Antimicrobial Resistance Trends in Urine Escherichia coli Isolates From Adult and Adolescent Females in the United States From 2011–2019: Rising ESBL Strains and Impact on Patient Management

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Summary: This study provides contemporary data on the prevalence and trends of antimicrobial resistance among *E. coli* isolated from female outpatient urine cultures in the US, 2011 to 2019. The prevalence of antimicrobial resistance is high and increasing for key phenotypes.
Abstract

Background

Uncomplicated urinary tract infection (uUTI) is predominantly caused by *Escherichia coli*, which has increasing antimicrobial resistance (AMR) at the US-community level. As uUTI is often treated empirically, assessing AMR is challenging and there are limited contemporary data characterizing period prevalence in the US.

Methods

This was a retrospective study of AMR using Becton, Dickinson and Company Insights Research Database (Franklin Lakes, NJ) data collected 2011–2019. Thirty-day, non-duplicate *Escherichia coli* urine isolates from US female outpatients (aged ≥12 years) were included. Isolates were evaluated for not-susceptibility (intermediate/resistant) to trimethoprim-sulfamethoxazole, fluoroquinolones, or nitrofurantoin, and assessed for extended-spectrum β-lactamase production (ESBL+) and for ≥2 or ≥3 drug-resistance phenotypes. Generalized estimating equations were used to model AMR trends over time and by US census region.

Results

Among 1,513,882 *Escherichia coli* isolates, the overall prevalence of isolates not-susceptible to trimethoprim-sulfamethoxazole, fluoroquinolones, and nitrofurantoin was 25.4%, 21.1%, and 3.8%, respectively. Among the isolates, 6.4% were ESBL+, 14.4% had ≥2 drug-resistance phenotypes, and 3.8% had ≥3. Modelling demonstrated a relative average yearly increase of 7.7% (95% confidence interval [CI], 7.2–8.2%) for ESBL+ isolates and 2.7% (95% CI, 2.2–3.2%) for ≥3 drug-phenotypes (both p<0.0001). Modelling also demonstrated significant variation in AMR prevalence between US census regions (p<0.001).
Conclusions

Period prevalence of AMR among US outpatient urine-isolated *Escherichia coli* was high, and for multi-drug-resistance phenotypes increased during the study period with significant variation between census regions. Knowledge of regional AMR rates helps inform empiric treatment of community-onset uUTI and highlights the AMR burden to physicians.

**Keywords:** *Escherichia coli*; antimicrobial resistance; uncomplicated urinary tract infection; antimicrobial stewardship
Introduction

Urinary tract infections (UTIs) are among the most common community-onset bacterial infections [1] and are treated by a variety of healthcare professionals. Uncomplicated UTIs (uUTIs), those occurring in females in the absence of underlying abnormalities of the urinary tract or immunosuppression, affect 10–12% of adult women at least once per year in the US, with 20–30% of those having a subsequent recurrent infection [2, 3]. The incidence of uUTI is bimodal, with peaks in young, sexually active women aged 15–24 years [4, 5] and in post-menopausal women [1]. The microbial etiology of uUTI is well characterized, with *Escherichia coli* (*E. coli*) being the predominant uropathogen isolated in community-onset uUTI [6, 7].

There has been a notable increase in antimicrobial resistance (AMR) among *E. coli* from community-onset uUTIs in the last 2 decades. A 2012 *in vitro* study of *E. coli* urine isolates from US outpatients (2001–2010) found significant increases in AMR to ciprofloxacin and trimethoprim-sulfamethoxazole (TMP-SMX) [8]. Similarly, in a study of urine isolates from 18 European countries in 2018, resistance to TMP-SMX was found in 32.7% (range: 23.1–56.2% across countries) of *E. coli* isolates from clinical urine samples and the prevalence of fluoroquinolone (FQ) resistance was >20% [9].

