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Multidrug Resistance of *Escherichia coli* From Outpatient Uncomplicated Urinary Tract Infections in a Large United States Integrated Healthcare Organization

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Background. Urinary tract infections (UTIs) cause significant disease and economic burden. Uncomplicated UTIs (uUTIs) occur in otherwise healthy individuals without underlying structural abnormalities, with uropathogenic *Escherichia coli* (UPEC) accounting for 80% of cases. With recent transitions in healthcare toward virtual visits, data on multidrug resistance (MDR) (resistant to ≥3 antibiotic classes) by care setting are needed to inform empiric treatment decision making.

Methods. We evaluated UPEC resistance over time by care setting (in-person vs virtual), in adults who received outpatient care for uUTI at Kaiser Permanente Southern California between January 2016 and December 2021.

Results. We included 174 185 individuals who had ≥1 UPEC uUTI (233 974 isolates) (92% female, 46% Hispanic, mean age 52 years [standard deviation 20]). Overall, prevalence of UPEC MDR decreased during the study period (13% to 12%) both in virtual and in-person settings (*P* for trend <.001). Resistance to penicillins overall (29%), coresistance to penicillins and trimethoprim-sulfamethoxazole (TMP-SMX) (12%), and MDR involving the 2 plus ≥1 antibiotic class were common (10%). Resistance to 1, 2, 3, and 4 antibiotic classes was found in 19%, 18%, 8%, and 4% of isolates, respectively; 1% were resistant to ≥5 antibiotic classes, and 50% were resistant to none. Similar resistance patterns were observed over time and by care setting.

Conclusions. We observed a slight decrease in both class-specific antimicrobial resistance and MDR of UPEC overall, most commonly involving penicillins and TMP-SMX. Resistance patterns were consistent over time and similar in both in-person and virtual settings. Virtual healthcare may expand access to UTI care.

Keywords. multidrug antibiotic resistance; urinary tract infection; uropathogenic *Escherichia coli*.

Urinary tract infections (UTIs) are the most common outpatient infections in the United States, causing 10.5 million outpatient visits in 2007 [1]. Uncomplicated UTIs (uUTI) occur in individuals without underlying structural abnormalities. In the United States, 1 in 3 women experience ≥1 UTI requiring antibiotic treatment in their lifetime, and 11% experience ≥1 uUTI per year [2, 3]. Antibiotic treatment for uUTI is often empiric without urine culture or susceptibility testing [4, 5]. Urine cultures are not generally required, but they are recommended for atypical symptoms, symptoms persisting >48 hours after treatment, pregnant women, or symptomatic postmenopausal women [6]. The empiric choice of antibiotic is usually based on national guidelines and local resistance profiles until antimicrobial susceptibilities are available [5]. The Infectious Disease Society of America (IDSA) recommends trimethoprim-sulfamethoxazole (TMP-SMX), or nitrofurantoin, or alternatively, fosfomycin as first-line therapy for uncomplicated cystitis [4]. The guidelines also recommend ciprofloxacin, fluoroquinolone, or TMP-SMX for acute pyelonephritis not requiring hospitalization, and intravenous antimicrobial regimen (fluoroquinolone, aminoglycoside, or carbapenem) for acute pyelonephritis requiring hospitalization [4].

Uropathogenic *Escherichia coli* (UPEC) cause 80% of all uUTIs [7]. In recent years, an increase of multidrug-resistant (resistance to ≥3 antibiotic classes) UPEC strains has complicated UTI treatment [8]. Outpatient data from the US Surveillance Network data showed significant increases in

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UPEC resistance to ciprofloxacin (3% to 17%) and TMP-SMX (0.8% to 1.6%) from 2000 to 2010 [9]. Nitrofurantoin retains a high level of antibiotic activity against UPEC with resistance approximately 0.9% between 2003 and 2012 in the United States [10]. Moreover, among multidrug-resistant phenotypes, treatment options are more limited because extended-spectrum beta-lactamase (ESBL)-bearing strains are prone to harboring other resistance genes [11]. In a recent US study, 72% of ESBL-*E coli* isolates were multidrug resistant, and ESBL-*E coli* prevalence in bacteriuria episodes increased from 17% to 24% between 2014 and 2020 [12]. Most ESBL-positive *Enterobacterales* are coresistant to common antibiotics, such as fluoroquinolones, TMP-SMX, and beta-lactams [11], rendering them unsuitable for empiric uUTI treatment. Therefore, up-to-date data on trends in UPEC resistance are critical to inform local empiric treatment decisions [13].

Virtual care in the US healthcare system has increased substantially in the last decade, especially during the coronavirus disease 2019 (COVID-19) pandemic [14, 15]. A US study reported an average annual increase in telemedicine by 52% from 2005 to 2014, by 261% from 2015 to 2017 [15], and by 86% during the COVID-19 stay-at-home order [14]. Another US study reported a 21% increase in UTI incidence for virtual visits, but a 3% decline for office visits among women between 2008 to 2017 [16]. Factors driving outpatient UPEC antimicrobial resistance (AMR) may be unique when comparing virtual and in-person visits. For example, patients with uUTI receiving virtual care are less likely to have a urinalysis or urine culture ordered compared with office visits [17, 18]. Inadequate empiric antibiotic therapies prescribed without susceptibility testing can lead to treatment discordant with antibiotic susceptibility (ie, isolate does not display susceptibility to antibiotic treatment), increasing selection for multidrug-resistant organisms [19, 20].

