AMERICAN SOCIETY FOR MICROBIOLOGY | Journal of Clinical Microbiology®

EPIDEMIOLOGY

Persistent Pandemic Lineages of Uropathogenic *Escherichia coli* in a College Community from 1999 to 2017

Reina Yamaji,[a] Julia Rubin,[a] Erika Thys,[a] Cindy R. Friedman,[b] Lee W. Riley[a]

[a]School of Public Health, Division of Infectious Diseases and Vaccinology, University of California, Berkeley, Berkeley, California, USA

[b]Enteric Diseases Epidemiology Branch, Centers for Disease Control and Prevention, Atlanta, Georgia, USA

ABSTRACT The incidence of drug-resistant community-acquired urinary tract infections (CA-UTI) continues to increase worldwide. In 1999 to 2000, a single lineage of uropathogenic *Escherichia coli* (UPEC) sequence type 69 (ST69) caused 51% of trimethoprim-sulfamethoxazole-resistant UTI in a Northern California university community. We compared the clonal distributions of UPEC and its impact on antimicrobial resistance prevalence in the same community during two periods separated by 17 years. We analyzed *E. coli* isolates from urine samples from patients with symptoms of UTI who visited a health service between September 2016 and May 2017 and compared them to UPEC isolates collected similarly between October 1999 and March 2000. Isolates were tested for antimicrobial drug susceptibility and genotyped by multilocus sequence typing. In 1999 to 2000, strains belonging to ST95, ST127, ST73, ST69, ST131, and ST10 caused 125 (56%) of 225 UTI cases, while the same STs caused 148 (64%) of 233 UTI cases in 2016 to 2017. The frequencies of ampicillin resistance and ciprofloxacin resistance rose from 24.4% to 41.6% ($P < 0.001$) and from 0.9% to 5.1% ($P < 0.003$), respectively. The six STs accounted for 78.6% and 72.7% of these increases, respectively. Prevalence of drug-resistant UTI in this community appears to be largely influenced by a small set of dominant UPEC STs circulating in the same community 17 years apart. Further research to determine the origin and reasons for persistence of these dominant genotypes is necessary to combat antimicrobial-resistant CA-UTI.

KEYWORDS *Escherichia coli*, molecular epidemiology, multilocus sequence typing, urinary tract infection, uropathogenic *E. coli*

Community-acquired urinary tract infection (CA-UTI) is one of the most common bacterial infectious diseases for women worldwide (1, 2). It accounts for a considerable number of outpatient health care visits and a considerable proportion of health care costs, and it negatively affects the quality of life of affected individuals (1, 2). In 1995, it was estimated that 11% of women aged 18 years and older had experienced at least one presumed UTI episode during the previous 12-month period and the annual cost of UTI was estimated at 11.6 billion dollars (2).

The most common causative agent of CA-UTI is uropathogenic *Escherichia coli* (UPEC) (3). Infectious Diseases Society of America (IDSA) recommends nitrofurantoin and fosfomycin as empirical treatment regimens for uncomplicated cystitis and pyelonephritis (4), but trimethoprim-sulfamethoxazole (TMP-SMZ) and fluoroquinolones are still widely used (5), and resistance to these drugs is increasing (6–9).

It is often believed that clinical use of antimicrobial agents contributes to the selection of drug-resistant strains of UPEC causing resistant CA-UTI. In a study of patients with symptoms of UTI at a Northern California university in 1999 to 2000, Manges et al. demonstrated that a single strain of UPEC, referred to as clonal group A

Received 14 December 2017 **Returned for modification** 2 January 2018 **Accepted** 1 February 2018

Accepted manuscript posted online 7 February 2018

Citation Yamaji R, Rubin J, Thys E, Friedman CR, Riley LW. 2018. Persistent pandemic lineages of uropathogenic *Escherichia coli* in a college community from 1999 to 2017. J Clin Microbiol 56:e01834-17. https://doi.org/10.1128/JCM.01834-17.

Editor Daniel J. Diekema, University of Iowa College of Medicine

Address correspondence to Lee W. Riley, lwriley@berkeley.edu.

(CgA), on the basis of enterobacterial repeat intergenic consensus 2 (ERIC2)-PCR typing (6), later classified as ST69 by multilocus sequence typing (MLST), accounted for 11% of 255 UPEC isolates and 51% of 55 TMP-SMZ-resistant isolates (6, 10). Another study conducted in the same community between 1999 and 2005 demonstrated that all initially pan-susceptible clonal groups remained pan-susceptible and that only four lineages accounted for 52% of multidrug-resistant (MDR) UPEC isolates over the 6-year study period (11).

Globally, *E. coli* genotypes ST10, ST69, ST73, ST95, ST127, and ST131 defined by MLST account for more than 50% of extraintestinal pathogenic *E. coli* (ExPEC) infections (12–14). These have come to be referred to as pandemic ExPEC lineages (15). Given the selective pressure exerted on bacteria by heavy antimicrobial use in human medical practices and animal husbandry, it is unclear why a large proportion of drug-resistant ExPEC infections are caused by a small set of genotypes. We used MLST to determine the distribution of UPEC genotypes and the prevalence of drug-resistant CA-UTI during two study periods separated by 17 years at one Northern California university community.

MATERIALS AND METHODS

Sample collection. *E. coli* was isolated from urine samples collected consecutively between 19 September 2016 and 4 May 2017 from the patients with symptoms of UTI seen at a university health service. All urine samples were collected as part of routine clinical care at the health service. We collected them before they were discarded without personal identifiers or clinical information. All urine samples were first tested at the health service by dipstick, and those specimens found to test positive for leukocytes, nitrates, protein, blood, or glucose were collected for this study and subjected to further microbiologic examination. A case of urinary tract infection was defined as a patient with a clean-catch urine specimen that contained more than 10^2 CFU of *E. coli* per milliliter (16).