The acquisition of AMR genes is especially important among Enterobacterales, as these are associated with the potential to confer cross- or co-resistance to multiple drug classes, causing multi-drug resistance (MDR) [10]. Production of extended-spectrum beta-lactamases (ESBLs) is one of the most clinically relevant MDR phenotypes [11]. The increasing prevalence of ESBL-producing (ESBL+) *E. coli*, which are often co-resistant to TMP-SMX and FQ [12], is of global concern and has implications for the empiric treatment of community-onset uUTI. The Centers for Disease Control and Prevention Threat Report (2019) classifies ESBL+ Enterobacterales as a serious health threat with $1.2 billion estimated attributable US healthcare costs in 2017 [11]. MDR phenotypes have historically been associated with nosocomial infections but have now emerged at the community level, limiting oral therapeutic options for uUTI [13, 14] and resulting in increased rates of treatment
failure, patient morbidity, and healthcare costs, as well as higher rates of hospitalization and increased use of broad-spectrum antibiotics [15, 16].

Treatment for uUTI is often empiric, with varying practices regarding initial oral antibiotic choice [7, 17-19]. The Infectious Diseases Society of America (IDSA) recommends either a 3-day course of TMP-SMX or a 5-day course of nitrofurantoin (NFT), or fosfomycin (single-dose) [7], while the European Association of Urology recommends fosfomycin (single dose), NFT (5-days) or pivmecillinam (3–5 days) for first-line therapy [17]. Urine cultures are generally not recommended for the first incident case of symptomatic uUTI, however they are recommended if no improvement is seen within 48 hours of treatment in the case of recurrent uUTI, or in post-menopausal women with intermittent uUTI symptoms [18]. Thus, evaluation of outpatient urine isolates often comprises a mixture of samples obtained at the time of initial presentation of uUTI and those obtained after failure of empiric therapy. The current IDSA guidelines for uUTI were published in 2011, and as such it would be informative to assess and characterize contemporary regional AMR burden among urinary isolates from outpatients.

This study investigated not-susceptibility among E. coli urine isolates collected from adolescent and adult female outpatients in the US between 2011 and 2019 to characterize trends and the geographic distribution among E. coli urine isolates over the study period.
Methods

Study Design

This was a retrospective, multicenter, cohort study among *E. coli* isolated from female urine cultures collected at US outpatient facilities included in the Becton, Dickinson and Company (BD) Insights Research Database (Franklin Lakes, NJ, USA; see Supplementary Text for additional information). The distribution of hospitals in the database is similar to that of the US as a whole [11], suggesting appropriate demographic coverage. Urine isolates collected from females ≥12 years of age who had a non-contaminant urine culture with reported identification of *E. coli* and a susceptibility result from the outpatient setting were included in this study. Isolates were collected between January 2011 and December 2019 (the study period). Eligible isolates were 30-day non-duplicate, defined as the first urine *E. coli* isolate per patient collected within 30 days [20]. Urine *E. coli* isolates from the same patient within 30 days were included if the *E. coli* isolate had different drug susceptibilities (>1 susceptibility interpretive criteria difference) and subsequent *E. coli* isolates were included if collected >30 days from the previous isolate. Data identified included: age; sex; isolated uropathogens; tested antibiotic agents; susceptibility testing methods; and institution type, size, and geographic location. Individual laboratories in each institution performed their own antimicrobial susceptibility testing using Clinical and Laboratory Standards Institute (CLSI)-approved methods and interpreted results using Food and Drug Administration (FDA)/CLSI breakpoints and interpretive criteria [21].