Despite increases in multidrug resistance and changing resistance patterns of UPEC in the last 2 decades [21–27], recent data on multidrug resistance of UPEC are scarce. Increasing multidrug resistance limits treatment options for uUTI and increases treatment failure rates, patient morbidity, healthcare costs, and hospitalization with more frequent use of broad-spectrum antibiotics [17, 28]. It is important for treating clinicians to be aware of the current trends of multidrug resistance to make more informed and appropriate decisions around empiric treatment of outpatient UTIs. Furthermore, because more virtual visits are occurring for uUTI care, it is becoming increasingly important to understand multidrug resistance pattern variations by care setting to inform empiric treatment decision making in different care settings. Leveraging electronic health records (EHRs) from Kaiser Permanente Southern California (KPSC), we examined patterns of UPEC multidrug resistance among outpatient uUTIs from 2016 to 2021, by healthcare delivery setting.

METHODS

Study Setting

We conducted a retrospective cohort study to evaluate antibiotic resistance trends in *E coli* and differences in resistance patterns in virtual versus in-person care settings, between 2016 and 2021 at KPSC, covering 15 medical centers and 236 medical offices in Southern California. Kaiser Permanente Southern California is a large, integrated healthcare organization serving >4.7 million residents of Southern California, closely mirroring the Southern California population [29]. Kaiser Permanente Southern California's EHR captures all aspects of members' health information, including demographic characteristics, diagnoses, laboratory tests, and medications from all care settings; documentation from care received outside is integrated into the EHR.

Patient Consent Statement

This study was reviewed and approved by the Kaiser Permanente Southern California Institutional Review Board, with a waiver for Informed Consent.

Study Population and Data Collection

Individuals with outpatient uUTI, aged ≥18 years with ≥1 year of continuous KPSC membership before their first uUTI between January 1, 2016 and December 31, 2021 were included. To identify uUTIs, we first identified all UTIs, defined by the following: (1) UTI diagnosis code with an antibiotic prescription within ±3 days of code date; or (2) positive urine culture with an antibiotic prescription within ±3 days of culture date; or (3) positive urine culture with a diagnosis code ±7 days of culture date (Supplementary Figure 1, Supplementary Table 1). The UTI occurrences were then categorized as uUTI (an infection in the absence of structural or functional abnormalities) or complicated UTI ([cUTI] infection in the presence of structural or functional abnormalities) using a definition adapted from criteria by Carreno et al [30]. We excluded cUTIs based on the following: (1) cUTI diagnosis codes or (2) combinations of UTI infection codes and codes indicating a structural abnormality/obstruction or procedure. We also excluded UTIs without positive culture results and isolates identified as pathogens other than *E coli*. Our definition of cUTI did not include diabetes, because women with well controlled diabetes without urological sequalae may have uUTI [4]. For the identified *E coli* isolates, we obtained susceptibility data from EHR on aminoglycosides, carbapenems, cephalosporins, fluoroquinolones, fosfomycin, nitrofurantoin, penicillins (amoxicillin, amoxicillin-clavulanate, ampicillin, ampicillin-sulbactam, dicloxacillin, nafcillin, oxacillin, and piperacillin-tazobactam), TMP-SMX, and other UTI-related antibiotics (aztreonam, colistin, daptomycin, linezolid, tigecycline, and vancomycin). Susceptibility data were obtained by standard testing with VITEK 2 AST Cards. All generations of cephalosporins were

grouped together for the analyses of antibiotic resistance trends (Figures 1, 2, and 3), but cephalosporins were separated out by generation in the analysis of prior antibiotic exposure (Figure 4). The KPSC laboratories adapted the updated 2010 Clinical and Laboratory Standards Institute's Enterobacterales breakpoints [31] in 2014, before the start of our study. The UTI components (diagnosis code, antibiotic prescription, or culture) occurring within 30 days were counted as a single event, with the event date defined as the earliest date of any component of the uUTI definition [16]. The UTIs with any component of the definition associated with an inpatient encounter were excluded. Index uUTI was defined as the first uUTI for each individual, with index date defined as the date of the earliest component of the uUTI definition of the index uUTI. Care setting was categorized as "in-person" (office visits and emergency department visits lasting <24 hours) or "virtual" (e-visit, video, and telephone advice visits).

Statistical Analysis

We described the demographic and clinical characteristics of our cohort, including sex, age, race/ethnicity, healthcare utilization, and comorbidities (identified by *International Classification of Diseases* codes, *9th* and *10th Revision*) (Supplementary Table 2), by the number of resistant antibiotic classes and by care setting. We used the Mantel-Haenszel method to assess for trend over time in resistance of UPEC to each antibiotic class and multidrug resistance (resistant to ≥3 antibiotic classes), overall, by care setting and by sex. To examine prior antibiotic exposure, we described the antibiotics dispensed in the 12 months before the index date, along with the primary diagnosis associated with prescribing. This study was reviewed and approved by the KPSC Institutional Review Board, with a waiver for Informed Consent. All analyses were conducted using SAS versions 9.3 and Enterprise Guide 8.2 software (SAS Institute, Cary, NC).

RESULTS

Study Cohort

We identified 777 817 adults with ≥1 UTI event between January 1, 2016 and December 31, 2021, with ≥1-year KPSC membership before index date (Supplementary Figure 1). After applying exclusions, the cohort included 475 013 individuals (475 013 index uUTIs). We further excluded 262 905 with no positive culture and an additional 37 923 with a pathogen other than *E coli*. Our final cohort included 174 185 individuals who had ≥1 outpatient uUTI caused by *E coli* between January 1, 2016 and December 31, 2021. A total of 233 974 outpatient uUTIs were identified during the study period (175 828 [75%] in-person and 58 156 [25%] virtual visits). Overall, a mean of 1.3 events (standard deviation [s.d.] = 0.8) occurred per individual (1.3 per individual [s.d. = 0.7], in-person setting; 1.2 per individual [s.d. = 0.5], virtual setting).