Microbiologic examinations. A 10-μl aliquot of urine sample was cultured on a MacConkey agar plate to isolate Gram-negative bacteria. Lactose-positive and indole-positive colonies were presumptively identified as *E. coli* and further analyzed. All *E. coli* isolates were screened for susceptibility to ampicillin, trimethoprim-sulfamethoxazole (TMP-SMZ), and ciprofloxacin (CIP) by the standard disc diffusion assay, according to the standard interpretive criteria of the Clinical and Laboratory Standards Institute (M100-S25; Clinical and Laboratory Standards Institute, 2015). *E. coli* 25922 from the American Type Culture Collection was used as a reference strain. Susceptibility to cephalosporin (cefotaxime [CTX], cefoxitin [FOX], and ceftazidime [CAZ]), nitrofurantoin (NIT), fosfomycin (FOS), and gentamicin (GEN) was also assessed for isolates belonging to major lineages by the disc diffusion method. Isolates with intermediate susceptibility were classified as resistant. Isolates with multidrug resistance were defined as isolates with resistance to three or more classes of antimicrobial agents (17).

Strain typing. Five colonies recovered from each urine culture were randomly picked and subtyped by ERIC2-PCR assay, as described previously (18, 19). Single colonies on tryptic soy agar plates were selected and inoculated into 2 ml of tryptic soy broth and incubated in a shaking incubator for 15 h at 37°C. The 2-ml aliquots of grown cultures were centrifuged, and the pellets were resuspended in a test tube with 350 μl of distilled water, boiled for 10 min in a water bath, and then cooled on ice for 2 min. The samples were centrifuged for 2 min at 13,000 rpm, and the supernatants were stored at −20°C before they were subjected to PCR tests.

The five colonies that had identical ERIC2 electrophoretic banding patterns by visual inspection were considered to belong to the same clonal group, and one of them was selected for further analysis by multilocus sequence typing (MLST). All *E. coli* isolates were genotyped by MLST based on the seven-gene scheme described at the PubMLST website (https://pubmlst.org/bigsdb?db=pubmlst_mlst_seqdef) (10). The allelic number and the corresponding genotype number were assigned by the curator of the MLST website. *E. coli* genotypes ST10, ST69, ST73, ST95, ST127, and ST131 were considered major genotypes since they account for more than 50% of ExPEC infections worldwide (12–14, 20). The other genotypes were considered minor genotypes.

Beta-lactamase gene identification. Ampicillin-resistant *E. coli* isolates were examined for beta-lactamase gene families by multiplex PCRs as described previously (21, 22). These beta-lactamase gene families included the following: TEM variants ($bla_{\text{TEM-1}}$ and $bla_{\text{TEM-2}}$), an SHV variant ($bla_{\text{SHV-1}}$), CTX-M group 1 ($bla_{\text{CTX-M-1}}$, $bla_{\text{CTX-M-3}}$, and $bla_{\text{CTX-M-15}}$), CTX-M group 2 ($bla_{\text{CTX-M-2}}$), CTX-M group 9 ($bla_{\text{CTX-M-9}}$ and $bla_{\text{CTX-M-14}}$), CTX-M group 8/25 ($bla_{\text{CTX-M-8}}$, $bla_{\text{CTX-M-25}}$, $bla_{\text{CTX-M-26}}$, and $bla_{\text{CTX-M-39}}$ to $bla_{\text{CTX-M-41}}$), OXA variants ($bla_{\text{OXA-1}}$, $bla_{\text{OXA-4}}$, and $bla_{\text{OXA-30}}$), and AmpC types ($bla_{\text{MOX-1}}$, $bla_{\text{MOX-2}}$, $bla_{\text{CMY-1}}$, $bla_{\text{CMY-8}}$ to $bla_{\text{CMY-11}}$, $bla_{\text{LAT-1}}$ to $bla_{\text{LAT-4}}$, $bla_{\text{CMY-2}}$ to $bla_{\text{CMY-7}}$, $bla_{\text{BIL-1}}$, $bla_{\text{DHA-1}}$, $bla_{\text{DHA-2}}$, bla_{ACC}, $bla_{\text{MIR-1T}}$, $bla_{\text{ACT-1}}$, and $bla_{\text{FOX-1}}$ to $bla_{\text{FOX-5b}}$). To detect the plasmid-mediated AmpC β-lactamase genes, we performed six types of multiplex PCR as described previously (22).

Comparison to *E. coli* isolates obtained from 1999 to 2000. Between September 1999 and January 2000, *E. coli* isolates were obtained from urine samples consecutively collected from patients with symptoms of UTI at the Northern California university campus health service, as described by Manges et al. (6). *E. coli* samples were stored in sterile 15% glycerol at −80°C. Aliquots of the stored samples were incubated at 37°C on tryptic soy agar plates overnight, and single colonies were selected and reinocu-

lated into 2 ml tryptic soy broth and incubated in a shaking incubator for 15 h at 37°C. The bacterial DNA was extracted by the freeze-boil method as described above. We conducted antimicrobial drug susceptibility testing and MLST analysis on the isolates as described above.

Statistical analysis. The difference in the prevalences of the *E. coli* genotypes and the drug resistance data between the two sampling periods was assessed by two-sided Fisher's exact test. Statistical significance was defined as a *P* value of less than 0.05. All analyses were performed by the use of R-Studio version 3.4.2.