Prevalence and Distribution of AMR (Primary Analysis)

AMR among non-duplicate *E. coli* was defined as not-susceptible (resistant or intermediate susceptibility results) to FQ, NFT, or TMP-SMX and also included isolates that were ESBL+ (confirmed by commercial laboratory panels or not-susceptibility to ceftriaxone, cefotaxime, ceftazidime, or cefepime). AMR and not-susceptibility are used interchangeably in this manuscript. The ≥2 and ≥3 not-susceptible phenotype categories were defined as isolates with 2 or more and 3 or more drug-
resistance phenotypes (not-susceptible to FQ, NFT, TMP-SMX, or ESBL+) respectively. Geospatial heatmaps were developed using Data-Driven-Documents (D3.js), a JavaScript visualization library, to geographically depict the proportion of isolates with each drug-resistance phenotype of interest. The heatmaps included data at the county level to understand differences in regional resistance in the US (Figure 3). For a county that did not have any isolates tested, the susceptibility results of the nearest county either within or across state lines were populated. Counties with insufficient isolates tested (<1% and <30 isolates tested) or states with no isolate results are marked in grey.

Minimum Inhibitory Concentration Breakpoints (Secondary Analysis)

The primary analysis was based on susceptibility results reported by each institution; however, the CLSI minimum inhibitory concentration (MIC) interpretive breakpoints for several antibiotics changed during the study period (Supplementary Table 1). It was not clear when new breakpoints were adopted by laboratories for cefazolin, cefepime, ciprofloxacin, and levofloxacin and, therefore, a secondary analysis was performed based on changes in the MIC interpretive standards for E. coli to cefazolin (2014 and 2019), cefepime (2014), levofloxacin (2019), and ciprofloxacin (2019) over the study period [21-25]. The secondary analysis was conducted only among isolates with available MIC values for these antibiotics, to further understand how the breakpoint changes and variation in implementation of new breakpoints potentially affected the primary analysis results.

Trends in resistance were assessed using the most recent MIC breakpoints for E. coli isolates (susceptible/intermediate/resistant [SIR]) to: cefazolin (≤16/≥2/≥32), cefepime (≤2/4-8 [susceptible dose-dependent]/≥16), ciprofloxacin (≤0.25/0.5/≥1), and levofloxacin (≤0.5/1/≥2)[21]. Isolates were excluded from this analysis when the MIC breakpoint data were either not reported or when the current interpretive criteria could not be applied to the original MIC (e.g., original MIC lying outside of the specific SIR category using current breakpoints and therefore deemed non-evaluable). Isolates were further excluded if they came from healthcare institutions where >50% of the isolates were...
deemed non-evaluable, in order to avoid the potential for overestimation of not-susceptible prevalence.

Statistical Analyses

AMR prevalence among *E. coli* was examined using descriptive statistics to report prevalence (%) and modelling methods (generalized estimating equations [GEE]) to estimate prevalence with 95% confidence intervals (CI). GEE models also assessed AMR trends (average yearly change) over time and by US census region. GEE models were adjusted for geographic (urban versus rural) status, healthcare facility characteristics (bed size and teaching status), and for the number of facilities per year (Supplementary Table 2). In the secondary analysis, generalized linear modelling (GLM) was used to evaluate AMR rates across the study period and to compare AMR rates between the original and new interpretative criteria. Bonferroni corrections were used when comparing rates for multiple years. Trends in AMR for each antibiotic were evaluated by year, and the relative average annual percent change in resistance was estimated based on GLM. All analyses were conducted using the Statistical Analysis System (SAS) V9.4 (SAS Institute, Cary, NC, USA).

Results

Overall Prevalence of AMR Among *E. coli* Isolates in the US

Overall, 1,513,882 non-duplicate urine *E. coli* isolates were included in the primary analyses. These were collected from 106 to 295 outpatient facilities distributed across the US between 2011 and 2019 (Supplementary Table 2). The age distribution of isolates included in the primary analysis was as follows: 12–17 (3.2%), 18–54 (46.3%), 55–64 (12.3%), 65–74 (14.7%), and ≥75 (23.5%) years. The overall prevalence of *E. coli* isolates not-susceptible to TMP-SMX, FQ, and NFT was 25.39% (95% CI, 25.32–25.46), 21.10% (95% CI, 21.03–21.16), and 3.76% (95% CI, 3.73–3.79), respectively (Figure 1). ESBL+ was found in 6.36% (95% CI, 6.32–6.40) of the *E. coli* isolates, while 14.36% (95% CI, 14.30–
14.41) and 3.81% (95% CI, 3.78–3.84), respectively, were in the ≥2 and ≥3 not-susceptible phenotype categories (Figure 1).