Characteristics of Individuals With Uncomplicated Urinary Tract Infection

The cohort was 92% female and 46% Hispanic, with a mean age of 52 years (s.d. = 20) (Table 1). The most common comorbidities included diabetes mellitus ($n = 32\,105$ [18%]) and chronic obstructive pulmonary disease ($n = 25\,584$ [15%]). Among 20 899 individuals with multidrug-resistant isolates (mean age,

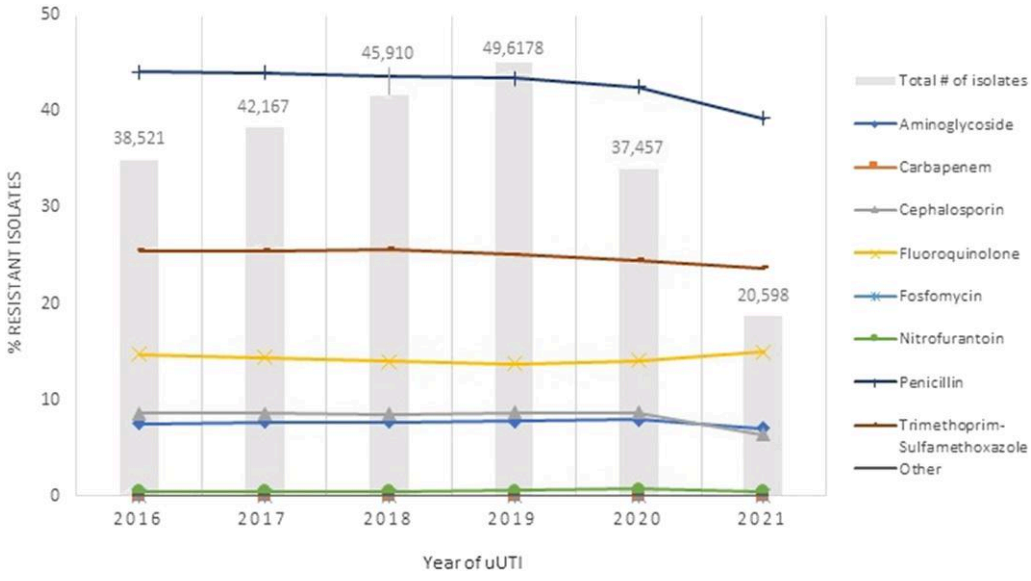

Figure 1. Change in antibiotic resistance of outpatient uncomplicated *Escherichia coli* urinary tract isolates, Kaiser Permanente Southern California, 2016–2021. uUTI, uncomplicated urinary tract infection.

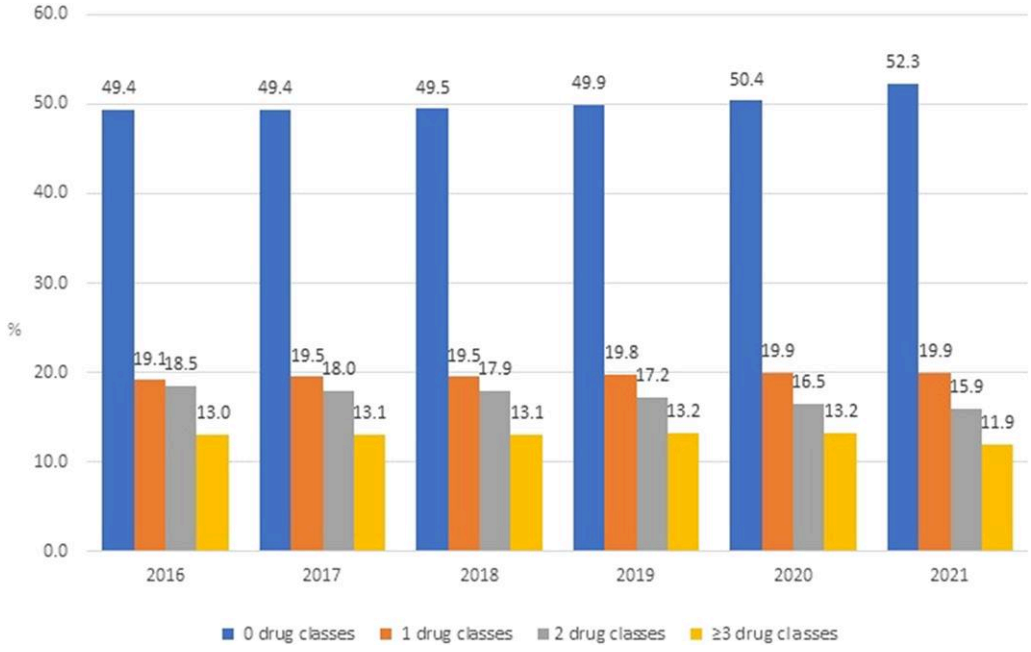

Figure 2. Outpatient uncomplicated urinary tract *Escherichia coli* events resistant to 0, 1, 2, or ≥3 antibiotic drug classes by year, Kaiser Permanente Southern California, 2016–2021.

Figure 3. Antibiotic resistance patterns of outpatient uncomplicated *Escherichia coli* urinary tract events, Kaiser Permanente Southern California, 2016–2021. AGS, aminoglycoside; CSP, cephalosporin; FLQ, fluoroquinolone; NFT, nitrofurantoin; PNC, penicillin; TMP-SMX, sulfamethoxazole and trimethoprim.

