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

Keith S. Kaye,[1] Vikas Gupta,[2] Aruni Mulgirigama,[3] Ashish V. Joshi,[4] Nicole E. Scangarella-Oman,[4] Kalvin Yu,[2] Gang Ye,[2] and Fanny S. Mitrani-Gold[4]

[1]University of Michigan, Ann Arbor, Michigan, USA; [2]Becton, Dickinson and Company (BD), Franklin Lakes, New Jersey, USA; [3]GlaxoSmithKline plc., London, United Kingdom; and [4]GlaxoSmithKline plc., Collegeville, Pennsylvania, USA

Background. Uncomplicated urinary tract infection (uUTI) is predominantly caused by *Escherichia coli*, which has increasing antimicrobial resistance (AMR) at the United States (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, New Jersey, US) data collected 2011–2019. Thirty-day, nonduplicate *Escherichia coli* urine isolates from US female outpatients (aged ≥12 years) were included. Isolates were evaluated for nonsusceptibility (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 *E. coli* isolates, the overall prevalence of isolates nonsusceptible 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. Modeling 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* < .0001). Modeling also demonstrated significant variation in AMR prevalence between US census regions (*P* < .001).

Conclusions. Period prevalence of AMR among US outpatient urine-isolated *E. coli* was high, and for multidrug-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.

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 United States (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 postmenopausal women [1]. The microbial etiology of uUTI is well characterized, with *Escherichia 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 multidrug 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], whereas 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 postmenopausal 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; as such, it would be informative to assess and characterize contemporary regional AMR burden among urinary isolates from outpatients.

This study investigated nonsusceptibility 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, New Jersey, USA; see Supplementary materials 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 noncontaminant 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 nonduplicate, 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 nonduplicate *E. coli* was defined as nonsusceptible (resistant or intermediate susceptibility results) to FQ, NFT, or TMP-SMX and also included isolates that were ESBL+ (confirmed by commercial laboratory panels or nonsusceptibility to ceftriaxone, cefotaxime, ceftazidime, or cefepime). The term "nonsusceptible" is used throughout per American Medical Association guidance, however, this aligns with the CLSI guidelines definition of not susceptible in this article; AMR and nonsusceptibility are also used interchangeably. The ≥2 and ≥3 nonsusceptible phenotype categories were defined as isolates with 2 or more and 3 or more drug-resistance phenotypes (nonsusceptible 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 gray.

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; therefore, a secondary analysis was performed based on changes in the MIC interpretive standards for *E. coli*
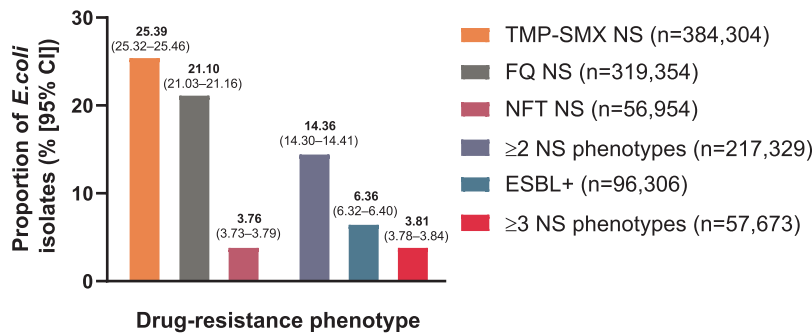
Figure 1. Overall AMR results in non-duplicate urine *E. coli* isolates (N = 1 513 882) from US females, 2011–2019. Abbreviations: AMR, antimicrobial resistance; CI, confidence interval; *E. coli, Escherichia coli*; ESBL+, extended-spectrum β-lactamase-producing; FQ, fluoroquinolone; NFT, nitrofurantoin; NS, nonsusceptible; TMP-SMX, trimethoprim-sulfamethoxazole.

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/–/≥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 (eg, 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 nonevaluable, in order to avoid the potential for overestimation of nonsusceptible 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 vs 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 modeling (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, North Carolina, USA).

RESULTS

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

Overall, 1 513 882 nonduplicate 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 nonsusceptible 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, whereas 14.36% (95% CI, 14.30–14.41) and 3.81% (95% CI, 3.78–3.84), respectively, were in the ≥2 and ≥3 nonsusceptible phenotype categories (Figure 1).