RESULTS

Study isolates. Between 19 September 2016 and 4 May 2017, we collected 1,087 nonduplicate urine samples from the university health service. Among those samples, 788 tested negative by culture, 56 grew lactose-negative bacteria, and 13 grew lactose-positive and indole-negative bacteria; 230 (21%) contained *E. coli*. From the study conducted by Manges et al. in 1999 to 2000 (6), 231 stored *E. coli* isolates were available for testing, and 225 of those *E. coli* isolates were recultured and genotyped by MLST.

Distribution of MLST genotypes. In 2016 to 2017, 227 of 230 samples contained one *E. coli* ST each and three contained two STs. Therefore, 233 *E. coli* isolates were analyzed; 225 *E. coli* isolates were assigned to 61 unique STs, whereas 8 could not be assigned an ST designation (Table 1). Among 225 *E. coli* isolates collected in 1999 to 2000, 216 were assigned to 63 unique STs whereas 9 could not be assigned an ST designation (Table 1). Five genotypes (ST95, ST127, ST73, ST69, and ST131) were composed of more than 10 isolates each in 2016 to 2017, whereas 51 (83.6%) genotypes had a frequency of fewer than three isolates each. The most common genotypes among UPEC strains in 2016 to 2017 (ST95, ST127, ST73, ST69, ST131, and ST10) were the same as the genotypes found in the UPEC strains from 1999 to 2000 (Table 2). In 2016 to 2017, the most common genotypes were ST95 (16.7%) and ST127 (15.9%); in 1999 to 2000, ST95 (15.1%) and ST69 (11.6%) were the most common. Between the two periods, the proportion of UPEC genotypes ST95, ST127, ST69, ST73, and ST131 increased from 50.7% to 60.9% ($P = 0.03$); however, there was no significant change in ST10 frequency during the two study periods. Of 61 genotypes identified in 2016 to 2017, 44 were not found in 1999 to 2000, and of 63 genotypes in 1999 to 2000, 46 were not found in 2016 to 2017 (Table 1).

Changes in prevalence of ampicillin, trimethoprim-sulfamethoxazole, and ciprofloxacin resistance. In 2016 to 2017, 97 (41.6%) *E. coli* isolates were resistant to ampicillin, compared with 55 (24.4%) in 1999 to 2000 ($P < 0.001$) (Table 3). Between 1999 to 2000 and 2016 to 2017, ampicillin resistance increased from 26.4% to 44.6% ($P = 0.002$) among the six major genotypes and increased from 22.0% to 36.4% ($P = 0.03$) among the minor genotypes. ST95, ST127, ST73, and ST131 comprised 46.4% of the ampicillin-resistant isolates in 2016 to 2017 but only 21.8% in 1999 to 2000 ($P = 0.0004$). Strikingly, only four of the six major STs (ST95, ST127, ST73, and ST131) contributed to 78.6% of the increase in ampicillin resistance.

Unlike the ampicillin resistance results, there was no significant change in TMP-SMZ resistance during the two study periods (Table 3). During both study periods, TMP-SMZ resistance was 17%, and the proportion of TMP-SMZ-resistant isolates was highest among the strains belonging to ST69 (65% in 1999 to 2000 and 68% in 2016 to 2017) (6). In 1999 to 2000, ST69 accounted for 44.7% of all TMP-SMZ-resistant isolates, while in 2016 to 2017, it accounted for 37.5%. During the two study periods, the proportions of ST73 and ST131 isolates that were resistant to TMP-SMZ increased from 4.3% to 21.9% and from 14.3% to 25.0%, respectively; they accounted for 25% of all TMP-SMZ-resistant isolates in 2016 to 2017 ($P = 0.02$) and 5.3% in 1999 to 2000.

In 2016 to 2017, 12 (5.1%) *E. coli* isolates were resistant to ciprofloxacin compared with only 1 (0.9%) in 1999 to 2000 ($P = 0.003$) (Table 3). ST131 accounted for more than half (58%) of 12 isolates from 2016 to 2017.

β-Lactamase gene types among ampicillin resistance strains. Among 55 ampicillin-resistant *E. coli* isolates collected in 1999 to 2000, β-lactamase TEM variants were detected in 49 (89%), 2 of which had OXA variants. No CTX-M group, SHV variant,

TABLE 1 Multilocus sequence types of uropathogenic *E. coli* isolates obtained from patients with urinary tract infection in a Northern California college community during 1999 to 2000 and 2016 to 2017

Genotype	1999–2000	2016–2017
95	34	39
127	24	37
73	23	32
69	26	22
131	7	12
10	11	6
12	2	6
141	2	6
420	9	4
2628	0	3
28	0	2
88	4	2
569	0	2
998	4	2
1948	0	2
2261	0	2
6767	0	2
13	0	1
34	0	1
38	1	1
59	1	1
80	1	1
83	0	1
91	0	1
101	0	1
117	2	1
200	0	1
224	0	1
280	0	1
345	0	1
363	0	1
372	1	1
379	0	1
416	0	1
472	0	1
550	0	1
636	1	1
746	0	1
906	0	1
929	0	1
945	0	1
964	0	1
989	0	1
1380	0	1
1643	0	1
1670	0	1
1844	0	1
1873	0	1
2003	0	1
2015	0	1
2165	0	1
2562	0	1
2646	0	1
2813	0	1
2831	0	1
3018	0	1
5016	0	1
5135	0	1
5150	0	1
5552	0	1
6143	0	1
14	2	0
58	2	0
62	3	0

(Continued on next page)

TABLE 1 (Continued)