There was variation in the prevalence of not-susceptible phenotypes across US census regions (Figure 2). The highest overall prevalence for most not-susceptible phenotypes (except ESBL+) was in the East South Central census region, where the prevalence of TMP-SMX, FQ and NFT not-susceptible *E. coli* was 30.2%, 27.0% and 4.6%, respectively. In this region, ESBL+ prevalence was 7.4% among *E. coli* isolates, with 18.7% and 5.1% of isolates, respectively, in the ≥2 and ≥3 not-susceptible phenotype categories. The lowest prevalence of not-susceptibility was consistently found in the New England region, where 17.9%, 13.8%, and 2.6% of *E. coli* isolates were TMP-SMX, FQ, and NFT not-susceptible, respectively; 4.6% were ESBL+, 8.7% were in the ≥2 not-susceptible phenotype category, and 2.3% were in the ≥3 not-susceptible phenotype category. The Pacific region had the highest ESBL+ rate, where 9.2% of isolates had this phenotype overall. Adjusted results were broadly similar to the unadjusted results (Table 1).

Figure 3 shows heatmaps of the distribution of the *E. coli* not-susceptible phenotypes at the US county level in 2019. These illustrate the high prevalence of not-susceptibility in the East South Central and Pacific regions, and also reveal concentrated areas of high not-susceptibility within other regions, notably in the south-western states and on the north-eastern coast.

*Trends in AMR Among E. coli Isolates in the US*

Trends in *E. coli* not-susceptible phenotypes between 2011 and 2019 are shown in Figure 4. Over the 9 years included, the ESBL+ rate increased every year (except 2018), beginning at 4.1% and increasing to 7.3%. TMP-SMX not-susceptible *E. coli* prevalence was consistently 25% or greater and ranged from 25.0% (2017) to 26.2% (2014). The prevalence of FQ not-susceptible *E. coli* decreased over the study period from 21.9% to 20.3%, however was consistently >20% (range: 20.2–21.9%). The prevalence of urine *E. coli* isolates in the ≥3 not-susceptible phenotype category increased from
3.1% (2011) to 4.0% (2019) over the study period, while the prevalence of *E. coli* isolates in the ≥2 not-susceptible phenotype category decreased by 1.0% and ranged from 13.7% (2018) to 15.3% (2014). Prevalence of isolates not-susceptible to NFT decreased over the study period from 4.0% in 2011 to 3.5% in 2019 (range: 5.3% [2014] to 3.0% [2017]).

GEE modelling results were broadly similar to this descriptive data. Modelling demonstrated a significant yearly relative increase of 7.7% (95% CI, 7.2–8.2%; p<0.0001) for the ESBL+ phenotype, and a significant yearly relative decreasing trend for FQ not-susceptible and ≥2 not-susceptible phenotype category (p<0.0001; Table 1). For the ≥3 not-susceptible phenotype category, modelling demonstrated a significant relative increase of 2.7% annually (95% CI, 2.2–3.2%; p<0.0001; Table 1). For NFT not-susceptibility, GEE modelling demonstrated a significant yearly relative decrease of 6.1% (95% CI, –6.5 to –5.6%; p<0.0001; Table 1). No significant trend for TMP-SMX not-susceptibility was shown by GEE modelling (Table 1).