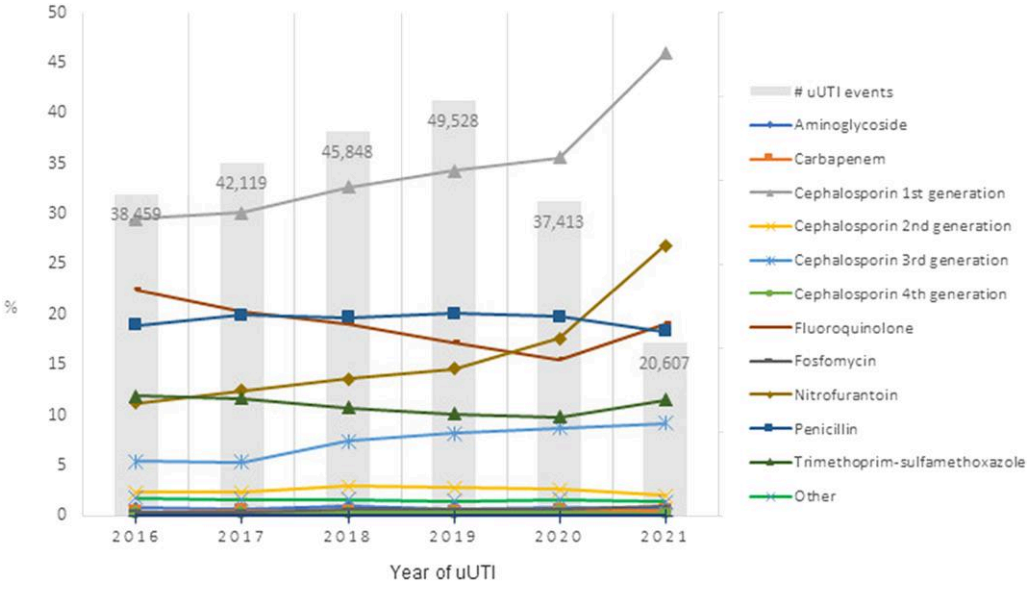

Figure 4. Antibiotics dispensed in the 12 months before outpatient uncomplicated *Escherichia coli* urinary tract infection event by year, Kaiser Permanente Southern California, 2016–2021. uUTI, uncomplicated urinary tract infection.

55 years [s.d. = 19]), 11 068 (53%) were Hispanic, 5138 (25%) had diabetes, 3061 (15%) had Charlson comorbidity index score ≥4, and 5601 (43%) among birthplace known were born outside the United States; 4196 (20%) had ≥20 outpatient encounters, and 250 (1%) had ≥4 inpatient encounters in the 12 months before index date. Among 88 679 individuals with isolates resistant to none of the tested antibiotics (mean age, 51 years [s.d. = 20]), 36 860 (42%) were Hispanic, 14 467 (16%) had diabetes, 7688 (9%) had Charlson comorbidity index score ≥4, and 14 156 (28%) among those with known birthplace were born outside the United States; 12 535 (14%) had ≥20 outpatient encounters, and 247 (0.3%) had ≥4 inpatient encounters in the 12 months before the index date. No differences were observed when stratified by care setting. In individuals who had a urine culture collected, UPEC was most frequently identified in those aged 60–69 years ($n = 40\,004$ [17%]), followed by 50–59 years (37 512 [16%]) and 18–29 years ($n = 36\,065$ [15%]), and were least common in those ≥80 years ($n = 22\,554$ [10%]).

Resistance Patterns

Among 233 974 isolates tested for susceptibility, 99.95% were tested for aminoglycosides, cephalosporins, fluoroquinolones, nitrofurantoin, penicillins, and TMP-SMX; 6.30%, 0.03%, and 0.03% were tested for carbapenems, fosfomycin, and others, respectively. Overall, UPEC resistance decreased over time and was similar in in-person and virtual care settings. For class-specific resistance, resistance to penicillins ($n = 101\,362$ [43%]) or TMP-SMX ($n = 58\,914$ [25%]) was most common (Figure 1). We observed a decrease in resistance for cephalosporins, penicillins, and TMP-SMX during the study period, overall and by care setting (Supplementary Table 3, Supplementary Figures 2 and 3). The proportion of multidrug-resistant UPEC isolates also decreased from 13% ($n = 4988$) in 2016% to 12% ($n = 2444$) in 2021 (P for trend <.001) (Figure 2), which was consistent in both virtual (P for trend <.001) and in-person settings (P for trend <.001), and female sex ($P =$ for trend <.001), but not for male sex (P for trend = .06) (Supplementary Table 4, Supplementary Figure 4). The most common antibiotic resistance in multidrug-resistant UPEC isolates were penicillins overall (29%) and coresistance to penicillins and TMP-SMX (12%) (Figure 3, Supplementary Figures 4 and 5). Multidrug resistance involving penicillins and TMP-SMX plus ≥1 antibiotic class was also common (7%). Multidrug resistance including penicillins accounted for 12% of all observed resistance patterns. Resistance to 1 antibiotic class and coresistance to 2 antibiotic classes were found in 19% and 17% of all UPEC isolates, and 8% and 4% of isolates were resistant to 3 and 4 antibiotic classes, respectively. Although 1% of isolates were resistant to ≥5 antibiotic classes, 50% were not resistant to any of the tested antibiotics. These patterns were consistently observed over time and by care setting.