There was variation in the prevalence of nonsusceptible phenotypes across US census regions (Figure 2). The highest overall prevalence for most nonsusceptible phenotypes (except ESBL+) was in the East South Central census region, where the prevalence of TMP-SMX, FQ, and NFT nonsusceptible *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 nonsusceptible phenotype categories. The lowest prevalence of nonsusceptibility 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 nonsusceptible, respectively; 4.6% were ESBL+, 8.7% were in the ≥2 nonsusceptible phenotype category, and 2.3% were in the ≥3 nonsusceptible 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).
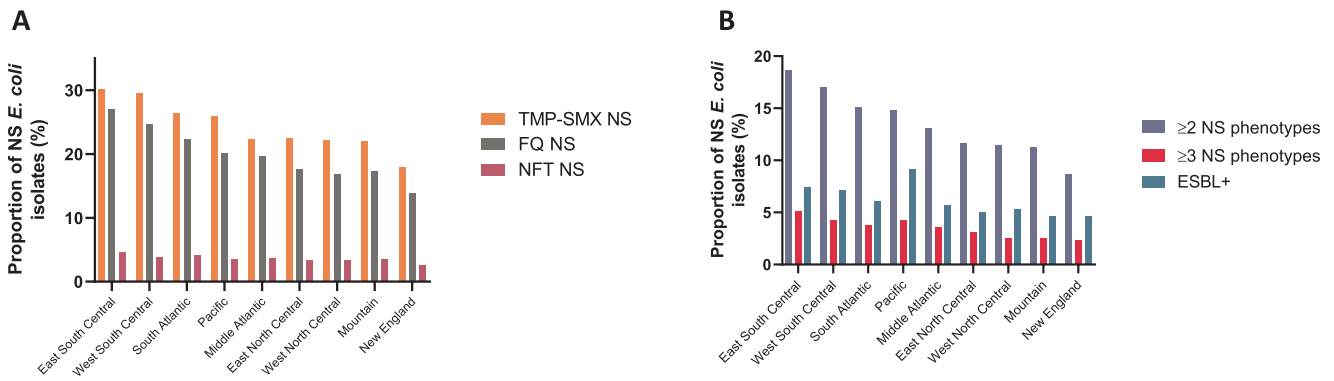
Figure 2. Overall proportion of (*A*) AMR and (*B*) ≥2 and ≥3 nonsusceptible phenotype category *E. coli* isolates by census region. New England: CT, MA, ME, NH, RI, VT; Middle Atlantic: NJ, NY, PA; East North Central: IL, IN, MI, OH, WI; West North Central: IA, KS, MN, MO, ND, NE, SD; South Atlantic: 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, nonsusceptible; TMP-SMX, trimethoprim-sulfamethoxazole.

Figure 3 shows heatmaps of the distribution of the *E. coli* nonsusceptible phenotypes at the US county level in 2019. These illustrate the high prevalence of nonsusceptibility in the East South Central and Pacific regions and also reveal concentrated areas of high nonsusceptibility within other regions, notably in the Southwestern states and on the Northeastern coast.

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

Trends in *E. coli* nonsusceptible 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 nonsusceptible *E. coli* prevalence was consistently 25% or greater and ranged from 25.0% (2017) to 26.2% (2014). The prevalence of FQ nonsusceptible *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 nonsusceptible 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 nonsusceptible phenotype category decreased by 1.0% and

Table 1. Model-Estimated Overall Prevalence of AMR for Each Phenotype, AMR Trend Over Year (2011–2019), and Regional Differences in Nonsusceptibility Among Outpatient Urine *E. coli* Isolates

	Phenotype Category (N = 1 513 882)					
	TMP-SMX NS (n = 384 304)	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 (2011–2019): 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* < .0001)	–6.1 (–6.5 to –5.6; *P* < .0001)	7.7 (7.2 to 8.2; *P* < .0001)	–0.8 (–1.1 to –0.6; *P* < .0001)	2.7 (2.2 to 3.2; *P* < .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)	3.7 (3.5 to 4.0)	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)	3.8 (3.5 to 4.1)	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)	3.6 (3.4 to 3.9)	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).

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, nonsusceptible; TMP-SMX, trimethoprim-sulfamethoxazole.