**Secondary Analysis (MIC Breakpoints)**

The secondary analysis assessed the resistance prevalence using the most recent MIC breakpoint values for cefazolin, cefepime, levofloxacin, and ciprofloxacin. Overall isolate prevalence determined to be not-susceptible from 2011–2019 for cefazolin and cefepime was lower in the secondary versus the primary analysis. Cefazolin not-susceptible isolate prevalence was 11.9% in the primary analysis and 8.6% in the secondary analysis with the most recent MIC breakpoints applied. For cefepime, not-susceptible isolate prevalence was 4.4% in the primary analysis and 3.2% in the secondary analysis. However, for ciprofloxacin and levofloxacin, not-susceptible isolate prevalence was higher when MICs were interpreted using secondary analysis criteria (Supplementary Table 1). The prevalence of ciprofloxacin not-susceptibility increased from 20.3% to 25.4% and levofloxacin not-susceptibility increased from 22.0% to 30.7%. GLM results are shown in Supplementary Table 3.
Discussion

Between 2011 and 2019, FQ not-susceptible and TMP-SMX not-susceptible prevalence was strikingly high among urine *E. coli* isolates from adult and adolescent female outpatients in the US. For FQ not-susceptible and TMP-SMX not-susceptible isolates, prevalence was consistently above 20% and, further, more than 14% of isolates were in the ≥2 not-susceptible phenotype category.

The IDSA recommends that if AMR is >20% in a given region, the antibiotic should cease to be used for empiric treatment [7]. While the overall annual prevalence of the TMP-SMX not-susceptible phenotype remained >20% over the study, there was regional variation in prevalence by year and GEE modelling did not identify a significant change in TMP-SMX not-susceptible trends from 2011 to 2019. Despite a significant decreasing trend in FQ not-susceptible *E. coli*, this phenotype was recorded for ~21% of included isolates examined over the study period. The FDA has issued a “black box” warning for the safety of FQ due to observed collagen-associated (tendons, muscles, joints) and neurological adverse effects [26, 27]. However, this warning was issued in 2016 and has not led to a significant reduction in FQ prescribing to date [28].

Perhaps the most concerning finding was the prevalence of ESBL+ *E. coli* isolates, which was 6.4% for the overall study period, with a significant relative annual increase of 7.7% demonstrated in GEE modelling (95% CI, 7.2–8.2%). This agrees with previous literature reporting increasing ESBL+ rates in the US [29-31]. The increasing prevalence of ESBL+ Enterobacterales is a global concern given that it limits effective empiric oral therapeutic options. Greater ESBL+ prevalence also has potential implications for the route of antibiotic administration and the care setting in which therapy can be provided. AMR in patients with outpatient uUTI is likely to create a greater burden on emergency departments and acute care settings, impacting healthcare costs and surge capacity [32].

NFT was the only agent that saw a reduction in the prevalence of not-susceptible isolates over time. This may be due to changes in prescribing practices influenced by the American Geriatrics Society (AGS), which in 2015 highlighted the need to consider not using NFT in the presence of low
creatinine clearance among elderly patients [33]. Additionally, the CDC’s 2016 Outpatient Antimicrobial Stewardship Guidelines championed retrospective outpatient antimicrobial use metrics and education to facilitate more appropriate antimicrobial prescribing [34]. Older patients with uUTI could be presumed to have inherent renal insufficiency and this, coupled with the AGS recommendations, may have changed NFT prescribing patterns. Similarly, asymptomatic bacteriuria is more prevalent in older-age groups and initiatives to decrease unnecessary antimicrobial use in these groups may have shifted the aggregate use of NFT from 2016 onwards.

The geographic distribution of not-susceptible E. coli showed a high prevalence in the East South Central census region across the study period, with the lowest prevalence seen in the New England region albeit with a limited number of BD sites (Supplementary Table 2). Notably, ESBL+ prevalence was highest in the Pacific region (descriptive and model-estimated results). Additionally, there were areas of high not-susceptibility at the county level, notably in states bordering Mexico. The high prevalence of not-susceptible E. coli in US southern-border regions has long been recognized and is often attributed to the availability of over-the-counter antimicrobial treatments, compounded by under-trained staff, in pharmacies outside the US [35-37]. Furthermore, antibiotic prescribing rates have been shown to be high in the southern US, with several states prescribing at a rate of >850 per 1000 population [38]; these data serve to highlight the need to educate physicians on best prescribing practice.