Prior Antibiotic Exposure

Among individuals with multidrug-resistant isolates, 2687 (13%) had drugs from ≥5 antibiotic classes dispensed in the 12 months before the index date, whereas among those whose isolates were not resistant to any of the tested antibiotic classes, 3615 (4%) had ≥5 antibiotics dispensed (Table 1). We also

Table 1. Characteristics of Individuals With Outpatient Uncomplicated *Escherichia coli* Urinary Tract Infection at Kaiser Permanente Southern California, by the Number of Resistant Drug Classes, 2016–2021

Characteristics	Resistant to 0 Drug Classes ($N = 88\,679$)	Resistant to ≥1 Drug Class ($N = 85\,506$)	Resistant to 1 Drug Class ($N = 34\,350$)	Resistant to 2 Drug Classes ($N = 30\,257$)	Resistant to ≥3 Drug Classes ($N = 20\,899$)	Total ($N = 174\,185$)
Female sex[a]	82 213 (92.7%)	78 247 (91.5%)	31 425 (91.5%)	27 955 (92.5%)	18 810 (90.1%)	160 460 (92.1%)
Age[a] (years)						
Mean (standard deviation)	50.8 (19.7)	52.3 (19.3)	51.3 (19.4)	51.8 (19.0)	54.8 (19.1)	51.5 (19.5)
Median (range)	51.0 (18.0–106.0)	53.0 (18.0–105.0)	51.0 (18.0–105.0)	52.0 (18.0–104.0)	56.0 (18.0–103.0)	52.0 (18.0–106.0)
18–39	29 669 (33.5%)	24 835 (29.0%)	10 796 (31.4%)	8924 (29.5%)	5115 (24.5%)	54 504 (31.3%)
40–59	26 865 (30.3%)	27 667 (32.4%)	10 986 (32.0%)	10 106 (33.4%)	6575 (31.5%)	54 532 (31.3%)
60–79	25 125 (28.3%)	25 979 (30.4%)	9901 (28.8%)	8964 (29.6%)	7114 (34.0%)	51 104 (29.3%)
80+	7020 (7.9%)	7025 (8.2%)	2667 (7.8%)	2263 (7.5%)	2095 (10.0%)	14 045 (8.1%)
Race and Ethnicity[a]						
Hispanic	36 860 (41.6%)	42 332 (49.5%)	15 871 (46.2%)	15 393 (50.9%)	11 068 (53.0%)	79 192 (45.5%)
White	34 690 (39.1%)	26 857 (31.4%)	11 552 (33.6%)	9285 (30.7%)	6020 (28.8%)	61 547 (35.3%)
Asian/Pacific Islander	8198 (9.2%)	8491 (9.9%)	3467 (10.1%)	2876 (9.5%)	2148 (10.3%)	16 689 (9.6%)
Black	6369 (7.2%)	5813 (6.8%)	2592 (7.5%)	2003 (6.6%)	1218 (5.8%)	12 182 (7.0%)
Multiple/Native Am Alaskan/ Others	1398 (1.6%)	1127 (1.3%)	498 (1.4%)	371 (1.2%)	258 (1.2%)	2525 (1.4%)
Unknown/Missing	1164 (1.3%)	886 (1.0%)	370 (1.1%)	329 (1.1%)	187 (0.9%)	2050 (1.2%)
Comorbidities[b]						
History of allergy to antibiotics	22 432 (25.3%)	20 560 (24.0%)	8284 (24.1%)	7017 (23.2%)	5329 (25.2%)	42 992 (24.7%)
Diabetes	14 467 (16.3%)	17 638 (20.6%)	6468 (18.8%)	6032 (19.9%)	5138 (24.6%)	32 105 (18.4%)
Chronic obstructive pulmonary disease	11 844 (13.4%)	13 270 (15.5%)	4754 (13.8%)	4391 (14.5%)	4125 (19.7%)	25 114 (14.4%)
Peripheral vascular disease	12 470 (14.1%)	13 114 (15.3%)	4918 (14.3%)	4467 (14.8%)	3729 (17.8%)	25 584 (14.7%)
Renal disease	7553 (8.5%)	8216 (9.6%)	2969 (8.6%)	2681 (8.9%)	2566 (12.3%)	15 769 (9.1%)
Liver disease	3146 (3.5%)	3926 (4.6%)	1393 (4.1%)	1341 (4.4%)	1192 (5.7%)	7072 (4.1%)
Cerebrovascular disease	2418 (2.7%)	2600 (3.0%)	879 (2.6%)	875 (2.9%)	846 (4.0%)	5018 (2.9%)
Cancer	2460 (2.8%)	2739 (3.2%)	990 (2.9%)	934 (3.1%)	815 (3.9%)	5199 (3.0%)
Congestive heart failure	2248 (2.5%)	2696 (3.2%)	866 (2.5%)	809 (2.7%)	1021 (4.9%)	4944 (2.8%)
Dementia	1680 (1.9%)	1968 (2.3%)	699 (2.0%)	600 (2.0%)	669 (3.2%)	3701 (2.1%)
Connective tissue disease-rheumatic disease	1860 (2.1%)	2281 (2.7%)	769 (2.2%)	824 (2.7%)	688 (3.3%)	4141 (2.4%)
History of myocardial infarction	1538 (1.7%)	1700 (2.0%)	610 (1.8%)	502 (1.7%)	588 (2.8%)	3238 (1.9%)
Metastatic carcinoma	844 (1.0%)	962 (1.1%)	352 (1.0%)	329 (1.1%)	281 (1.3%)	1806 (1.0%)
HIV/AIDS	48 (0.1%)	85 (0.1%)	26 (0.1%)	33 (0.1%)	26 (0.1%)	133 (0.1%)
Weighted Charlson Comorbidities Score[b]						
0	53 974 (60.9%)	47 504 (55.6%)	20 008 (58.2%)	17 147 (56.7%)	10 349 (49.5%)	101 478 (58.3%)
1	15 115 (17.0%)	15 712 (18.4%)	6200 (18.0%)	5693 (18.8%)	3819 (18.3%)	30 827 (17.7%)
2	7846 (8.8%)	8512 (10.0%)	3288 (9.6%)	2891 (9.6%)	2333 (11.2%)	16 358 (9.4%)
3	4056 (4.6%)	4567 (5.3%)	1687 (4.9%)	1543 (5.1%)	1337 (6.4%)	8623 (5.0%)
4+	7688 (8.7%)	9211 (10.8%)	3167 (9.2%)	2983 (9.9%)	3061 (14.6%)	16 899 (9.7%)
Insurance Type[a]						
Commercial	55 439 (62.5%)	51 840 (60.6%)	21 430 (62.4%)	18 590 (61.4%)	11 820 (56.6%)	107 279 (61.6%)
Medicare	23 458 (26.5%)	24 100 (28.2%)	9119 (26.5%)	8199 (27.1%)	6782 (32.5%)	47 558 (27.3%)
Medicaid	5560 (6.3%)	5754 (6.7%)	2305 (6.7%)	2075 (6.9%)	1374 (6.6%)	11 314 (6.5%)
Private pay	4145 (4.7%)	3748 (4.4%)	1469 (4.3%)	1372 (4.5%)	907 (4.3%)	7893 (4.5%)
Other	17 (<0.1%)	20 (<0.1%)	12 (<0.1%)	6 (<0.1%)	2 (<0.1%)	37 (<0.1%)
Uninsured	60 (0.1%)	44 (0.1%)	15 (<0.1%)	15 (<0.1%)	14 (0.1%)	104 (0.1%)
Body Mass Index[c]						
<18.5 (underweight)	1499 (1.9%)	1347 (1.7%)	572 (1.8%)	436 (1.6%)	339 (1.7%)	2846 (1.8%)
18.5–24.9 (healthy weight)	25 863 (32.2%)	23 076 (29.4%)	9503 (30.3%)	8197 (29.5%)	5376 (27.6%)	48 939 (30.8%)
25.0–29.9 (overweight)	25 190 (31.4%)	25 031 (31.8%)	9731 (31.1%)	8973 (32.3%)	6327 (32.5%)	50 221 (31.6%)
30.0–39.9 (obese)	22 613 (28.2%)	23 737 (30.2%)	9337 (29.8%)	8313 (29.9%)	6087 (31.2%)	46 350 (29.2%)
>39.9 (extreme obese)	5049 (6.3%)	5429 (6.9%)	2188 (7.0%)	1880 (6.8%)	1361 (7.0%)	10 478 (6.6%)
Missing	8465	6886	3019	2458	1409	15 351