Genotype	1999–2000	2016–2017
65	1	0
93	2	0
130	1	0
135	1	0
155	1	0
218	1	0
226	1	0
295	3	0
297	1	0
349	1	0
355	1	0
358	1	0
362	1	0
404	1	0
405	1	0
410	1	0
446	1	0
448	1	0
453	3	0
484	1	0
491	1	0
522	1	0
538	2	0
544	3	0
547	1	0
555	4	0
706	1	0
847	1	0
867	1	0
1039	1	0
1064	1	0
1119	1	0
1170	3	0
1312	1	0
1465	1	0
1735	1	0
1867	1	0
2554	1	0
3386	1	0
4377	1	0
4774	1	0
5463	1	0
6439	1	0
Total	216	225

or AmpC-type gene was found (Fig. 1). Among 97 ampicillin-resistant *E. coli* isolates collected in 2016 to 2017, the percentage of isolates possessing only TEM variants decreased to 64.9% ($P < 0.01$). One isolate had CTX-M group 1; two isolates had OXA variants; two isolates had TEM variants and CTX-M group 1; two isolates had TEM variants and CTX-M group 9; one isolate had a TEM variant, CTX-M group 1, and OXA variants; four isolates had TEM variants and OXA variants; and one isolate had SHV variants. The *E. coli* isolates possessing CTX-M groups, OXA variants, and SHV variants accounted for 13.4% in 2016 to 2017 (Fig. 1); the major genotypes were responsible for 70% of the CTX-M-carrying strains (Table 4). During the two study periods, there was no isolate with an AmpC-type gene. Six (10.9%) and 21 (21.6%) of ampicillin-resistant isolates in the two study periods, respectively, did not have any TEM variants, CTX-M groups, OXA variants, SHV variants, or AmpC-type genes.

Association of MLST genotypes with antibiotic susceptibility. To assess the association of MLST genotypes with resistance to different antibiotic classes, we tested the susceptibility of all six major ST isolates to six additional antimicrobial agents. Most *E. coli* isolates from the six major STs in the 1999–2000 study were susceptible to

TABLE 2 Six major multilocus sequence types of uropathogenic *E. coli* strains obtained in a Northern California college community during 1999 to 2000 and 2016 to 2017[a]

Lineage category and ST	No. (%) of isolates typed		
	1999–2000 (n = 225)	2016–2017 (n = 233)	P value
Major			
ST95	34 (15.1)	39 (16.7)	0.70
ST127	24 (10.7)	37 (15.9)	0.12
ST73	23 (10.2)	32 (13.7)	0.25
ST69	26 (11.6)	22 (9.4)	0.54
ST131	7 (3.1)	12 (5.2)	0.35
ST10	11 (9.0)	6 (4.0)	0.22
Total	125 (55.6)	148 (63.5)	0.08
Minor	100 (45.8)	85 (36.5)	0.08

[a]Multilocus sequence typing was performed according to the PubMLST website (https://pubmlst.org/bigsdb?db=pubmlst_mlst_seqdef). ST, sequence type. P values are based on Fisher's exact test for categorical variables.

cephalosporins (cefotaxime, cefoxitin, and ceftazidime), nitrofurantoin, fosfomycin, and gentamicin; resistance to fosfomycin and gentamicin was found in only two ST95 strains. In contrast, in 2016 to 2017, nine (6.1%) isolates from the six major lineages were resistant to gentamicin; seven (4.7%) were extended-spectrum-β-lactamase (ESBL)-producing strains. All ESBL-producing strains of ST69, ST131, and ST10 were MDR. Resistance to nitrofurantoin and fosfomycin was found in only one strain each of ST73 and ST69, respectively.

DISCUSSION

In this university community, the six most common genotypes accounted for more than half (63%) of all the UPEC isolates in 2016 to 2017. These genotypes were also the most common genotypes in a collection of UPEC isolates obtained 17 years earlier in the same community, although the compositions of the minor genotypes had completely changed. These six major genotypes accounted for nearly 80% of the increase in ampicillin resistance and 73% of the increase in resistance to ciprofloxacin. The other genotypes accounted for only 21% and 27% of the increases in ampicillin and ciprofloxacin resistance, respectively. The proportions of isolates with TMP-SMZ resistance did not differ significantly between the periods separated by 17 years. These results indicate that the prevalence of resistant CA-UTI in this population is largely influenced by a few circulating dominant *E. coli* lineages.

TABLE 3 Frequency of ampicillin, trimethoprim-sulfamethoxazole, and ciprofloxacin resistance of uropathogenic *E. coli* during 1999 to 2000 and 2016 to 2017

Lineage category and ST	No. of isolates with indicated result/total no. of isolates typed (% of isolates with indicated result)[a]								
	Ampicillin resistance			Trimethoprim-sulfamethoxazole resistance			Ciprofloxacin resistance		
	1999–2000	2016–2017	P value	1999–2000	2016–2017	P value	1999–2000	2016–2017	P value
Major									
ST95	1/34 (2.9)	8/39 (20.5)	0.03	1/34 (2.9)	1/39 (2.6)	1.00	0/34 (0.0)	0/39 (0.0)	1.00
ST127	3/24 (12.5)	8/37 (21.6)	0.51	1/24 (4.2)	2/37 (5.4)	1.00	0/24 (0.0)	0/37 (0.0)	1.00
ST73	6/23 (26.1)	20/32 (62.5)	0.01	1/23 (4.3)	7/32 (21.9)	0.12	0/23 (0.0)	0/32 (0.0)	1.00
ST69	19/26 (73.1)	17/22 (77.3)	1.00	17/26 (65.4)	15/22 (68.2)	1.00	0/26 (0.0)	1/22 (4.5)	0.46
ST131	2/7 (28.6)	9/12 (75.0)	0.07	1/7 (14.3)	3/12 (25.0)	1.00	0/7 (0.0)	7/12 (58.3)	0.01
ST10	2/11 (18.2)	4/6 (66.7)	0.10	2/11 (18.2)	1/6 (16.7)	1.00	0/11 (0.0)	0/6 (0.0)	1.00
Total	33/125 (26.4)	66/148 (44.6)	0.002	23/125 (18.4)	29/148 (19.6)	0.88	0/125 (0.0)	8/148 (5.4)	0.009
Minor	22/100 (22.0)	31/85 (36.4)	0.03	15/100 (15.0)	11/85 (12.9)	0.83	1/100 (0.10)	4/85 (4.7)	0.18
Total	55/225 (24.4)	97/233 (41.6)	<0.001	38/225 (16.9)	40/233 (17.1)	0.80	1/225 (0.9)	12/233 (5.1)	0.003