This study represents (to the authors’ knowledge) the largest published sample of E. coli isolated from urine cultures among US outpatients and addresses a gap in the scientific literature, which currently lacks surveillance data for AMR in outpatient UTI. A further strength of the study was the secondary analysis addressing the change in certain MIC breakpoints over the study period. For most recent MIC breakpoints, overall lower rates of E. coli not-susceptible to cefazolin and cefepime and higher not-susceptible rates for ciprofloxacin and levofloxacin were observed. The secondary analysis excluded a large number of isolates that were not evaluable, although the directional rate of
change in not susceptibility within this evaluable cohort was similar to that of the overall cohort when including facilities where the majority of isolates were evaluable (>50%).

Study limitations include the fact that susceptibility testing and results are based on local laboratory practice. While all laboratories in the US follow CLSI and American Society for Microbiology guidelines, susceptibility results were based on local laboratory practices and reporting. The data used in this study could not be definitively linked to clinically confirmed cases of uUTI due to lack of confirmation of clinical symptoms, diagnoses (International Classification of Diseases-9/10 diagnosis codes), and pharmacy claims. However, it is important to note that there have been no changes in the recommendations for culturing practices during the study period and even with the inability to conclusively link the data to uUTI, these are the best available real-world data pertaining to AMR in outpatient UTI [6]. While the data set has ample coverage of the US and robust representation of the population, there were also under-represented areas in the US (Supplementary Table 2). Finally, the study methodology included only non-duplicate urine samples from outpatients without recent known hospitalization; however, the possibility of hospitalization in a non-affiliated healthcare center could not be ruled out. Additionally, more than one isolate from the same patient could have been included if collected >30 days from previous isolate, suggesting that the study population included patients with recurrent UTIs and potentially overestimated resistance.
Conclusions

Using a large dataset of urine *E. coli* isolates from females attending outpatient facilities in the US, this study demonstrated a high prevalence of not-susceptible *E. coli*, with significant variation in prevalence depending on geographic location within the US. Moreover, the prevalence of ESBL+ and *E. coli* isolates in the ≥3 not-susceptible phenotype category increased annually between 2011 and 2019. High rates of AMR and MDR *E. coli* limit the effective empiric options for the treatment of uUTI. Raising awareness of current regional patterns of not-susceptible *E. coli* isolates from outpatient UTIs can help to guide empiric treatment decisions of physicians and demonstrate the need for both antimicrobial stewardship efforts in outpatient settings, as well as new oral antibiotics to address the growing prevalence of resistant *E. coli* in the US.
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Potential conflicts of interest

K. S. K. reports no potential conflicts. V. G. is an employee and shareholder of Becton, Dickinson and Company, which received funding from GlaxoSmithKline plc. to conduct this study. A. M. is an employee and shareholder of GlaxoSmithKline plc. A. V. J. is an employee and shareholder of GlaxoSmithKline plc. N. E. S.-O. is an employee and shareholder of GlaxoSmithKline plc. K. Y. is an employee and shareholder of Becton, Dickinson and Company, which received funding from GlaxoSmithKline plc. to conduct this study. G. Y. is an employee of Becton, Dickinson and Company, which received funding from GlaxoSmithKline plc. to conduct this study. F. S. M.-G. is an employee and shareholder of GlaxoSmithKline plc.
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### Table 1. Model-estimated overall prevalence of AMR for each phenotype, AMR trend over year (2011–2019), and regional differences in not-susceptibility among outpatient urine *E. coli* isolates