*Significant variation between regions and age groups was found, *P* < .0001.
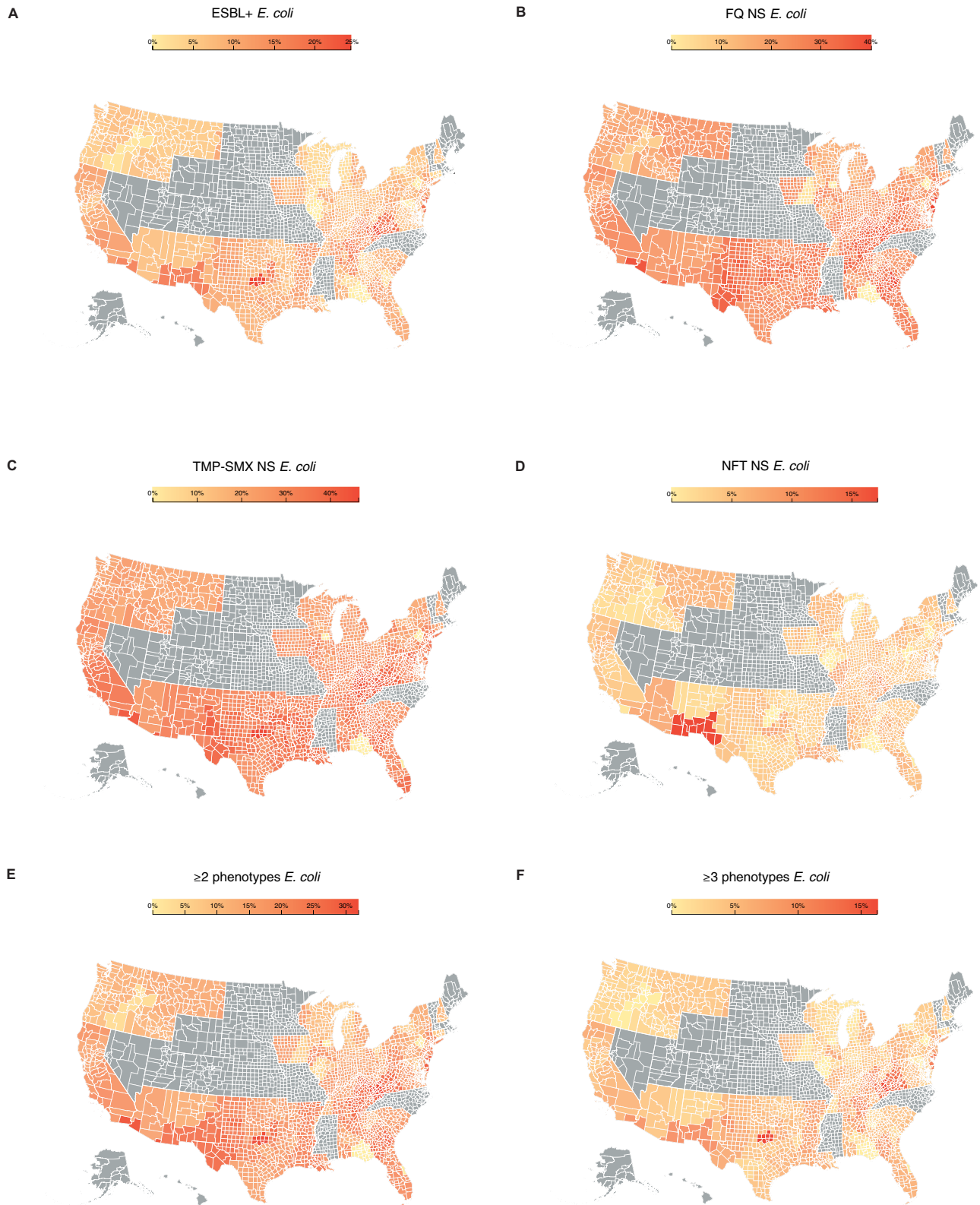
Figure 3. Regional distribution of *E. coli* AMR phenotypes in the US, 2019. (*A*) ESBL+; (*B*) FQ NS; (*C*) TMP-SMX NS; (*D*) NFT NS; (*E*) ≥2 nonsusceptible phenotypes; (*F*) ≥3 nonsusceptible phenotypes. For a county that did not have any isolates tested, the susceptibility results of the nearest 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, nonsusceptible; TMP-SMX, trimethoprim-sulfamethoxazole.
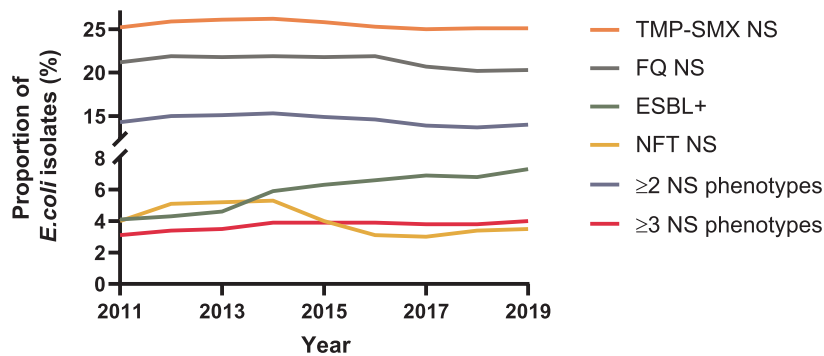
Figure 4. Trends in AMR among *E. coli* isolates, 2011–2019. Abbreviations: AMR, antimicrobial resistance; *E. coli, Escherichia coli;* ESBL+, extended-spectrum β-lactamase-producing; FQ, fluoroquinolone; NFT, nitrofurantoin; NS, nonsusceptible; TMP-SMX, trimethoprim-sulfamethoxazole.