[a]Numbers in parentheses represent the percentages of isolates within one genotype in each sampling period. P values are based on Fisher's exact test for categorical variables.

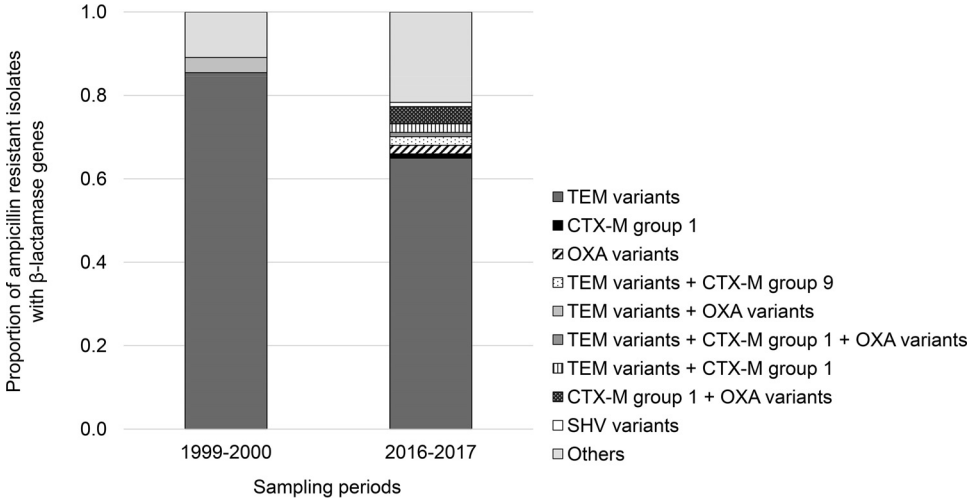

FIG 1 Distribution of β-lactamase gene types among ampicillin-resistant isolates from 1999 to 2000 and 2016 to 2017.

In this study, MLST was used to genotype *E. coli* isolates. Although conventional 7-locus MLST is based on a small set of housekeeping genes of a bacterial genome, phylogenic classification based on this MLST scheme of *E. coli* isolates closely matches that based on their whole-genome sequences (23–25). The observation that a small set of dominant evolutionarily related UPEC lineages persisted to cause UTI in the same community 17 years apart suggests the existence of common-source reservoirs.

Interestingly, these same genotypes (ST95, ST127, ST73, ST69, ST131, and ST10) account for a large proportion of both CA-UTI and bloodstream infections (BSI) in many other communities around the world (12–14, 26–28). The predominance of these major genotypes varies geographically. For example, ST127, the second-most-common genotype in our study, is less frequently reported in studies from Europe, Canada, or Japan (12–14, 27, 28), but it was the third-most-common genotype in the Seattle region (26). The predominance of ST127 in the West Coast cities in the United States is not explained. However, these types of observations suggest that most cases of CA-UTI occur as outbreaks and that the dominant genotypes may be spread by contaminated

TABLE 4 Genotypes of uropathogenic *E. coli* isolates possessing β-lactamase genes other than TEM variants

Lineage category and sequence type	β-Lactamase gene type(s) (no. of isolates)[a]
Major	
ST69	*bla*TEM type + *bla*CTX-M group 1 (1)
ST127	*bla*CTX-M group 1 (1)
ST131	*bla*CTX-M group 1 + *bla*OXA type (4)
	*bla*TEM type + *bla*CTX-M group 9 (1)
	*bla*OXA type (1)
Minor	
ST59	*bla*OXA type (1)
ST280	*bla*TEM type + *bla*CTX-M group 1 + *bla*OXA type (1)
ST2003	*bla*TEM type + *bla*CTX-M group 9 (1)
ST2261	*bla*SHV-1 (1)
Unknown	*bla*TEM type + *bla*CTX-M group 1 (1)

[a]*bla*TEM type, bla_{TEM-1} and bla_{TEM-2}; *bla*SHV type, bla_{SHV-1}; *bla*CTX-M group 1, $bla_{CTX-M-1}$, $bla_{CTX-M-3}$, and $bla_{CTX-M-15}$; *bla*CTX-M group 2, $bla_{CTX-M-2}$; *bla*CTX-M group 9, $bla_{CTX-M-9}$ and $bla_{CTX-M-14}$; *bla*CTX-M group 8/25, $bla_{CTX-M-8}$, $bla_{CTX-M-25}$, $bla_{CTX-M-26}$, and $bla_{CTX-M-39}$ to $bla_{CTX-M-41}$; *bla*OXA type, bla_{OXA-1}, bla_{OXA-4}, and bla_{OXA-30}. Numbers in parentheses following gene designations represent the percentages of isolates possessing CTX-M groups or SHV variants among the *E. coli* isolates obtained in 2016 to 2017.

vehicles distributed locally, regionally, or globally. It also suggests that the selective pressure of antimicrobial use exerts differential effects on ExPEC genotypes such that certain genotypes become progressively more resistant.