| Phenotype category (N=1,513,882) | TMP-SMX NS | FQ NS (n=319,354) | NFT NS (n=56,954) | ESBL+ (n=96,306) | NS ≥2 drug classes (n=217,329) | NS ≥3 drug classes (n=57,637) |
|----------------------------------|------------|--------------------|--------------------|-------------------|-------------------------------|-------------------------------|
| **Overall (across years)**       |            |                    |                    |                   |                               |                               |
| estimate of AMR, % (95% CI)      | 26.0 (25.9 to 26.1) | 23.0 (22.9 to 23.2) | 4.0 (4.0 to 4.1)   | 6.8 (6.7 to 6.8)   | 15.7 (15.5 to 15.8)          | 4.2 (4.1 to 4.3)              |
| **Trend over year (2011 to 2019)**: average yearly change in NS, % (95% CI) | 0.0 (-0.2 to 0.1; p=0.6737) | -0.6 (-0.8 to -0.4; p<0.0001) | -6.1 (-6.5 to -5.6; p<0.0001) | 7.7 (7.2 to 8.2; p<0.0001) | -0.8 (-1.1 to -0.6; p<0.0001) | 2.7 (2.2 to 3.2; p<0.0001) |
| **Variation in AMR by US Census Region (2011–2019), % (95% CI)** |            |                    |                    |                   |                               |                               |
| East North Central (n=354,353)   | 22.3 (21.8 to 22.7) | 15.2 (14.8 to 15.7) | 3.4 (3.2 to 3.6)   | 4.1 (3.9 to 4.4)   | 10.7 (10.3 to 11.1)          | 2.8 (2.6 to 3.0)              |
| East South Central (n=173,127)  | 29.4 (28.9 to 30.1) | 22.8 (22.2 to 23.5) | 4.5 (4.2 to 4.7)   | 6.5 (6.1 to 6.9)   | 16.7 (16.1 to 17.3)          | 4.4 (4.1 to 4.7)              |
| Middle Atlantic (n=265,840)     | 21.9 (21.4 to 22.3) | 15.8 (15.3 to 16.3) | 1.7 (1.5 to 2.0)   | 4.7 (4.4 to 5.0)   | 11.3 (10.9 to 11.8)          | 3.1 (2.8 to 3.3)              |
| Mountain (n=58,407)             | 21.6 (21.0 to 22.2) | 14.8 (14.3 to 15.4) | 1.8 (1.5 to 2.1)   | 3.9 (3.6 to 4.2)   | 10.3 (9.8 to 10.8)           | 2.2 (2.0 to 2.4)              |
| New England (n=19,450)          | 17.1 (16.3 to 17.9) | 10.6 (10.0 to 11.2) | 2.5 (2.2 to 2.9)   | 3.0 (2.7 to 3.4)   | 7.0 (6.5 to 7.5)             | 1.6 (1.4 to 1.9)              |
| Pacific (n=173,228)             | 25.3 (24.7 to 25.9) | 16.5 (16.0 to 17.0) | 1.6 (1.4 to 1.9)   | 7.5 (7.0 to 8.0)   | 12.9 (12.4 to 13.4)          | 3.7 (3.4 to 4.0)              |
| South Atlantic (n=205,042)      | 26.2 (25.6 to 26.8) | 19.3 (18.7 to 19.9) | 4.4 (4.2 to 4.7)   | 5.1 (4.8 to 5.5)   | 13.9 (13.4 to 14.4)          | 3.5 (3.2 to 3.8)              |
| West North Central (n=18,448)   | 21.3 (20.4 to 22.2) | 11.7 (11.1 to 12.4) | 3.1 (2.7 to 3.5)   | 3.5 (3.2 to 3.9)   | 8.5 (7.9 to 9.1)             | 1.6 (1.4 to 1.8)              |
| West South Central (n=245,987)  | 29.1 (28.5 to 29.7) | 20.1 (19.5 to 20.7) | 3.7 (3.5 to 3.9)   | 5.8 (5.4 to 6.1)   | 14.7 (14.2 to 15.3)          | 3.5 (3.3 to 3.8)              |

Models were adjusted for hospital characteristics (bed size, urban/rural status, and teaching status); *Significant variation between regions and age groups was found, p<0.0001.