Table 1. Continued

Characteristics	Resistant to 0 Drug Classes (*N* = 88 679)	Resistant to ≥1 Drug Class (*N* = 85 506)	Resistant to 1 Drug Class (*N* = 34 350)	Resistant to 2 Drug Classes (*N* = 30 257)	Resistant to ≥3 Drug Classes (*N* = 20 899)	Total (*N* = 174 185)
Smoking Status[c]						
Current	5596 (6.3%)	5230 (6.1%)	2227 (6.5%)	1860 (6.1%)	1143 (5.5%)	10 826 (6.2%)
Former	14 540 (16.4%)	14 191 (16.6%)	5708 (16.6%)	4796 (15.9%)	3687 (17.6%)	28 731 (16.5%)
Never	66 512 (75.0%)	64 273 (75.2%)	25 686 (74.8%)	22 945 (75.8%)	15 642 (74.8%)	130 785(75.1%)
Unknown	2031 (2.3%)	1812 (2.1%)	729 (2.1%)	656 (2.2%)	427 (2.0%)	3843 (2.2%)
Foreign Born						
No	36 122 (71.8%)	31 857 (62.9%)	13 407 (67.9%)	11 045 (61.8%)	7405 (56.9%)	67 979 (67.4%)
Yes	14 156 (28.2%)	18 790 (37.1%)	6348 (32.1%)	6841 (38.2%)	5601 (43.1%)	32 946 (32.6%)
Missing	38 401	34 859	14 595	12 371	7893	73 260
Pregnant[a]	1851 (2.1%)	1521 (1.8%)	680 (2.0%)	533 (1.8%)	308 (1.5%)	3372 (1.9%)
Polymicrobial UTI (≥1 organism identified other than *E coli*)	2088 (2.4%)	2049 (2.4%)	772 (2.2%)	715 (2.4%)	562 (2.7%)	4137 (2.4%)
Number of Outpatient Encounters[b]						
0	3862 (4.4%)	3231 (3.8%)	1428 (4.2%)	1161 (3.8%)	642 (3.1%)	7093 (4.1%)
1–3	18 047 (20.4%)	15 672 (18.3%)	6743 (19.6%)	5616 (18.6%)	3313 (15.9%)	33 719 (19.4%)
4–6	17 868 (20.1%)	16 214 (19.0%)	6750 (19.7%)	5917 (19.6%)	3547 (17.0%)	34 082 (19.6%)
7–10	16 747 (18.9%)	15 982 (18.7%)	6452 (18.8%)	5652 (18.7%)	3878 (18.6%)	32 729 (18.8%)
11–20	19 620 (22.1%)	20 359 (23.8%)	7884 (23.0%)	7152 (23.6%)	5323 (25.5%)	39 979 (23.0%)
20+	12 549 (14.1%)	14 048 (16.4%)	5093 (14.8%)	4759 (15.7%)	4196 (20.1%)	26 583 (15.3%)
Number of Inpatient Encounters[b]						
0	80 913 (91.2%)	76 106 (89.0%)	31 049 (90.4%)	27 216 (89.9%)	17 841 (85.4%)	157 019 (90.1%)
1	5992 (6.8%)	6749 (7.9%)	2529 (7.4%)	2240 (7.4%)	1980 (9.5%)	12 741 (7.3%)
2	1172 (1.3%)	1580 (1.8%)	489 (1.4%)	498 (1.6%)	593 (2.8%)	2752 (1.6%)
3	355 (0.4%)	576 (0.7%)	165 (0.5%)	176 (0.6%)	235 (1.1%)	931 (0.5%)
4+	247 (0.3%)	495 (0.6%)	118 (0.3%)	127 (0.4%)	250 (1.2%)	742 (0.4%)
Number of Emergency Department Encounters[b]						
0	69 722 (78.6%)	64 267 (75.2%)	26 503 (77.2%)	23 011 (76.1%)	14 753 (70.6%)	133 989 (76.9%)
1	12 940 (14.6%)	13 680 (16.0%)	5243 (15.3%)	4779 (15.8%)	3658 (17.5%)	26 620 (15.3%)
2	3592 (4.1%)	4170 (4.9%)	1475 (4.3%)	1428 (4.7%)	1267 (6.1%)	7762 (4.5%)
3	1295 (1.5%)	1667 (1.9%)	611 (1.8%)	515 (1.7%)	541 (2.6%)	2962 (1.7%)
4+	1130 (1.3%)	1722 (2.0%)	518 (1.5%)	524 (1.7%)	680 (3.3%)	2852 (1.6%)
Number of Antibiotics Filled[b]						
0	50 337 (56.8%)	…	…	…	…	…
1	18 985 (21.4%)	41 586 (48.6%)	18 113 (52.7%)	14 918 (49.3%)	8555 (40.9%)	91 923 (52.8%)
2	8989 (10.1%)	19 048 (22.3%)	7751 (22.6%)	6887 (22.8%)	4410 (21.1%)	38 033 (21.8%)
3	4491 (5.1%)	10 033 (11.7%)	3790 (11.0%)	3603 (11.9%)	2640 (12.6%)	19 022 (10.9%)
4	2262 (2.6%)	5336 (6.2%)	1887 (5.5%)	1837 (6.1%)	1612 (7.7%)	9827 (5.6%)
5+	3615 (4.1%)	6452 (7.5%)	1748 (5.1%)	2018 (6.7%)	2687 (12.9%)	10 067 (5.8%)