Recently, several epidemiological studies have resulted in reports that *E. coli* causing UTI may be transmitted by contaminated food products (27, 29–35). A case-control study suggested that antimicrobial-resistant UPEC could have a food reservoir, possibly in poultry or pork (34). *E. coli* genotypes identified on the basis of ERIC2-PCR and pulsed-field gel electrophoresis (PFGE) results that were shared between CA-UTI isolates and retail meat concurrently obtained from the same geographic region have been observed (31, 33, 35). However, despite those studies suggesting foodborne transmission of UTI, the reservoir of these common lineages, how they are introduced into the food chain, and why only these lineages predominate in human populations remain unclear.

In the mid-2000s in the United States, fluoroquinolones replaced TMP-SMZ as the most widely prescribed antimicrobial agent for treatment of uncomplicated UTI (36). In 2016 to 2017, we found 12 ciprofloxacin-resistant strains, of which more than half were due to ST131, whereas, in 1999 to 2000, only 1 was identified. In early 2000, the university health service replaced TMP-SMZ with ciprofloxacin as the first-line empirical drug used to treat UTI. Despite this change, fluoroquinolone resistance occurred in only one genotype during the ensuing 17 years. Dominant genotypes ST95 and ST127 remained susceptible to most antimicrobial agents, while others, such as ST131, evolved to become MDR during the same period. ST131 is well recognized globally as an extensively resistant ExPEC clonal group (37–40). During the two study periods, ST95 was the most common dominant genotype, and the prevalence of ST127 increased from 11% to 16%. Drug resistance does not seem to be the driving force responsible for a UPEC genotype becoming dominant, as indicated by the ST95 and ST127 data.

A similar observation was made in a population dynamics analysis of ExPEC lineages in England over an 11-year period, which found ST73 to be the most common lineage among pandemic strains ST69, ST95, and ST131 (14). ST73 was consistently susceptible to most antibiotics, and it was suggested that drug resistance was not the main reason for the prevalence of *E. coli* lineages in this population (14). The community dominance of these lineages may be due to their intrinsic biological fitness together with epidemiologic factors that contribute to their global dissemination.

Limitations of this study included a lack of patient clinical and exposure history in both study periods. While the UTI subjects were largely women attending a Northern California university, we do not have information about their previous use of antimicrobial agents; such use could have influenced the resistance status of their UTI episodes and thus the differences in the prevalences of resistant UTI in the two periods. However, such a factor would not explain the dominance of a small set of UPEC genotypes in the two study periods.

We observed that six UPEC genotypes were persistently dominant in all CA-UTI cases at one university community in Northern California during two study periods separated by 17 years. These findings suggest that the community prevalence of drug-resistant CA-UTI is largely determined by the number and proportion of dominant UPEC genotypes circulating in that community. Antimicrobial agents may select for drug-resistant strains, but they do not appear to exert their effect equally on all UPEC strains. Control of drug-resistant CA-UTI will likely require new interventions in addition to antibiotic stewardship programs in outpatient clinical settings. Further studies are needed to elucidate the mechanisms by which these common lineages disseminate and prevail within a community.

ACKNOWLEDGMENTS

We thank Holly Berryman Stern and the other staff members of the Tang Center of University of California, Berkeley (UC Berkeley)-affiliated health care service for their time and support of this project. We are grateful to Amee Manges for providing us with the data for antimicrobial susceptibility to ciprofloxacin and trimethoprim-sulfamethoxazole for *E.*

coli isolates in 1999 to 2000. We also thank all the members of the Riley laboratory for fruitful discussion and their contributions to this study.

This work was supported by Centers for Disease Control and Prevention investments to combat antibiotic resistance under BAA 200-2016-91939. The contents of this work are solely the responsibility of the authors and do not necessarily represent the official views of the Centers for Disease Control and Prevention. The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

