 to 0.78) and the least for ampicillin (aPR ranged from 0.78 to 0.89). Only two regions did not have significantly different aPRs for all antibiotics: the South Central (not significant for ceftriaxone and gentamicin) and North Central (not significant for gentamicin). We observed that ampicillin had the most similar estimates, on average, to the Central region with the lowest aPR for the North Central region (aPR: 0.78; 95% CI: 0.64-0.95). The South Central region aPRs was most similar to the Central region across all antibiotics; and the South Central and Northwest regions have some of most extreme aPRs, with greater differences in AMR compared the Central region, across all the antibiotics.

Discussion

This study utilized urinary isolates positive for *E. coli* from outpatients, primarily female, in Washington state from 2013-2019. The five oral drugs selected for the analysis represent five different classes of antibiotics; resistance ranged from 3.2% for ceftriaxone to 37.0% for AMP. Compared to the Central PHEPR (containing Seattle), most other regions had significantly lower prevalence of AMR; no regions had significantly higher aPR of resistance for any of the five antibiotics. Differences in resistance between the Central and other regions varied by antibiotic with regional differences largest for ceftriaxone (low aPRs compared to the Central PHEPR) and smallest for AMP.

With over 40,000 isolates analyzed, this is one of the largest studies in the literature with outpatient isolates when exploring AMR in community acquired UTIs. The magnitude of the differences in resistance suggests that implementation of community specific antibiograms could alter prescribing recommendations. While prescribing recommendations are more or less uniform,[30,31] there should be additional emphasis to use as regionally specific an antibiogram as available when making decisions for outpatient treatment.

A study utilizing data from the Global Burden of Diseases, Injuries, and Risk Factors Study found regional differences in the rates of morbidity and mortality caused by antimicrobial resistance to drugs[32]. Specific to *E. coli*, countries were found to have differing levels of AMR in the early 2000s[33]. Similarly, there have been studies internationally that describe regional differences in AMR for pathogens within a country[34–37] and one discussing observed geographic AMR differences between the United States and Canada.[38] The findings of this study are therefore consistent with previous studies. Furthermore, this study supports that those regional differences exist on even smaller scales than previously examined and reiterates the suggestion that regional differences in AMR should be considered when planning programs and interventions to reduce AMR or increase patient treatment outcomes.

While few studies have been able to delve into exploring reasons for regional AMR differences, an ecologic study from France found positive associations between extended spectrum beta-lactamase producing *E. coli*, a common resistance mechanism, and several covariates including percentage of people over 65 years, number of hospital beds, third-generation cephalosporin use, percentage of agriculture land, and poultry and pig density.[39] Some of these group level associations could explain some of the differences in resistance across the state as we see that the most urban region, the Central region, in the state has the highest resistance. There was a significantly higher prevalence of multidrug resistance to outpatient *E. coli* and *Klebsiella* species in the urban compared to the rural regions in Uganda[34] and similar findings that resistance was higher closer to a major city in Nepal[40]. Contrarily, a study in Germany found that the rural and urban differences were primarily inconsequential[41], so it is inconclusive if and how urbanicity and rurality contributed to our findings. Additional mechanisms behind these differences could be different prescribing and usage of antibiotics, population differences in susceptibility to infection, wastewater persistence of AMR genes and antibiotics[42], and agricultural uses of antibiotics for crops and livestock[41,43] . These and other possible causes for variation should be further explored.

Antibiograms have been used extensively, particularly in the hospital setting in the fight against AMR as they allow physicians to prescribe the most appropriate antibiotic in a timely manner, before the 48-72 hour window when patient specific susceptibility results come back.[44] While the utility of this tool is known, creating antibiograms requires specialized microbiologic knowledge so not all hospitals are able to do this in-house and have their own antibiograms. This tool is utilized frequently for in-patient care, yet the construction of outpatient antibiograms can be difficult but important as inpatient and outpatient antibiograms are known to be significantly different.[45,46] While institutional antibiograms are useful, clinics and hospitals do not all have their own antibiograms, which is where understanding regional antibiograms for outpatients may be helpful so that region specific antibiograms may be able to fill those gaps.