Abbreviations: AIDS, acquired immune deficiency syndrome; HIV, human immunodeficiency virus; UTI, urinary tract infection.

[a]At index date.

[b]In the 12 months before index date.

[c]Most recent in the 12 months before index date.

examined antibiotics dispensed in the 12 months before each uUTI. Most commonly dispensed antibiotics in the 12 months before each uUTI included first-generation cephalosporins ($n = 78\,740$ [34%]), penicillins ($n = 45\,751$ [20%]), and fluoroquinolones ($n = 44\,122$ [19%]) with an increase in dispensing of first-generation cephalosporins (30% to 46%), nitrofurantoin (11% to 27%), and third-generation cephalosporins (5% to 9%) between 2016 and 2021 (Figure 4). Similar trends were observed when stratified by care setting (Supplementary Figure 6). The most common primary diagnosis associated with antibiotic dispensing was UTI ($n = 140\,135$ [26%]), followed by chronic sinusitis ($n = 36\,382$ [3%]), and dysuria ($n = 3772$ [2%]).

DISCUSSION

We evaluated AMR of *E coli* urine isolates from individuals with outpatient uUTI at KPSC between 2016 and 2021. We observed a slight decrease in both class-specific AMR and

multidrug resistance of UPEC overall, with the highest prevalence of resistance observed in penicillins, TMP-SMX, and fluoroquinolones. We observed a small decrease in the prevalence of multidrug resistance, with coresistance to penicillins and TMP-SMX being the most common multidrug resistance pattern. We observed similar trends for both in-person and virtual care settings. Consistent with the 2011 guidelines [4, 13], we observed an increase in the use of TMP-SMX and nitrofurantoin in the year before uUTIs since 2016. We also observed low resistance of nitrofurantoin (<1%), supporting the current guidelines. Previous US studies on UPEC from female outpatients showed an increase in TMP-SMX resistance from 7% to 18% between 1989 and 1999 [32, 33]. Another US study reported increases in TMP-SMX resistance (15% to 16%), nitrofurantoin (0.4% to 0.7%), and ciprofloxacin (0.7% to 2.5%) between 1995 and 2001 [34]. Similar to our findings, more recent US studies have reported UPEC resistance to TMP-SMX to be approximately ≥20%, ≤1% to fluoroquinolones, and ≤2% to nitrofurantoin [22, 34–36]. We also observed a high prevalence of resistance to penicillins and fluoroquinolones, as previously reported [10, 36, 37]. These patterns may be explained by common use of these antibiotics in treating previous uUTIs and other infections with antimicrobial coverage similar to UTI. In our study, UTI and chronic sinusitis were among the most common diagnoses associated with antibiotics dispensed in the year before uUTIs. A recent report examining antimicrobial resistance trends in California after SB27, which banned routine preventive use of antibiotics in food-animal production and any antibiotic use without a veterinarian's prescription, estimated a 7% decline in extended-spectrum cephalosporins associated with SB27 [38]. The study findings may help explain the overall low resistance we observed in our study. We also observed a low uUTI prevalence in individuals aged ≥80 years in our study, which may be due to smaller sample size, more frequent testing, or more frequent history of a prior cUTI in this group, compared to younger groups. Finally, our study included some males (8%), and the clinical practice guidelines refer to uUTIs in women only [4]. The prevalence of AMR in females decreased over time whereas the prevalence remained largely unchanged in males. These findings are consistent with previous studies showing higher risk of infection with pathogens with AMR in men compared with women [39].