REFERENCES

1. Hooton TM, Scholes D, Hughes JP, Winter C, Roberts PL, Stapleton AE, Stergachis A, Stamm WE. 1996. A prospective study of risk factors for symptomatic urinary tract infection in young women. N Engl J Med 335:468–474. https://doi.org/10.1056/NEJM199608153350703.
2. Foxman B, Barlow R, D'Arcy H, Gillespie B, Sobel JD. 2000. Urinary tract infection: self-reported incidence and associated costs. Ann Epidemiol 10:509–515. https://doi.org/10.1016/S1047-2797(00)00072-7.
3. Flores-Mireles AL, Walker JN, Caparon M, Hultgren SJ. 2015. Urinary tract infections: epidemiology, mechanisms of infection and treatment options. Nat Rev Microbiol 13:269–284. https://doi.org/10.1038/nrmicro3432.
4. Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG, Moran GJ, Nicolle LE, Raz R, Schaeffer AJ, Soper DE. 2011. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis 52:e103–e120. https://doi.org/10.1093/cid/ciq257.
5. Grigoryan L, Trautner BW, Gupta K. 2014. Diagnosis and management of urinary tract infections in the outpatient setting: a review. JAMA 312:1677–1684. https://doi.org/10.1001/jama.2014.12842.
6. Manges AR, Johnson JR, Foxman B, O'Bryan TT, Fullerton KE, Riley LW. 2001. Widespread distribution of urinary tract infections caused by a multidrug-resistant *Escherichia coli* clonal group. N Engl J Med 345:1007–1013. https://doi.org/10.1056/NEJMoa011265.
7. Karlowsky JA, Kelly LJ, Thornsberry C, Jones ME, Sahm DF. 2002. Trends in antimicrobial resistance among urinary tract infection isolates of *Escherichia coli* from female outpatients in the United States. Antimicrob Agents Chemother 46:2540–2545. https://doi.org/10.1128/AAC.46.8.2540-2545.2002.
8. Kim ES, Hooper DC. 2014. Clinical importance and epidemiology of quinolone resistance. Infect Chemother 46:226–238. https://doi.org/10.3947/ic.2014.46.4.226.
9. Park KH, Oh WS, Kim ES, Park SW, Hur JA, Kim YK, Moon C, Lee JH, Lee CS, Kim BN. 2014. Factors associated with ciprofloxacin- and cefotaxime-resistant *Escherichia coli* in women with acute pyelonephritis in the emergency department. Int J Infect Dis 23:8–13. https://doi.org/10.1016/j.ijid.2013.12.021.
10. Tartof SY, Solberg OD, Manges AR, Riley LW. 2005. Analysis of a uropathogenic *Escherichia coli* clonal group by multilocus sequence typing. J Clin Microbiol 43:5860–5864. https://doi.org/10.1128/JCM.43.12.5860-5864.2005.
11. Smith SP, Manges AR, Riley LW. 2008. Temporal changes in the prevalence of community-acquired antimicrobial-resistant urinary tract infection affected by *Escherichia coli* clonal group composition. Clin Infect Dis 46:689–695. https://doi.org/10.1086/527386.
12. Adams-Sapper S, Diep BA, Perdreau-Remington F, Riley LW. 2013. Clonal composition and community clustering of drug-susceptible and -resistant *Escherichia coli* isolates from bloodstream infections. Antimicrob Agents Chemother 57:490–497. https://doi.org/10.1128/AAC.01025-12.
13. Gibreel TM, Dodgson AR, Cheesbrough J, Fox AJ, Bolton FJ, Upton M. 2012. Population structure, virulence potential and antibiotic susceptibility of uropathogenic *Escherichia coli* from Northwest England. J Antimicrob Chemother 67:346–356. https://doi.org/10.1093/jac/dkr451.
14. Kallonen T, Brodrick HJ, Harris SR, Corander J, Brown NM, Martin V, Peacock SJ, Parkhill J. 18 July 2017. Systematic longitudinal survey of invasive *Escherichia coli* in England demonstrates a stable population structure only transiently disturbed by the emergence of ST131. Genome Res https://doi.org/10.1101/gr.216606.116.
15. Riley LW. 2014. Pandemic lineages of extraintestinal pathogenic *Escherichia coli*. Clin Microbiol Infect 20:380–390. https://doi.org/10.1111/1469-0691.12646.
16. Hooton TM, Stamm WE. 1997. Diagnosis and treatment of uncomplicated urinary tract infection. Infect Dis Clin North Am 11:551–581. https://doi.org/10.1016/S0891-5520(05)70373-1.
17. Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, Harbarth S, Hindler JF, Kahlmeter G, Olsson-Liljequist B, Paterson DL, Rice LB, Stelling J, Struelens MJ, Vatopoulos A, Weber JT, Monnet DL. 2012. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect 18:268–281. https://doi.org/10.1111/j.1469-0691.2011.03570.x.
18. Wilson LA, Sharp PM. 2006. Enterobacterial repetitive intergenic consensus (ERIC) sequences in *Escherichia coli*: evolution and implications for ERIC-PCR. Mol Biol Evol 23:1156–1168. https://doi.org/10.1093/molbev/msj125.
19. Hulton CS, Higgins CF, Sharp PM. 1991. ERIC sequences: a novel family of repetitive elements in the genomes of *Escherichia coli*, *Salmonella typhimurium* and other enterobacteria. Mol Microbiol 5:825–834. https://doi.org/10.1111/j.1365-2958.1991.tb00755.x.
20. Lau SH, Reddy S, Cheesbrough J, Bolton FJ, Willshaw G, Cheasty T, Fox AJ, Upton M. 2008. Major uropathogenic *Escherichia coli* strain isolated in the northwest of England identified by multilocus sequence typing. J Clin Microbiol 46:1076–1080. https://doi.org/10.1128/JCM.02065-07.
21. Dallenne C, Da Costa A, Decre D, Favier C, Arlet G. 2010. Development of a set of multiplex PCR assays for the detection of genes encoding important beta-lactamases in Enterobacteriaceae. J Antimicrob Chemother 65:490–495. https://doi.org/10.1093/jac/dkp498.
22. Pérez-Pérez FJ, Hanson ND. 2002. Detection of plasmid-mediated AmpC beta-lactamase genes in clinical isolates by using multiplex PCR. J Clin Microbiol 40:2153–2162. https://doi.org/10.1128/JCM.40.6.2153-2162.2002.
23. Kovanen SM, Kivisto RI, Rossi M, Schott T, Karkkainen UM, Tuuminen T, Uksila J, Rautelin H, Hanninen ML. 2014. Multilocus sequence typing (MLST) and whole-genome MLST of *Campylobacter jejuni* isolates from human infections in three districts during a seasonal peak in Finland. J Clin Microbiol 52:4147–4154. https://doi.org/10.1128/JCM.01959-14.
24. Jolley KA, Maiden MC. 2013. Automated extraction of typing information for bacterial pathogens from whole genome sequence data: *Neisseria meningitidis* as an exemplar. Euro Surveill 18:20379. https://doi.org/10.2807/ese.18.04.20379-en.
25. Joensen KG, Scheutz F, Lund O, Hasman H, Kaas RS, Nielsen EM, Aarestrup FM. 2014. Real-time whole-genome sequencing for routine typing, surveillance, and outbreak detection of verotoxigenic *Escherichia coli*. J Clin Microbiol 52:1501–1510. https://doi.org/10.1128/JCM.03617-13.
26. Salipante SJ, Roach DJ, Kitzman JO, Snyder MW, Stackhouse B, Butler-Wu SM, Lee C, Cookson BT, Shendure J. 2015. Large-scale genomic sequencing of extraintestinal pathogenic *Escherichia coli* strains. Genome Res 25:119–128. https://doi.org/10.1101/gr.180190.114.
27. Manges AR, Harel J, Masson L, Edens TJ, Portt A, Reid-Smith RJ, Zhanel GG, Kropinski AM, Boerlin P. 2015. Multilocus sequence typing and virulence gene profiles associated with *Escherichia coli* from human and animal sources. Foodborne Pathog Dis 12:302–310. https://doi.org/10.1089/fpd.2014.1860.
28. Umene YD, Wong LK, Satoh T, Yamane K, Matsui M, Riley LW, Arakawa Y, Suzuki S. 2015. Molecular epidemiological characterization of uropatho-