The Washington State Department of Health publishes some hospital inpatient antibiograms from around the state that can be consulted by anyone, yet these are not able to be generalized to other hospitals, regions, or outpatients infections.[45,46] Properly prescribing antibiotics not only helps with patient outcomes, but it prevents development of further resistance.[44]

These findings provide important insights in geographic variation in AMR. The large differences in AMR across Washington state suggest that prescribing patterns should be regionally specific and therefore regionally specific antibiograms could be beneficial preventing further AMR and improving patient outcomes. Analysis of multisite outpatient urinary *E. coli* culture results provided further understanding of outpatient community specific AMR patterns, as demonstrated at a large scale throughout the state, but there are potentially more meaningful differences in smaller geographic communities than the trends seen across the PHEPRs. While the geographic differences are the primary emphasis of the study, differences in adjusted resistance were observed by age group, year of isolate collection, and sex of patient which should all be taken into consideration for antibiogram development.

The analysis was limited to grouping patients by PHEPR because of insufficient isolate sample size at a finer geographic level such as county. The commercial laboratory does not have service points uniformly throughout the state, which resulted in counties with no data or minimal data which led to lower powered analyses. The limited number of isolates from males does not allow the regional analysis to be performed in a stratified manner as might have been more appropriate to account for potential AMR differences between the sexes.[47] There should be exploration of further covariates in regions that could be predicting differences in AMR such as rurality, antibiotic usage on nearby farms, antibiotics sprayed in orchards, hospital bed density or other regionally specific data that could further lead to understanding regional differences in resistance better.[4]

By using only the first isolate per unique individual, recurrent infections in the data source were minimized. Although we used only the first isolate, it is likely that some people with previous *E. coli* infections that were not tested through Quest Diagnostics or occurred before the study window were still included in the analysis, resulting in some recurrent infections being included. Only using the first specimen collected during 2013-2019 will likely bias the results to appear as if there is less AMR because recent treatment with an antibiotic is associated with increased AMR, so these results may underestimate community AMR and specifically AMR for populations with recurrent infections[11–15,48].

Additionally, there may be differences in people who accessed care through an outpatient center that utilize a commercial laboratory and those who have access to a medical facility that has laboratory capacity in-house, which would result in potential selection bias. This study used only samples from outpatient tests, but this doesn't eliminate the possibility that people could have been recently discharged from the hospital and been included in the dataset. Using outpatient samples only, this study cannot be generalized to the inpatient population and their antibiograms.

While there were limitations in this analysis, this study included a substantial number of outpatient isolates from the entirety of Washington state as serviced by Quest Diagnostics and allowed for comparisons of regions within politically meaningful boundaries. The findings suggest that we should be tailoring antibiograms to be more regionally specific to best support treatment of patients and to reduce the emergence of AMR in clinically important outpatient antibiotics. In the future, more studies should investigate geographic differences in AMR to see at what level (i.e. county, region of state, neighborhood, etc.) is the most meaningful when creating community specific antibiograms and delve into the different drivers behind resistance so that distal drivers of emergence can be identified and used prevent further AMR.

Tables and Figures:

Figure 1: Map of Washington state divided up by Public Health Emergency Preparedness Region