ranged from 13.7% (2018) to 15.3% (2014). Prevalence of isolates nonsusceptible 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 modeling results were broadly similar to this descriptive data. Modeling demonstrated a significant yearly relative increase of 7.7% (95% CI, 7.2–8.2%; $P < .0001$) for the ESBL+ phenotype and a significant yearly relative decreasing trend for FQ nonsusceptible and ≥2 nonsusceptible phenotype category ($P < .0001$; Table 1). For the ≥3 nonsusceptible phenotype category, modelling demonstrated a significant relative increase of 2.7% annually (95% CI, 2.2–3.2%; $P < .0001$; Table 1). For NFT nonsusceptibility, GEE modeling demonstrated a significant yearly relative decrease of 6.1% (95% CI, −6.5% to −5.6%; $P < .0001$; Table 1). No significant trend for TMP-SMX nonsusceptibility was shown by GEE modeling (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 nonsusceptible from 2011 to 2019 for cefazolin and cefepime was lower in the secondary versus the primary analysis. Cefazolin nonsusceptible 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, nonsusceptible isolate prevalence was 4.4% in the primary analysis and 3.2% in the secondary analysis. However, for ciprofloxacin and levofloxacin, nonsusceptible isolate prevalence was higher when MICs were interpreted using secondary analysis criteria (Supplementary Table 1). The prevalence of ciprofloxacin nonsusceptibility increased from 20.3% to 25.4% and levofloxacin nonsusceptibility increased from 22.0% to 30.7%. GLM results are shown in Supplementary Table 3.

DISCUSSION

Between 2011 and 2019, FQ nonsusceptible and TMP-SMX nonsusceptible prevalence was strikingly high among urine *E. coli* isolates from adult and adolescent female outpatients in the US. For FQ nonsusceptible and TMP-SMX nonsusceptible isolates, prevalence was consistently above 20%; further, more than 14% of isolates were in the ≥2 nonsusceptible 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]. Although the overall annual prevalence of the TMP-SMX nonsusceptible phenotype remained >20% over the study, there was regional variation in prevalence by year, and GEE modeling did not identify a significant change in TMP-SMX nonsusceptible trends from 2011 to 2019. Despite a significant decreasing trend in FQ nonsusceptible *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 nonsusceptible 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 onward.

The geographic distribution of nonsusceptible *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 nonsusceptibility at the county level, notably in states bordering Mexico. The high prevalence of nonsusceptible *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* nonsusceptible to cefazolin and cefepime and higher nonsusceptible 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 nonsusceptible 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. Although 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]. Although 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 nonduplicate urine samples from outpatients without recent known hospitalization; however, the possibility of hospitalization in a nonaffiliated 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.

CONCLUSION

Using a large data set of urine *E. coli* isolates from females attending outpatient facilities in the US, this study demonstrated a high prevalence of nonsusceptible *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 nonsusceptible 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 nonsusceptible *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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