Several studies have reported on multidrug resistance patterns of UPEC in North America. In the United States, coresistance to ampicillin and TMP-SMX, and multidrug resistance involving ampicillin, TMP-SMX, and ciprofloxacin, have been frequently reported, whereas nitrofurantoin resistance appeared unrelated to ampicillin, TMP-SMX, or ciprofloxacin resistance [22, 34, 40]. A US study in 2000 reported multidrug resistance in 7% of UPEC, including resistance to ampicillin (98%), TMP-SMX (93%), cephalosporin (87%), ciprofloxacin (39%), and nitrofurantoin (8%) among the isolates [22]. A more recent US study (2020) found that the risk of nitrofurantoin and TMP-SMX resistance was 4 times higher and the risk of ciprofloxacin resistance was 13 times higher for ESBL-*E coli*, compared with bacteriuria caused by non-ESBL-*E coli* [12]. In our study, coresistance between penicillins and TMP-SMX was most common (12%) among the observed resistance patterns. Among nitrofurantoin-resistant isolates, approximately 70% were coresistant to either TMP-SMX or fluoroquinolones. This coresistance pattern likely reflects (1) the recent increase in their use and (2) resistance developing in patients repeatedly treated for recurrent UTIs or inappropriate treatment of asymptomatic bacteriuria. Furthermore, resistance patterns involving beta-lactams commonly observed in our study, including penicillins and cephalosporins, are concerning because ESBL-producing strains, coresistant with other common antibiotics used for uUTIs, render beta-lactam antibiotics unsuitable for empiric treatment of uUTIs. Furthermore, ESBL-producing strains are no longer confined to the hospital setting, and they are becoming increasingly prevalent in outpatient UTIs [11, 12]. Beta-lactams are also frequently used for many other conditions such as chronic sinusitis and pneumonia, further increasing exposure and risk of developing multidrug resistance [41, 42]. Nevertheless, approximately half of *E coli* urine isolates were resistant to none of the tested antibiotics, which is encouraging. However, we observed a small group of isolates (1%) resistant to ≥5 antibiotic classes. Such cases are concerning because the choice of antibiotics available for treatment is limited, and these infections often require intravenous antibiotic therapy, which incurs greater costs and is more likely to lead to hospitalizations and adverse events [43, 44].

The uUTIs can be treated in both in-person and virtual settings. In this study, we observed very similar AMR patterns for both settings. This has important implications because virtual care has been increasingly used in the United States due to cost effectiveness and convenience. Previous studies have noted some differences between UTI care in virtual and office visits. Some reported that providers were less likely to order urinary laboratory testing in a virtual visit compared with an office visit [16–18]. Others have noted that guideline-adherent antibiotics were more likely to be prescribed in a virtual visit compared with an office visit [17], whereas others suggest that guideline-adherent antibiotic selection was similar between virtual and office visits [18]. In addition, individuals receiving virtual care were less likely to have a UTI-related revisit within 7 days [17]. Collectively, these findings support that virtual visits may be a tool to offer a convenient, cost-effective option for care without evidence of increased risk of MDR. These findings are corroborated by our data showing similar AMR patterns between care received in either setting.

Our study has some limitations. First, the KPSC laboratory thresholds used for the positive culture definition are lower than the common diagnostic threshold of $\geq 10^5$ colony-forming units/mL, which are more sensitive for acute cystitis, but may

detect asymptomatic bacteriuria [16]. Second, because uUTI symptoms are not routinely recorded, our uUTI definition did not incorporate symptoms, and may have included some asymptomatic bacteriuria. However, to minimize such misclassification, we required a combination of diagnosis codes, antibiotic orders, and susceptibility testing. Third, we conducted analyses at the level of antibiotic class, grouping some antibiotic classes with a range of antimicrobial coverage into 1 antibiotic class (ie, penicillins). For example, isolates with resistance to piperacillin-tazobactam or ampicillin-sulbactam is much more clinically meaningful and concerning than penicillin or amoxicillin within the same drug class. However, antibiotic drugs within certain classes (ie, fluoroquinolones) typically share the same mechanisms of resistance, thus our results on most antibiotic drug classes (with the exception of penicillins and cephalosporins) can be applied broadly in the clinical setting. Fourth, although UTI symptoms usually prompt seeking of medical care, our cohort may have missed some cases that were not medically attended. In addition, to evaluate trends in resistance over time, isolates from the same individual (>30 days apart from each other) were included as separate isolates in the analysis. This may have skewed the results because isolates from recurrent UTIs tend to be more resistant than initial events. In addition, the rapid decrease in laboratory testing during the COVID-19 pandemic resulted in a small sample size in 2020 and 2021, which may have affected our ability to evaluate temporal trends in AMR. Our data during this period may capture AMR patterns in more severe/symptomatic cases, because less severe cases were less likely to seek care. However, overall, AMR patterns did not change substantially during this period compared with the previous years. Fourth, we did not evaluate dose and duration of antibiotics included in the analysis, which are contributing factors to development of AMR. Finally, urine cultures are only recommended for certain groups of patients with UTI (eg, symptomatic postmenopausal women), and we are characterizing multidrug resistance patterns for these groups only, potentially limiting generalizability. In addition, it is important to note the difference in the proportions of uUTIs with urine culture in virtual versus in-person settings, because our study includes UTIs with culture results only. In our population, 23% of those with a uUTI seen in a virtual visit had a urine culture collected, whereas 40% among those seen in an in-person visit did (Supplementary Figure 1). Because clinicians are more likely to order urine cultures in the setting of treatment failure and/or previous resistance, and AMR is more common in these settings, AMR may have been overestimated.

CONCLUSIONS

In conclusion, the prevalence of AMR of UPEC from outpatient uUTIs at KPSC has slightly decreased between 2016 and 2021, both for in-person and virtual settings, although the magnitude of the decrease was mostly small. Resistance to penicillins, fluoroquinolones, and TMP-SMX was common. Nitrofurantoin sustained high susceptibility, although some concerning multidrug resistance patterns with fluoroquinolones and TMP-SMX coresistance were observed. Prevalence and patterns of both single-class resistance and multidrug resistance of UPEC did not differ by care setting. Virtual healthcare may expand access to UTI care, without increased risk of multidrug resistance. Ongoing surveillance of local microbial prevalence and resistance patterns are needed to further guide appropriate prescribing for UTI empiric therapy.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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