genic *Escherichia coli* from an outpatient urology clinic in rural Japan. J Clin Microbiol 53:681–683. https://doi.org/10.1128/JCM.03068-14.
29. Johnson TJ, Logue CM, Wannemuehler Y, Kariyawasam S, Doetkott C, DebRoy C, White DG, Nolan LK. 2009. Examination of the source and extended virulence genotypes of *Escherichia coli* contaminating retail poultry meat. Foodborne Pathog Dis 6:657–667. https://doi.org/10.1089/fpd.2009.0266.
30. Mora A, Lopez C, Dabhi G, Blanco M, Blanco JE, Alonso MP, Herrera A, Mamani R, Bonacorsi S, Moulin-Schouleur M, Blanco J. 2009. Extraintestinal pathogenic *Escherichia coli* O1:K1:H7/NM from human and avian origin: detection of clonal groups B2 ST95 and D ST59 with different host distribution. BMC Microbiol 9:132. https://doi.org/10.1186/1471-2180-9-132.
31. Vincent C, Boerlin P, Daignault D, Dozois CM, Dutil L, Galanakis C, Reid-Smith RJ, Tellier PP, Tellis PA, Ziebell K, Manges AR. 2010. Food reservoir for *Escherichia coli* causing urinary tract infections. Emerg Infect Dis 16:88–95. https://doi.org/10.3201/eid1601.091118.
32. Johnson TJ, Kariyawasam S, Wannemuehler Y, Mangiamele P, Johnson SJ, Doetkott C, Skyberg JA, Lynne AM, Johnson JR, Nolan LK. 2007. The genome sequence of avian pathogenic *Escherichia coli* strain O1:K1:H7 shares strong similarities with human extraintestinal pathogenic *E. coli* genomes. J Bacteriol 189:3228–3236. https://doi.org/10.1128/JB.01726-06.
33. Ramchandani M, Manges AR, DebRoy C, Smith SP, Johnson JR, Riley LW. 2005. Possible animal origin of human-associated, multidrug-resistant, uropathogenic *Escherichia coli*. Clin Infect Dis 40:251–257. https://doi.org/10.1086/426819.
34. Manges AR, Smith SP, Lau BJ, Nuval CJ, Eisenberg JN, Dietrich PS, Riley LW. 2007. Retail meat consumption and the acquisition of antimicrobial resistant *Escherichia coli* causing urinary tract infections: a case-control study. Foodborne Pathog Dis 4:419–431. https://doi.org/10.1089/fpd.2007.0026.
35. Johnson JR, Delavari P, O'Bryan TT, Smith KE, Tatini S. 2005. Contamination of retail foods, particularly turkey, from community markets (Minnesota, 1999–2000) with antimicrobial-resistant and extraintestinal pathogenic *Escherichia coli*. Foodborne Pathog Dis 2:38–49. https://doi.org/10.1089/fpd.2005.2.38.
36. Kallen AJ, Welch HG, Sirovich BE. 2006. Current antibiotic therapy for isolated urinary tract infections in women. Arch Intern Med 166:635–639. https://doi.org/10.1001/archinte.166.6.635.
37. Petty NK, Ben Zakour NL, Stanton-Cook M, Skippington E, Totsika M, Forde BM, Phan MD, Gomes Moriel D, Peters KM, Davies M, Rogers BA, Dougan G, Rodriguez-Bano J, Pascual A, Pitout JD, Upton M, Paterson DL, Walsh TR, Schembri MA, Beatson SA. 2014. Global dissemination of a multidrug resistant *Escherichia coli* clone. Proc Natl Acad Sci U S A 111:5694–5699. https://doi.org/10.1073/pnas.1322678111.
38. Banerjee R, Johnson JR. 2014. A new clone sweeps clean: the enigmatic emergence of *Escherichia coli* sequence type 131. Antimicrob Agents Chemother 58:4997–5004. https://doi.org/10.1128/AAC.02824-14.
39. Nicolas-Chanoine MH, Blanco J, Leflon-Guibout V, Demarty R, Alonso MP, Canica MM, Park YJ, Lavigne JP, Pitout J, Johnson JR. 2008. Intercontinental emergence of *Escherichia coli* clone O25:H4-ST131 producing CTX-M-15. J Antimicrob Chemother 61:273–281. https://doi.org/10.1093/jac/dkm464.
40. Rogers BA, Sidjabat HE, Paterson DL. 2011. *Escherichia coli* O25b-ST131: a pandemic, multiresistant, community-associated strain. J Antimicrob Chemother 66:1–14. https://doi.org/10.1093/jac/dkq415.