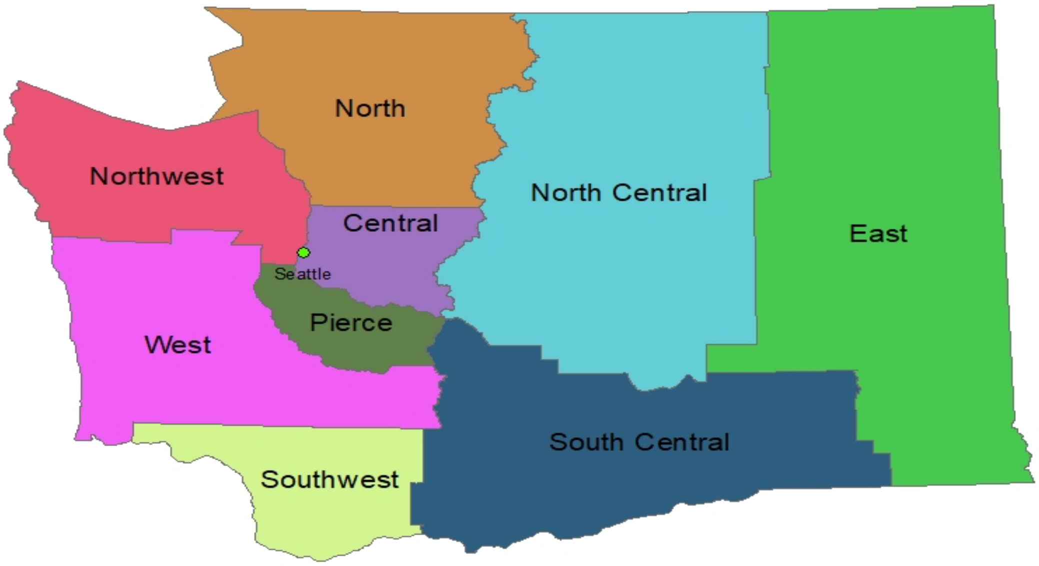

Figure 1: The map of Washington State is divided up from into the Public Health Emergency Preparedness Regions. Seattle is denoted by a green dot in the Central region.

Table 1: Demographics of outpatient E. coli patients and their isolates from Washington state in 2013-2019

	N=40,217	n (%)
Region (PHEPR)*		
Central	8097	20.1
East	2783	6.9
North	7451	18.5
North Central	474	1.2
Northwest	1300	3.2
Pierce	5962	14.8
South Central	1189	3.0
Southwest	7857	19.5
West	5104	12.7
Year of collection		
2013	4271	10.6
2014	3499	8.7
2015	4086	10.2
2016	4313	10.7
2017	7656	19.0
2018	7563	18.8
2019	8829	22.0

Sex		
Male	2589	6.4
Female	37628	93.6
Age Group (years)		
0-18	3781	9.3
19-50	18326	44.8
>50	18110	44.3

Table 1: Regions are the nine Public Health Emergency Preparedness Regions of Washington state. No covariates were missing more than 5% of the data. This table describes the characteristics of the patients and isolates included in the analyses.

Table 2. Adjusted PR for outpatient *E. coli* antibiotic resistance to five antibiotics from Washington state residents from 2013-2019

			Ampicillin (AMP) (n=40,042)	Ciprofloxacin (CIP) (n=40,214)	Ceftriaxone (CRO) (n=40,017)	Gentamicin (GEN) (n=40,217)	Trimethoprim / sulfamethoxazole (SXT) (n=40,170)
Overall resistance			0.37	0.10	0.032	0.050	0.18
	n	(%)	adjusted PR (95% CI)	adjusted PR (95% CI)	adjusted PR (95% CI)	adjusted PR (95% CI)	adjusted PR (95% CI)
Region (PHEPR*)							
Central	8097	20.1	*Ref.*	*Ref.*	*Ref.*	*Ref.*	*Ref.*
East	2783	6.9	0.89 (0.81-0.98)	0.73 (0.62-0.85)	0.46 (0.35-0.60)	0.71 (0.57-0.88)	0.67 (0.59-0.75)
North	7451	18.5	0.82 (0.76-0.88)	0.81 (0.72-0.90)	0.61 (0.51-0.72)	0.83 (0.72-0.97)	0.76 (0.70-0.83)
North Central	474	1.2	0.78 (0.64-0.95)	0.64 (0.46-0.90)	0.20 (0.06-0.63)	0.86 (0.56-1.31)	0.76 (0.59-0.97)
Northwest	1300	3.2	0.79 (0.70-0.90)	0.70 (0.57-0.86)	0.42 (0.26-0.65)	0.70 (0.53-0.93)	0.57 (0.48-0.67)
Pierce	5962	14.8	0.84 (0.78-0.90)	0.78 (0.70-0.87)	0.65 (0.53-0.78)	0.69 (0.59-0.81)	0.70 (0.64-0.76)
South Central	1189	3.0	0.88 (0.77-1.00⊥)	0.80 (0.65-0.99)	0.78 (0.57-1.08)	0.98 (0.75-1.28)	0.84 (0.72-0.99)
Southwest	7857	19.5	0.79 (0.74-0.84)	0.67 (0.60-0.75)	0.57 (0.48-0.68)	0.66 (0.57-0.77)	0.66 (0.61-0.72)
West	5104	12.7	0.84 (0.78-0.91)	0.73 (0.65-0.82)	0.61 (0.49-0.75)	0.75 (0.64-0.89)	0.70 (0.64-0.76)

Table 2: Regions are the nine Public Health Emergency Preparedness Regions of Washington state. Adjusted PRs are adjusted for year of isolate collection, sex of patient, and age group of patient. ⊥ This confidence interval does not include 1.00 but due to rounding 1.00 is the upper limit for the table

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