East North Central: IL, IN, MI, OH, WI; East South Central: AL, KY, MS, TN; Middle Atlantic: NJ, NY, PA; Mountain: AZ, CO, ID, MT, NM, NV, UT, WY; New England: CT, MA, ME, NH, RI, VT; Pacific: AK, CA, OR, WA; South Atlantic: DE, DC, FL, GA, MD, NC, SC, VA, WV; West North Central: IA, KS, MN, MO, ND, NE, SD; West South Central: AR, LA, OK, TX.

Abbreviations: AMR, antimicrobial resistance; CI, confidence interval; *E. coli*, *Escherichia coli*; ESBL+, extended-spectrum β-lactamase-producing; FQ, fluoroquinolone; NFT, nitrofurantoin; NS, not-susceptible; TMP-SMX, trimethoprim-sulfamethoxazole.
Figure legends

**Figure 1.** Overall AMR results in non-duplicate urine *E. coli* isolates (N=1,513,882) from US females, 2011–2019

Abbreviations: AMR, antimicrobial resistance; CI, confidence interval; *E. coli*, *Escherichia coli*; ESBL+, extended-spectrum β-lactamase-producing; FQ, fluoroquinolone; NFT, nitrofurantoin; NS, not-susceptible; TMP-SMX, trimethoprim-sulfamethoxazole.

**Figure 2.** Overall proportion of A: AMR and B: ≥2 and ≥3 not-susceptible phenotype category *E. coli* isolates by census region

New England: CT, MA, ME, NH, RI, VT; Middle Atlantic: NJ, NY, PA; East North Central: IL, IN, MI, OH, WI; West North Central: IA, KS, MN, MO, ND, NE, SD; South Atlantic: DE, DC, FL, GA, MD, NC, SC, VA, WV; East South Central: AL, KY, MS, TN; West South Central: AR, LA, OK, TX; Mountain: AZ, CO, ID, MT, NM, NV, UT, WY; Pacific: AK, CA, OR, WA.

Abbreviations: AMR, antimicrobial resistance; *E. coli*, *Escherichia coli*; ESBL+, extended-spectrum β-lactamase-producing; FQ, fluoroquinolone; NFT, nitrofurantoin; NS, not-susceptible; TMP-SMX, trimethoprim-sulfamethoxazole.

**Figure 3.** Regional distribution of *E. coli* AMR phenotypes in the US, 2019. A: ESBL+; B: FQ NS; C: TMP-SMX NS; D: NFT NS; E: ≥2 not-susceptible phenotypes; F: ≥3 not-susceptible phenotypes

For a county that did not have any isolates tested, the susceptibility results of the nearest county either within or across state lines were populated. Counties with insufficient isolates tested (<1% and <30 isolates tested) or states with no isolate results are marked in gray.

Abbreviations: AMR, antimicrobial resistance; *E. coli*, *Escherichia coli*; ESBL+, extended-spectrum β-lactamase-producing; FQ, fluoroquinolone; NFT, nitrofurantoin; NS, not-susceptible; TMP-SMX, trimethoprim-sulfamethoxazole.
**Figure 4.** Trends in AMR among *E. coli* isolates, 2011–2019

Abbreviations: AMR, antimicrobial resistance; *E. coli*, *Escherichia coli*; ESBL+, extended-spectrum β-lactamase-producing; FQ, fluoroquinolone; NFT, nitrofurantoin; NS, not-susceptible; TMP-SMX, trimethoprim-sulfamethoxazole.
Figure 1

Proportion of E. coli isolates (% [95% CI])

- **TMP-SMX NS** (n=384,304)
- **FQ NS** (n=319,354)
- **NFT NS** (n=56,954)
- ≥2 NS phenotypes (n=217,329)
- **ESBL+** (n=96,306)
- ≥3 NS phenotypes (n=57,673)
Figure 2
